Section IV

Antiaging

Part 1: Cosmeceuticals

Chapter 34: Botanicals

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BASIC CONCEPTS

- Botanicals represent a class of frequently used active agents in cosmeceuticals.
- The constituents of a botanical can be influenced by growing conditions, harvesting procedures, the part of the plant utilized, and extraction methods.
- Botanical extracts must be evaluated for cleanliness, purity, and contaminants.
- Botanicals contain terpenoids, alkaloids, and phenolics, which have been chemically characterized for their biologic effects.
- Products containing botanical extracts should be rigidly evaluated using the scientific method for efficacy.

Introduction

The number of skincare products with "active" ingredients extracted from plants has increased to annual sales of $12.5 billion [1]. Herbs are species of higher plants whose extracts have medicinal, fragrance or flavoring use [2]. One-quarter of US adults used an herbal remedy to treat a medical illness in 2003 [3].

Herb-based products usually also provide multiple functionalities and stable formulations of highly reactive ingredients such as antioxidants. While it is difficult to create efficacious and stable cosmeceutical formulations, herbs contain unique active ingredients normally existing in nature [4]. While 73% of women polled said it is important to have younger looking skin, the vast majority of topical botanical products promise youth but lack clinical evidence [5]. It remains unclear whether antioxidants actually improve photodamaged skin [6]. The vast majority of the more than 320 herbs used in skincare products are at concentrations far below therapeutic ranges.

International regulations

A surprising 78.7% of women polled did not know that claims made for skincare products are not regulated, evaluated, or verified by any governmental agency [4]. Only in the USA are herbal products sold as dietary supplements which is governed by the Dietary Supplement, Health and Education Act, 1994. Such products are intended to affect the structure and function of the human body, not just as an energy source.

Certain US cosmeceutical ingredients may be claimed to be therapeutic for very common skin diseases. They are regulated as over-the-counter (OTC) drug monographs for acne, dermatitis/psoriasis, skin protectant, topical analgesia, and sunscreens, by the Food and Drug Administration (FDA). Non-prescription products that list the active ingredients used in a certain concentration range in certain formulations may claim the finished product to be effective and safe therapy for the specific skin conditions listed in the FDA OTC drug monographs [4].

Regulation of herbal products is under federal law in Germany, Japan, Australia, India, China, and the European Union. The German Commission E approves traditional phytomedicine products based on the quality of scientific clinical evidence of the herbal effects upon diseases and conditions as well as its safety. Certain herbs may be registered as prescription medicines if the evidence of therapeutic effect compares to synthetic ingredients. In Japan, herbal products may be prescription drugs but also may be OTC "quasi-drugs," or in functional foods. Both of the latter are allowed to make very restricted therapeutic claims [2,7,8].

There is no consistent definition of "natural" in US skincare products [9]. It was recently recommended that a definition of natural might read: "Five percent or more of the ingredients are found in nature." In contrast, organic products are certified free of synthetic chemicals during agriculture and product manufacture [8]. The FDA has certification criteria for this designation.

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Factors affecting concentration and quality of active ingredients

The skincare practitioner should select an herb for a specific desired beneficial effect based on scientific research and/or traditional medical knowledge founded on ethnobotany. The interest in phytomedicines for improving health, as well as treating disease, is rapidly growing resulting in many exotic species creating cosmeceutical fads. Most of these exotic ingredients are added at subtherapeutic doses for marketing cache, as little is known about their efficacy and safety.

Some herbs are obtained by wildcrafting, which is harvesting wild plants for commercial use. Unfortunately, this activity has brought certain plant species, such as American ginseng (*Panax quinquefolium*), to the brink of being an endangered species as a result of unregulated overharvesting. It is important that all botanical species are harvested in a sustainable fashion, noting those substances that are listed on the International Trade in Endangered Species of Fauna and Flora (www.cites.org) [10].

Herbal extracts exhibit more variation than synthetic products because of solubility, stability, pharmacokinetics, pharmacology, and toxicity of the active ingredients. Sources of variability include:

1 Growing conditions of the plant contribute to variation in botanical extracts. These variables include climate, habitat, weather including catastrophes such as hurricanes, time of year, elevation, number of sunny days, hours of daylight, amount of rain or lack thereof, soil conditions such as leaching of nitrogen in a year of heavy rain fall, wind conditions, type and amount of fertilizer, ambient temperatures, pests, and plant disease exposure, and if cultivated or in its natural habitat, plant growth periods and diurnal variation.

2 The conditions following harvesting may also affect the constituents of the botanical. These variables include harvesting time, care of botanical products during transport, storage time for the botanical, processing methods, and manufacturing of the finished product.

3 The biologic activity of the herbal extract is affected by the condition of the plant, which must be healthy and disease free [11].

4 Botanicals are affected by the portion of the plant selected for harvesting. There are differences in the mix and concentrations of the active ingredients between flowers, berries, stems, bark, roots, and rhizomes. Familiarity with phytomedicine is important to ensure the recommended product contains the correct plant parts for the desired effect.

5 Proper processing is necessary to insure herbal potency. The timing, degree, and type of processing determine the functionality of the herbal product. The first step in processing is air or oven drying to achieve a moisture content ≤10% and prevent mildew. This material is then milled into pieces less than 1 cm in diameter. If the desired actives are highly sensitive to light, heat, dessication, oxygen, or enzymes, they need to be extracted without drying as soon as the plant is harvested. For example, volatile essential oils evaporate during drying so the plant source should undergo steam distillation as soon as harvested. Other processing methods include crushing, pressing, grinding, comminuting (fracturing) followed by extraction [2,8,10,11]. The methods for extraction are discussed below.

Extraction methods

The active ingredients of plants are generally small molecules not involved in regular metabolic processes, known as secondary metabolites (SM). The goal of extraction processes is to improve consistency of SM concentration, increase SM potency, and increase product purity. The most common extraction method is placing the dried plant material in the solvent of choice. The extraction duration and temperature must be optimized.

Milled dried plant material is exposed to one or more solvents selected from water, alcohol, butylene glycol, glycerin, methanol, and an oil or ester. Herbal enzymes, such as cellulases, may be used to break cell walls releasing SM.

A secondary purification is usually performed with a different solvent after alcohol extraction. Column chromatography is then used to separate the resulting two or more solutes. Ultrafiltration or nanofiltration are used to purify aqueous extracts. A "green" extraction process uses CO_2 supercritical fluids, which includes pressure and low heat to convert CO_2 into a fluid is the most efficient methods to extract non-polar constituents such as carotenoids and essential oils. Nitrogen blankets used during filling of the final packages significantly prolong stability of SM with highly reactive SM such as catechins and salicylates.

The standardization of the SM in the extract for consistency is performed by analytical chemistry methods, including chromatography and/or a DNA fingerprint [2,10,11].

Quality control

The major quality issues of herbal products revolve around the extract itself. Other significant issues involve quality of the finished product regarding its safety and product effectiveness.

Quality control evaluation must include:

1 Identify the active SM and the plant part with the optimum concentration for desired activity.

2 Evaluate cleanliness of extract. Foreign organic matter is limited to 2% dry weight and ash value of 3–5% by weight by the US Department of Agriculture.

3 Purity must be determined to ensure no destructive adulterants or microbes are present. Dangerous adulterants

include: heavy metals, radioactive ingredients, and most pesticides. *Salmonella* and *Escherichia coli* are microbial contaminants that must not be present in herbal formulations. **4** Contaminants may reduce activity since they may dilute the SM out of the therapeutic concentration. Because most synthetic pharmaceutical and cosmeceutical active ingredients produce their cutaneous modulation at 1% or less, even the above allowed concentrations of foreign organic material may dilute SM enough to blunt expected product activity.

Maximum concentration limits for more than 30 pesticides have been set by the US Pharmacopia in the chemical tests section for dietary supplements but not for cosmetics. Pesticides not listed in this reference are known as toxins and must not be present in any product [2,10,11].

Safety

The US woman uses an average of nine products daily on her skin, so the skincare professional has an obligation to be concerned about product safety. Thus, safety studies should be performed on all herbal products. Fortunately, the incidence of dangerous adverse reactions to herbal medicines is extremely rare. The clinical relevance of topical safety tests is that 40% of US women claim to have sensitive skin [2,4–6].

A "natural" product does not equal a safe product. Chinese practitioners are concerned about the well-known side effects of hepatotoxicity, contact dermatitis, and teratogenicity which occur in up to one-third of people using topical Chinese herbal preparations. Moreover, a significant number of congenital anomalies occur when these herbs are used topically during pregnancy [12].

Another risk of herbal products is the relatively high incidence of cross-reactivity with other herbs. For example, in 106 dermatitis afflicted people, 12 were allergic to tea tree oil and all 12 had one or more patch test reactions to 10 other herbs [13]. A preferred safety test for a cosmeceutical product would be the Repeat Insult Patch Test (RIPT) on 50 panelists to evaluate risk of contact irritant and allergic dermatitis with topical use. It will not predict systemic reactions, however, such as gynecomastia with topical lavender [2,11].

Effectiveness

Double-blinded, placebo-controlled studies do not exist for all ancient and herbal medicines. Yet, there have been many such studies conducted on herbal products throughout Asia, India, and Europe [12].

Rarely, herbal products have shown statistically significant superiority to placebo or an approved prescription drug in double-blind clinical trials, which is the most convincing scientific evidence of therapeutic efficacy. The vast majority have never undergone this type of clinical evaluation because cosmetics cannot claim cutaneous structure change, but only temporary change in appearance claims. Cosmeceutical claims for a product should be supported by at least one double-blind clinical trial with enough panelists to determine statistical significance [2,5,6].

A major challenge to the clinical efficacy of any herbal extract is the delivery of therapeutic concentration(s) of the desired active ingredients across the stratum corneum intact to affect organelles, cells, receptors, and metabolic and cell signaling pathways. The different solubilities, polarities, size, and architecture of the several to hundreds of SM in herbal extracts creates difficulty. Moreover, the degree of biodegradability, biocompatibility, toxicity, release profile, and antigenicity also vary among the multitude of SM in one extract. Contributing to the challenge is different SM bind to cells and receptors in different cutaneous strata.

To meet this challenge of negotiating the tortuous proteohydrolipid stratum corneum several novel methodologies have been developed. The first group is biochemical delivery via manipulating the barrier itself by:

1 Modulating the synthesis of the three key physiologic lipids of stratum corneum lipid lamellae: cholesterol, ceramide, and free fatty acids; as well as the metabolism and catabolism of them.

2 Inducing phase separation within and between the lipid lamellae with application of anomalous or excess three key lipids and their precursors [14].

The second group consists of manipulation of the formulation itself using microemulsion, liposome, phytosome, nanoemulsion, nanocrystal, nanosome, or pearlescent beads. These methods enhance bioavailability, depth, and speed of penetration and increase concentration of SM delivered [15]. Microemulsions use lecithin and alkyl glucoride to encapsulate non-polar molecules including arbutin, kojic acid, and cinnamates.

Liposomes often composed of soy phospholipids, deliver hydrophilic, lipophilic, and amphiphilic compounds such as 2% citrus into the outermost epidermal strata. Phytosomes consist of herbal extracts complexed within phospholipids. Silymarin's soothing activity was increased by sixfold, while grape seed, gingko biloba, hawthorn, green tea, and ginseng respond better in phytosomes than liposomes.

Other herbal SM are delivered by nanotechnology.

Ginseng's delivery is also improved with nanosomes. Flavonoids have increased delivery with nanocrystals where large crystals are milled in a water-based stabilizer solution producing nanometer-sized drug crystals. Nanoemulsions have a droplet size of 20–300 nm with those ≤70 are transparent and >100 are opaque. Both hydrophilic and lipophilic herbal extracts have increased bioavilability with these nanoemulsions. Aloe vera has improved delivery when formulated in pearlescent beads [15].

Finally, mechanical modulation of the barrier can be affected by sound waves (sonophoresis), electrical current,

ionic gradients (iontophoresis), vibration, ultrasound, water stream devices, and microdermabrasion infusion.

Mechanism of action of herbal actives via secondary metabolites

Phytomedicines usually consist of mixtures of molecules which often act on two or more human cellular processes to treat and/or prevent diseases. These multifunctional extracts usually consist of multiple SM. Plants are also equipped with protective defensive mechanisms, which include low molecular weight compound SM. SM are not used in primary metabolic processes such as photosynthesis, respiration, assimilation of nutrients, transport, growth, or differentiation. They are rarely used as storage compounds, but usually provide protection against UV light and herbivores, such as parasites and pathogenic microbes as well as animals. SM are also useful for producing color and smell to attract pollinators and for seed dispersal. Certain fatty acids and carbohydrates function within both metabolic processes and as SM. The purified SM are equal in activity to synthetic molecules if equal concentration and weight.

About 20% of the higher plants have been studied with spectrometry, nuclear magnetic resonance, and/or X-ray diffraction which have identified about 40 000 SM. Several have been useful to humans for millennia such as indigo for dye, strychnine and curare for poisons, caffeine and nicotine as stimulants, essential oils such as rosehip and lavender for fragrances, as well as mustard, vanilla, and turmeric as food spices [2].

To produce a measurable or clinical effect the SM must modulate at least one molecular target in human skin but often multiple are affected because SM usually reside within complex mixtures with other SM. The molecular targets occur at any of the cell sites such as:

- Cell membrane receptors, ion channels, phospholipid bilayer, transporters, signal transduction;
- *Cytoplasm:* enzymes, cytoskeleton actin, microtubules;
- *Ribosomes:* protein biosynthesis, post-translational protein modification;
- *Gogli apparatus:* post-translational protein modification, protein biosynthesis, enzymes;
- *Lysosome:* enzymes;
- *Mitochondria:* enzymes, electron transport, nucleic acid replication, transcription and repair;
- *Nucleus:* nucleic acid replication, transcription and repair;
- *Endoplasmic reticulum:* biosynthetic enzymes.

SM are divided into more than 15 500 terpenoids, 12 000 alkaloids, and 6000 phenolics that have been chemically characterized from herbal extracts, as have 10 other chemical classes representing the other 6500 SM [2,11].

Terpenes are generally highly lipophilic compounds that readily penetrating organism and cellular membranes including the blood–brain barrier. Monoterpenes consist of 10 carbon atoms, sesquiterpenes have 15, diterpenes have 20, triterpenes have 30, tetraterpenes have 40, and polyterpenes up to 1000 carbon atoms. Most essential oils are monoterpenes and sesquiterpenes. Phytosteroids contain 27 carbon atoms, are derived from triterpenes, and mimic the functionality of endogenous glucocorticoids. Saponins are water-soluble triterpenes with attached saccharides that are synthesized by 70% of all plants. They are also anti-inflammatory, inhibit phospholipases, oxygenases, complex with membrane cholesterol and modulate nuclear receptors to impact gene function, increase cell membrane fluidity, modulate the architecture of the membrane itself, damage ionic channels and membrane transporters to induce cell content leakage and disturb signal transduction, while providing broad-spectrum antimicrobial effects and cytotoxicity effects. Sesquiterpene lactones have a high risk of inducing allergic contact dermatitis. Carotenoids such as beta-carotene, lutein, lycopene, and zeaxanthine are tetraterpenes.

About 15% of plants synthesize alkaloids. The targeted cell functions include: neuroreceptor agonist, ionic channels, neurotransmitter deactivating enzymes, uptake and release of synaptic vesicles, ionic channel restoring enzymes, and modulate signal pathway enzymes such as adenyl cyclase, phosphodiesterase, phospholipase C, protein kinase C, and tyrosine kinase. They also intercalate or alkylate DNA, inhibit microtubular assembly, inhibit carbohydrate processing enzymes, and induce aptosis. Caffeine is an alkaloid.

The third major group of SM are compounds that have a phenolic (6 carbon) ring. Polyphenols have several rings of different numbers of carbon atoms. Phenolics are anti-inflammatory, antioxidant, antimicrobial, and modulate cell replication. Well-known phenolics include salicylic acid, salicin from willow bark, cinnamic and caffeic acids, furocoumarins, psoralens, and lignans.

This phenylpropanoid subgroup is the foundation for flavonoids, which includes naringenin; isoflavones such as genistein, flavones, and flavonols; stilbenes such as resveratrol; chalcones such as liquiritin; catechins such as epigallocatechin gallate (ECGC); and anthocyanins.

Tannins are catechins with 20 or more hydroxyl groups. Catechins polymerize to form oligomeric procyanidins (OPCs). The greater number of hydroxyl groups in catechins is correlated with greater therapeutic potency of the extract. Other biologic effects of certain phenolic SM inhibition of tyrosine kinases, astringent, denatures protein, agonist for signal transduction and inhibits enzymes and prostaglandin and leukotriene formation as well as alkylate DNA and bind peptides and proteins.

Mucilages contain hexose and pentose polysaccharides to soothe skin. A polyketide used in cosmeceuticals for depigmenting and antibacterial activities is arbutin [2,10,11].

Cosmeceutical product development

Producing an effective and safe non-prescription topical product requires complying with a known development path to overcome previously mentioned challenges. Laboratory data of function of an herbal extract cannot lead to the assumption of its effectiveness in treating human skin conditions with topical application because only 1 in 350 new chemical entities by *in vitro* data reach human prescription drug approval by the FDA. Moreover, of the 8000+ known antioxidants, only about 30 have been tested in human clinical studies to treat photoaging, with only 20 producing statistically significant positive results.

This product development path should also be followed to ensure the finished product is safe. One must be aware that US fatalities have been reported to topical use of 10 different herbal extracts including arnica and comfrey. Herbs rich in certain SM, particularly sesquiterpene lactones extracted from feverfew and arnica, induce a high rate of allergic reactions including life-threatening anaphylaxis. Certain companies have developed manufacturing processes to remove toxic parthenolide and helanaline in feverfew and arnica, respectively, from the marketed products. Remember cosmeceutical products with these extracts are not regulated, so buyer beware of the risk to the user. Allantoin, the oldest SM in time of market use, is now synthesized rather than extracted from comfrey to improve consistent potency [7,8,11,12].

To help separate true scientifically based herbal cosmeceuticals from "snake oil" products, and before making a decision on retailing or recommending any particular brand of skincare product, the practitioner should ask the following questions:

1 Is the herb being used in other living breathing organisms (i.e. used as a veterinary or dental medicine), or a part of traditional Asian or homeopathic medicines, or used in food technology for mammalian exposure?

2 Is the biologically active or therapeutic concentration range known and used in the cosmeceutical?

3 The development of the formulation should include chemical, physical, and photostability to ensure efficacy and that toxic metabolites are not formed. Stability with other interacting actives must be achieved as with other ingredients necessary to product a cosmetically acceptable product. Every human tissue contains 6–8 antioxidants to regenerate each other or they become pro-oxidants. How can a practitioner expect significant, much less optimal, clinical results with a single antioxidant SM?

4 Does the herbal SM penetrate the stratum corneum permeability barrier in its active state at a high enough concentration to manipulate its target cell, organelle, enzyme, receptor, or compound? Soothing mucilage or occlusive SM function by placement upon the mucocutaneous surface, thus need not penetrate SC.

5 When was the finished product manufactured? Freshness matters with herbal products. All cosmeceutical active ingredients including antioxidants, vitamins, and herbal SM undergo chemical reactions when combined in any formulation. This auto-oxidation reaction is affected by formulation manufacturing method. For example, heating speeds up the auto-oxidation process. Thus, the longer the time between product use from the manufacturing date is important in regards to optimum clinical benefit or lack thereof and increased risk of adverse reactions.

Caution must be raised for any cosmeceutical that is sold by companies where products are contract manufactured in small quantities because minimum production volumes may be 12–18 months of finished product. If the product has been tested for stability for an 18-month period, then the preservative system is robust and the product can claim stability for the tested period.

6 Does the product really work in the skin? The only way a skincare practitioner can confidently recommend and sell herbal cosmeceuticals that are not based on "ingredient of the month" or "voodoo science" is by a prospective, double-blind, controlled clinical trial for treatment of any or all parameters of photoaging. These trials must include enough panelists to establish statistical significance with a p value <0.05 against placebo or an approved prescription product. The tested product should be the final marketed formulation, not just one marquee ingredient in a stripped down preservative formulation. The clinical trial should be conducted by an established independent researcher. The FDA has established these studies are sufficiently unbiased to draw valid conclusions of product efficacy, even when paid for (sponsored) by a company. The tested parameters should include panelists' subjective analysis of visible changes, not just statistical measurements to assure clinical relevance of the statistics. Observations of employee responses are not considered unbiased. If the herb is approved the German Commission E or other international regulatory group, its efficacy and safety have been thoroughly reviewed.

7 Has the skincare practitioner thoroughly evaluated the product? Patients/clients when consulting with a skincare practitioner assume that any product has undergone the practitioner's evaluation for efficacy and safety. They expect the practitioner to be a clearing house for accurate information for all skin products, prescriptions, and treatments. Moreover, the patient/client assumes the practitioner uses the same criteria to establish which prescription drugs and treatments are offered as is used to determine which cosmeceuticals are recommended and sold. Patients/clients do not consider themselves "profit centers" so practitioners should fulfill their Hippocratic obligations and commitments.

The cosmeceutical product development steps include the following:

1 Select and optimize the ingredient concentrations of the excipients of the type of a formulation (i.e. gel or lotion) to maximize the physicochemical activity and stability of the active ingredients.
2 Select and optimize the suitable stratum corneum penetration enhancers based on the physicochemical properties of the active.
3 Document the active ingredient will leave the formulation to cross through the membrane permeability barrier.
4 Document the permeation of the active ingredient through human stratum corneum. Also document the concentration to make sure it is high enough to produce the desired clinical effect.
5 Conduct human *in vivo* localized patch studies for formulation cosmetic acceptability, and to see if the formulation effectively changes a visible skin parameter such as roughness, wrinkling, or erythema. These human tests are much more accurate than animal tests because human skin is about six times more resistant to penetration than mouse skin.
6 The basic safety test is the aforementioned RIPT.
7 Determine the excretion and catabolism of the SM if it is not known to establish clearance from the body. This information is available if the extract is used in other biologically active systems such as health care, or food or veterinary fields.
8 Perform human double-blind clinical studies as previously mentioned [4,7,8,16,17].

To ensure effective delivery through the stratum corneum permeability barrier of an herbal SM requires employing the following principles of drug delivery (dermatopharmacokinetics):
1 The SM must be completely dissolved in the vehicle molecules.
2 Completely cover the skin surface with the formulation.
3 The SM must be released from the topical formulation and move (partition) into the lipophilic stratum corneum.
4 The SM must permeate through the entire stratum corneum.
5 The SM must partition into the aqueous epidermis.
6 The SM must permeate through the entire epidermis, transit through the basement membrane into the dermis if the SM targets reside there.
7 The SM is excreted via dermal vasculature or catabolized in the epidermis or dermis.
Failure of the formulation to comply with any of these principles will likely result in performance failure or inadequate clinical response to the product [14].

When evaluating the scientific validity of clinical trial data several factors must be considered:
1 Was the herbal product compared head to head with an approved prescription or heavily studied non-prescription product, or placebo controlled?
2 Were the same parameters including anatomic site, duration, time of year, frequency of use, climate, age of patient, and race compared?
3 Determine if the trial was conducted in-house or sponsored like an FDA trial and conducted by an independent research organization.
4 Was the finished marketed product studied?
5 Has the data been presented in peer reviewed journals or as poster exhibits at refereed meetings such as the American Academy of Dermatology?
6 Do the panelists observe any visible or palpable skin changes on subjective analysis?

Specific safety issues

Certain regulatory and safety issues have been published. These include:
1 The National Cancer Institute has officially recognized the chemopreventive effect of glycyrrhizia, a primary constituent of licorice (*Glycyrrhiza glabra*) [18].
2 Allantoin is listed in the US FDA OTC drug monograph as a skin protectant at 0.5–2.0% concentration [19].
3 Oat is approved as an US FDA OTC drug monograph as skin protectant at 0.007% concentration if the only active in a bath or by weight in a bath with oil [20].
4 Lavender has demonstrated toxicity to fibroblasts. Topical lavender products induced gynecomastia in one boy and two teenagers using lavender products with high concentrations over widespread areas of their body for many months [3,8].
5 Tea tree oil (*Melaleuca alternifolia*) is a potent UV photosensitizer and phototoxic agent, so be careful using products containing it for use on sun-exposed body parts [3,7,8].

Specific herbs with esthetic utility

There have been multiple reviews of herbal-based products in dermatology and cosmetic journals in the past 2 years. Licorice, green tea, soy and its isoflavones have been discussed in at least 18 recent publications, and so will not be included. This review is focused on herbs that were cited in 5–15 publications. More than 50 other herbs were cited 1–4 times each.

The major clinical parameters evaluated in clinical studies for products treating photoaging include tactile roughness, mottled hyperpigmentation, fine lines, wrinkles, laxity, sallowness, and neoplasia. Many of the 320 herbs mentioned in publications in cosmeceutical products for treatment of skin aging and conditions are antioxidants. Of the approximately 900 herbs used in industry and traditional medicine reviewed by this author, 190 have anti-inflammatory functionality. About 130 of these contain antioxidant SM while the other 60 consist of anti-inflammatory natural steroids, salicylates, and other non-antioxidants.

Table 34.1 consists of the 27 herbal extracts used in topical cosmeceuticals and/or oral products tested in human clinical

Table 34.1 Antiaging with clinical studies in humans.

Aloe (*Aloe barbadensis, A. capensis, A. vera*)
Apple (*Malus domestica*)
Avocado (*Persea americana*)
Black cohosh (*Cimicifuga racemosa*)
Blueberry (*Vaccinium myrtillus*): oral only
Cat's claw (*Uncaria guianensis, U. tomentosa*)
Coffeeberry (*Coffea arabica*)*
Date palm kernel (*Phoenix dactylifera*)*
Flax (*Linum usitatissimum*)
German chamomile (*Matricaria recutita*)†
Grapefruit (*Citrus paradisi*): oral only
Grape seed (*Vitis vinifera*): oral only
Green tea (*Camellia sinensis*)*†
Lavender (*Lavandula angustifolia*)
Licorice (*Glycyrrhiza glabra, G. inflate, G. uralensis*): oral only
Mangosteen (*Garcinia mangostana*)
Meadowfoam (*Limnanthes alba*)
Mushroom–wheat complex
Pomegranate (*Punica granatum*)†
Rose hips (*Rosa canina*)
Safflower (*Carthamus tinctorius*)
Soy milk, total soy (*Glycine soja, G. max*), Soy protease inhibitors*†
Sweet orange (*Citrus sinensis*): oral only
Tomato (*Lycopersicon esculentum*): oral only
White sandalwood (*Santalum album*)
White tea (*Camellia sinensis*)†
White willow (*Salix alba*)

* Single active in product; † Is oral + topical administration.

trials, either double-blinded or open label, that effectively treated signs of photoaging. Only four extracts contained one herb as the sole active ingredient: coffeeberry, date palm kernel, soy milk, total soy and soy protease inhibitors [21–25]. Green tea was used as a solitary active but was administered orally and topically in the studies [17,24].

The other 22 herbs were used in products with mixtures of only herbs or with synthetic active ingredients. Seven mixtures were tested with double-blind, controlled clinical trials against placebo or approved prescription topicals including:

1 Purified date palm, meadowfoam, flax, avocado, safflower, apple, rose hips, and lavender [26].

2 White willow, date, and meadowfoam [27].

3 Green tea, white tea, mangosteen and pomegranate, aloe, grapefruit, lavender, soybean, sweet orange, and synthetic antioxidants [28].

4 Bisabolol from chamomile, caffeine, glycyrrhetinic acid from licorice along with two synthetic active ingredients [29].

5 Cat's claw and ursolic acid with two synthetic antioxidants [30].

6 Black cohosh with two synthetic antiaging actives [31].

Table 34.2 Emollients.

Almond (*Prunus dulcis*)
Aloe (*Aloe barbadensis, A. capensis, A. vera*)
Avocado (*Persea americana*)
Borage (*Borago officinalis*)
Coconut (*Cocos nucifera*)
Cucumber (*Ecballium elaterium*)
Fenugreek (*Trigonella foenum-graecum*)
Grape (*Vitis vinifera*)
Jojoba (*Simmondsia chinensis*)
Licorice (*Glycyrrhiza glabra, G. inflate, G. uralensis*)
Macadamia (*Macadamia integrifolia, M. tetraphylla*)
Peanut (*Arachis hypogaea*)
Pomegranate (*Punica granatum*)
Safflower (*Carthamus tinctorius*)
Sesame (*Sesamum orientale*)
Slippery elm (*Ulmus rubra*)

7 Multiple mushrooms and a wheat protein proprietary mix [32].

Three oral preparations containing mixtures of synthetic and herbal antioxidants selected from those listed on Table 34.1 has positive clinical trials for reversing photoaging [16,33]. A number of herbal extracts are claimed to modulate one or more abnormalities which occur in extrinsically aged skin. Thus, these should be beneficial in reducing visible skin aging. Table 34.2 consists of 16 herbs that yield effective emollient SM to reverse photoaging roughness and replace petroleum emollients [3,7,8,25–32,34–37]. The lighteners/brighteners in Table 34.3 consist of 25 herbs documented to lessen or reverse mottled hyperpigmentation, melasma, and/or lentigines [3,7,8,25–32,34–37]. The eight tighteners in Table 34.4 reverse skin laxity and help reverse fine lines and cellulite [7,8,25–32,34–37]. Table 34.5 consists of SM found to modulate nucleic acids which include cat's claw and six types of mushrooms [7,8,38]. Table 34.6 lists photoprotective herbs. These 11 herbs are used as solitary actives or in mixtures but are all administered orally [3,7,8,25–32,34–38]. Orally administered photoprotective products should be an important lifestyle adjunct as only 40% of the population routinely wear sunscreen [39]. Incorporating active herbal extracts into mineral makeup also assists in photoprotection [40].

Aloe (*Aloe barbadensis, A. capensis, A. vera*)

Aloe may cross-react in people allergic to garlic, onions, and tulip. The leaves are the best source for SM. The gel is rich in aloe resins, dithranol, chrysorobin, allantoin, salicylates, flavonoids, and polysaccharides. Aloe is antibacterial to *Heliobacter pylori*, *Bacillus subtilis*, and methacillin-resistant *Staphylococcus aureus*. It is anti-antihistaminic (AH), anti-inflammatory (AI), and antioxidant (AO). This herb increases

Table 34.3 Lighteners/brighteners.

Aloesin (*Aloe barbadensis, A. carpensis, A. vera*)
Bearberry (*Arctostaphylos uva-ursi*)
Black mulberry (*Morus nigra*)
Blueberry (*Vaccinium angustifolium*)
Blue skull cap (*Scutellaria lateriflora*)
Carrot (*Daucus carota*)
Citrus fruit flavonoid [Hesperidin]
Cranberry (*Vaccinium macrocarpon, V. oxycoccos, V. erythrocarpus*)
Cucumber (*Ecballium elaterium*)
Echinacea (*Echinacea angustifolia, E. pallida, E. purpurea*)
Ginseng, American (*Panax quinquefolius*)
Ginseng, Asian (*Panax ginseng*)
Ginseng, Siberian (*Eleutherococcus senticosus*)
Gingko (*Gingko biloba*)
Grape seed (*Vitis vinifera*)
Hibiscus (*Hibiscus sabdariffa*)
Indian gooseberry (*Emblica officinalis*)
Licorice (*Glycyrrhiza glabra, G. inflata, G. uralensis*) [ammonium glycyrrhizinate], [glabridin], [liquiritin]
Pear (*Pyrus communis*)
Saxifrage (*Pimpinella saxifraga*)
Soy (*Glycine soja, G. max*)
White mulberry (*Morus alba*)
White willow (*Salix alba*)
Wormwood (*Artemisia absinthium*)
Yellow dock (*Rumex crispus, R. obtusifolius*)

Table 34.4 Tighteners.

Birch (*Betula alba*)
Gingko (*Gingko biloba*)
Hops (*Humulus lupulus*)
Horse chestnut (*Aesculus hippocastanum*)
Peppermint (*Mentha piperita*)
Red sandalwood (*Pterocarpus santalinus*)
Rose hips (*Rosa canina*)
Spearmint (*Mentha spicata*)
Witchhazel (*Hamamelis virginiana*)

Table 34.5 Modulates nucleic acids.

Cat's claw (*Uncaria guianensis, U. tomentosa*)
Mushrooms: *Agaricus blazei*
Cordyceps sinesis
Coriolus (*Tremetes versicolor*)
Maitake (*Grifolia frondosa*)
Reishi (*Ganoderma lucidum*)
Shiitake (*Lentinula edodes*)

Table 34.6 Photoprotective.

Black tea (*Camellia sinensis*)
Cocoa (*Theobroma cacao*): oral only
Feverfew (*Tanacetum parthenium*)
Golden fern (*Polypodium leukotomas*): oral only
Grapeseed (*Vitis vinifera*)*
Green tea (*Camillia sinensis*)*
Oat (*Avena sativa*)
Olive (*Olea europea*)
Pomegranate (*Punica granatum*)*
Tamarind (*Tamarindus indica*)
White sandalwood (*Santalum album*)

* Is oral + topical administration.

collagen synthesis and is a vasoconstrictor. Aloe gel is antiviral against herpes simplex, varicella zoster, and influenza. This gel had positive clinical trials for both psoriasis and herpes simplex therapy. Wound healing and acne have had mixed results in clinical trials. Aloe did not decrease UVB-induced erythema in a human *in vivo* study.

Aloesin extract is a potent tyrosinase inhibitor and inhibits UV-induced melanogenesis but less so than kojic acid. As one of five herbal ingredients plus synthetic antioxidants, aloe effectively reversed the signs of photodamaging in a placebo controlled trial [7,8,19,37,41].

Bromelain and papain – enzymes from pineapple (*Ananas comosus*)

These cysteine proteinase enzymes of pineapple stem and root have skin débridement, AI, and anticarcinogenic (AC) properties. Allergic reactions to these may cross-react with wheat, grass, celery, carrot, echinacea, chamomile, ragweed, marigold, and daisy. The clinical effects on therapy of traumatic and surgical cutaneous injury had both positive and negative clinical studies [7,8,36].

Coffee (*Coffea arabica, C. canephora*)

Coffea arabica yields three commercial products: coffee beans which are the seeds, the fruit which is coffeeberry, and coffee charcoal which is roasted (until black) green fruit. The major actives of coffee include purine alkaloids such as caffeine, theobromine, and theophylline from the beans and caffeine from the charcoal. The beans also include the phenolics caffeic, chlorogenic, and ferulic acids, diterpenes, phytoestrogens, and magnesium. Coffee charcoal is approved by German Commission E for mucositis therapy. Coffee beverage is AO. Adverse reactions include three deaths from rectal enemas; coma, stroke, and anaphylactic immunoglobulin E (IgE) reactions are rare.

Caffeine extracted from the *C. arabica* leaf is the major ingredient in many cellulite products which are supported by human clinical trials. Murine studies suggest caffeine has

AC effects similar to green tea catechins while improving skin roughness and fine lines [42].

Coffeeberry extract is obtained from subripe coffee fruit which is rich in such polyphenols as chlorogenic and ferulic acids, proanthocyanidins, and saccharides. The Oxygen Radical Absorbance Capacity (ORAC) score is allegedly 10-fold higher than green tea, 20-fold higher than vitamin C, yet is only one-sixteenth that of feverfew. A 6-week, double-blind study of a formulation with only coffeeberry as the active used on 20 females applying it to the full face compared with baseline concluded there was a significant 30% improvement in hyperpigmentation, 20% improvement in fine lines and wrinkles. In a 10 female, split face companion trial versus placebo there was a significant 25% vs. 3% improvement in fine lines and wrinkles and a 15% vs. 5% improvement in hyperpigmentation [7,8,22,32,43].

Feverfew (*Tanacetum parthenium*)

About 40 SM are extracted from this total herb or only a leaf. Parthenolide is a sesquiterpene lactone that is the most active SM but also the most toxic. Other SM include the flavonoids, tanetin and apigenin, polyynes, volatile oils such as camphor, chrysanthyl acetate, linalool, and melatonin. The commercially available powdered leaves lack sesquiterpene lactones, yet are AC, AI, AH, AO, photoprotective, vasoconstrictor, inhibit serotonin release and gene transcription. Feverfew's ORAC for AO activity score is 144 000 which is 16-fold stronger than coffeeberry's score. Its inhibition of tumor necrosis factor (TNF) release was 35–1000 times higher than black, green, and white tea, echinacea, chamomile, aloe vera, and licorice. This tremendous AI potency resulted in developing methods to extract the dangerous parthenolide.

A double-blind study of 31 women with sensitive skin using a parthenolide-free feverfew moisturizer twice daily for 3 weeks produced statistically significant decrease ($p < 0.05$) in erythema, tactile roughness, and overall irritation. It was also effective therapy for shaving irritation.

Feverfew is a Compositae so it cross-reacts with marigold, daisy, ragweed, bromelain, arnica, and chamomile. Feverfew should not be used during pregnancy and lactation, or in children under 2 years of age [3,7,8,32,35–37,43].

German chamomile (*Matricaria recutita*)

The major SM of this herb are mucilages extracted from the entire plant. Volatile oils such as bisabolol and flavonoids such as apigenin, quercetin, chalmazulene, rutin, and coumarins are extracted from the flower. Chamomile has AC, AH, AI (superior to 0.5% hydrocortisone), and AO effects as well as antibacterial against staphylococcus, antiviral, and anticandida. It is an effective wound healing and inflammatory skin condition therapy as approved by German Commission E. It is reported to relieve rough, xerotic, inelastic skin and signs of photodamage.

This herb is a member of the Compositae family thus cross-reacts with marigold, daisy, ragweed, arnica, feverfew, and bromelain. There has been at least one death to anaphylactic reactions and uncommonly allergic contact dermatitis occurs [1,3,7,8,32,36].

Golden fern (*Polypodium leucotomos*)

This herb has documented therapeutic efficacy in clinical trials for vitiligo, psoriasis, sunburn, phototoxic and UVA-induced photodamage when administered orally. A topical 10–50% concentration lotion also reduced photodamage *in vivo*.

The primary SM are obtained from the rhizome and aerial parts. These include the phenolics, chlorogenic, ferulic, and caffeic acids. This extract is AI, inhibits mast cells, AO yet stimulates humoral immunity. Orally administered golden fern significantly decreases erythema, sunburn cells, mast cells, pyrimidine dimers ($p < 0.05$), and epidermal proliferation while reducing loss of Langerhans cells in nine panelists with Fitzpatrick type II or III skin. In another trial treating 25 panelists with polymorphous light eruption and solar urticaria with 480 mg/day orally, 41% improved more than 50% compared with baseline [3,24,32,35–37,44–46].

Grape (*Vitis vinifera*)

Grape products are obtained from the seed, fruit, fruit skin, and leaf. They are rich in flavonoids including quercetin, tannins, monomeric catechins, oligomeric proanthocyanidins (OPC) polymers, resveratrol, and fruit acids. These SM provide potent AC, AH, AI, AO, and vasodilating matrix metalloproteinases (MMP) inhibition, stabilize collagen, and are cytotoxic to neoplastic cells. The OPCs in grape are 50-fold more potent than AO vitamins C or E. They also stimulate terminal hairs from telogen to anagen phase increasing hair growth. There is a significant correlation between total phenolic content, pro-anthocyanidin content, and AO activity of the grape product. Taken orally, grape seed significantly reduced melasma in Japanese women by 6 months. When combined in an oral antiaging product with soy, white tea, chamomile, tomato, fish protein, and polysaccharides it improved skin firmness and structures by 6 months. There is one report of non-fatal anaphylactic reaction to grape skin [3,7,8,33,47,48].

Milk thistle (*Silybum marianum*)

Silybin, a flavonoid, accounts for 75% of the volume of this extract taken from the seeds or total plant. It provides AC against human skin cancer cells, AI, inhibits UVB sunburn, AO, and stabilizes membranes. Other SM from the seeds include fatty oils and other flavonoids such as apigenin and quercetin. The total herb also contains sterols, glucosides, fumaric acid, and polyynes.

This herb is a member of the Compositae family thus cross-reacts with ragweed, marigold, daisy, arnica, chamomile, feverfew, and bromelain allergy [7,8,16,17,36].

Mushrooms

The major medicinal mushrooms come from Asian traditional medicine. These include *Cordyceps sinensis*, *Coriolus* (*Trametei versicolor*), reishi in Japan, lingzhi in China (*Ganoderma lucidum*), maitake (*Grifola frondosa*), and shiitake (*Lentinus edodes*). Less known are *Agaricus blazei*, *Hypsizygus ulmarius*, and yambushitake (*Hericium erinaceum*). The entire herb body is a rich source of immune stimulating polysaccharides such as beta glucan. Mushroom extracts also contain potent AO peptides, triterpenes, polyphenols, and AI sphingolipids. These SM have AC, AI, AO, and broad-spectrum antibacterial and anti-HIV effects. Maitake inhibits *in vitro* photoaging markers on UVA-exposed human fibroblasts. Several mushrooms inhibit MMPs and activating protein-1. In a 45 patient 4-week *in vivo* study, a mushroom–wheat protein complex was used twice daily to induce epidermal cell renewal and turnover. An open clinical study of topically applied mushroom complex treated 31 women with moderate photoaging. Statistically significant improvements in texture, clarity, and fine lines within 4 weeks, and irregular pigmentation, overall photoaging, with improved pinch recoil by 8 weeks versus baseline occurred [3,7,8,24,35–37].

Oat (*Avena sativa*)

This herb has been approved by German Commission E for treatment of inflamed skin, which have been supported by positive clinical trials for relief of pruritic skin, xerosis, and seborrheic dermatitis. The SM are extracted from bran, whole grain, or dehulled kernels. They include polysaccharides, such as beta glucan, steroid saponins, flavonoids such as apigenin, and polyphenols such as avenathramide, phenolics including caffeic and ferulic acids, hydroxycinnamate, coumaric acids, and tocotrienols. Oat is AI, AO, and UVA blocking.

Avenanthramides at 3% were nearly comparable to 1% hydrocortisone in anti-inflammatory effect. In an open trial treating epidermal growth factor receptor agonists, 60% achieved complete remission and 30% partial response of the acneiform eruption that afflicts two-thirds of these patients. Oat can be safely used in people with celiac disease. Contact dermatitis to oat occurs infrequently [3,7,8,20,32,35–37].

Pomegranate (*Punica granatum*)

Pomegranate juice and fruit contains more polyphenols than green tea, red wine, cranberry, blueberry or orange juice, with AO activity three times higher than green tea or red wine. Other SM include tannins such as ellagic acid, citric and tartaric acids. Pomegranate juice is antiviral HIV, antibacterial to *Staphylococcus aureus*, antifungal, and antiparasitic.

Pomegranate seed oil is also rich in linoleic acid and estrogenic substances. It stimulates keratinocyte proliferation, AC, and AO.

The major SM of pomegranate fruit peel is a group of tannins that improve wound healing as well as inhibiting MMP-1, increase procollagen synthesis by fibroblasts, raises the minimal erythema dose (MED) to UVB with oral ingestion. Its ellagic acid inhibits melanin synthesis.

In one open human trial, oral (300 mg) twice daily plus topical sunscreen and topical pomegranate raised the MED to UVB to a significant degree ($p < 0.05$) [1,3,7,8,36].

Pycnogenol (*Pinus pinaster*, *P. maritima*)

This herbal extract is from the bark of the French maritime pine tree. Its SM include flavonoid monomers, dimers, oligomers and polymers of catechins, epicatechin, and taxifolin. These larger molecules are known as OPC. Pycnogenol also contains phenolics such as ferulic, caffeic and coumaric acids, and polysaccharides. Pycnogenol has AH, AI, and AO functions, by recycling ascorbic acid and tocopherol. This ingested herb effectively treats chronic venous insufficiency, reduces UVB-induced photosensitivity and sunburn, stimulates wound healing, inhibits MMPs, stimulates cellular and humoral immunity. Clinical trials document it is effective therapy for psoriasis, atopic dermatitis, and lupus.

In a 30-day, open human clinical trial for melasma therapy, there was highly statistical significant ($p < 0.001$) decrease in melasma area and pigment intensity with oral dose at 30 mg, three times daily [1,7,8,17,24,49].

Turmeric (*Curcuma longa*, *C. domestica*)

This herb is best known as the food spice, curry. Curcumin is the therapeutic component extracted from the rhizosome that is AC, AI, AO, and stimulates wound healing. SM include volatile oils such as tumerone, the source of the aroma; curcuminoids including curcumin, the yellow pigment; and polysaccharides. Tumerone inhibits mast cells. Curcumin has weak estrogenic effects binding to estrogen and progesterone receptors, prevents genetic transcription, suppresses MMPs, has greater AI than ibuprofen, and inhibits angiogenesis while stimulating immunity. Curcumin is antibacterial, antiviral against HIV, and antiprotozoal. When combined with neem, it effectively treated scabies with topical application.

Topical curcumin is considered one of the few safe therapies for radiation dermatitis wound repair. Turmeric extracts should not be used in pregnancy [1,3,7,8,32,33,50].

Scientific evaluation of herbal extracts have found clinically valuable SM common to several of the herbs to have known effectiveness in treating skin conditions. These include allantoin, apigenin, bisabolol, beta-carotene, caffeic

acid, caffeine, ellagic acid, ferulic acid, genistein, lutein, lycopene, quercetin, resveratrol, soy proteinases, sesquiterpene lactones, and triterpenes.

Conclusions

The use of botanicals remains a very active area of research in cosmetic formulations. Their popularity is in part a result of the perceived safety of botanicals, which are derived from nature. Consumer perceptions of botanicals as positive ingredients also make them a welcome addition to otherwise mundane formulations. This chapter has evaluated some of the key considerations when evaluating and testing cosmetic products.

References

1 Choi C. (2006) Seminars in cutaneous medicine and surgery. *Cosmeceuticals* **25**, 163–8.
2 VanWyk BE, Wink M. (2004) In: *Medicinal Plants of the World*. Portland, OR: Timber Press, pp. 16–26, 371–94.
3 Baumann L. (2007) Less-known botanical cosmeceuticals. *Dermatol Ther* **20**, 330–42.
4 Winnington P. (2007) Skin care and medical dermatology. *Pract Dermatol* **Nov**, 35–44.
5 Baumann L. (2007) Products promise youth, but lack evidence. *Dermatol Times* **Dec**, 56–63.
6 Matsui M, Spencer J, Draelos Z. (2008) Anti-oxidants: truth or hype? *Dermatol Times* **19**, 26.
7 Greenwald J, Brendler T, Jaenicke C, eds. (2007) *PDR for Herbal Medicines*, 4th edn. Montvale, NJ: Thomson Healthcare.
8 Jellin JM, ed. (2007) In: *Natural Medicines Comprehensive Data Base*, 9th edn. Stockton, CA: Therapeutic Research Faculty.
9 Draelos Z. (2008) Optimizing redness reduction, part 2. *Cosmet Dermatol* **21**, 433–6.
10 Cornuelle T, Lenhart J. (2006) Topical botanicals. In: *Cosmetic Formulations of Skin Care Products*. New York: Taylor and Francis, pp. 299–308.
11 Skidmore-Roth L. (2006) *Herbs and Natural Supplements*, 3rd edn. Philadelphia, PA: Elsevier Mosby, pp. xiii, xvii.
12 Koo J, Arain S. (1999) Traditional Chinese medicine in dermatology. *Clin Dermatol* **17**, 21–7.
13 Jancin B. (2002) Cross-sensitivity in tea tree oil allergy. *Skin Allergy News* **Mar**, 38.
14 Thornfeldt C, Mak V, Elias PM, Feingold FR. (1999) Interference of stratum corneum lipid biogenetics: an approach to enhance transdermal drug delivery. In: Bronaugh RC, Maibach HI, eds. *Percutanous Absorption*. New York: Marcel Dekker, pp. 418–25.
15 Chanchal D, Swarnlata S. (2008) Novel approaches in herbal cosmetics. *J Cosmet Dermatol* **7**, 89–95.
16 Rabe JH, Marmelak AJ, McElgunn PJ, Morison WL, Sauder DL. (2006) Photoaging: Mechanisms and repair. *J Am Acad Dermatol* **55**, 1–22.
17 Bruce S. (2008) Cosmeceuticals for attenuation of extrinsic and intrinsic dermal aging. *J Drugs Dermatol* **7**, (Suppl 2), S17–S22.
18 Craig WJ. (1999) Health promoting properties of common herbs. *Am J Clin Nutr* **70**, 4915–95.
19 Draelos Z. (2008) Cosmetic consultation. *Cosmet Dermatol* **21**, 433–6.
20 Kurtz E, Wallo W. (2007) Colloidal oatmeal: history, chemistry and clinical properties. *J Drugs Dermatol* **6**, 167–70.
21 Bauza E, Dal Farra C, Berghi A, Oberto G, Peyronel D, Domloge N. (2002) Date palm kernel extract exhibits antiaging properties and significantly reduces skin wrinkles. *Int J Tissue React* **24**, 131–6.
22 Cohen J. (2007) Coffeeberry. *Skin Allergy News* **1**, 34.
23 Wallo W, Nebus J, Leyden J. (2007) Efficacy of a soy moisturizer in photoaging: a double-blind, vehicle controlled, 12-week study. *J Drugs Dermatol* **6**, 917–22.
24 Berson D. (2008) Natural antioxidants. *J Drugs Dermatol* **7** (Suppl), 7–11.
25 Baumann LS, Wu J. (2008) Cosmeceutical Critique Compendium. *Skin Allergy News Suppl*, pp. 1–19.
26 Thornfeldt C, Sigler M. (2006) A cosmeceutical with novel mechanisms of action effectively reduces signs of extrinsic aging. Poster presented at: Am Acad Dermatol 64th Annual Conference, San Francisco, CA. Poster 1128.
27 Thornfeldt C, Sigler M. (2006) Comedolytic anti-inflammatory cosmeceutical reduces signs of maturity. Poster presented at Am Acad Dermatol 64th Annual Conference, San Francisco, CA. Poster 229
28 Hsu J, Skover G, Goldman M. (2007) Evaluating the efficacy in improving facial photodamage with a mixture of topical antioxidants. *J Drugs Dermatol* **6**, 1141–8.
29 Lupo M, Cohen J, Rendon M. (2007) Novel eye cream containing a mixture of human growth factors and cytokines for periorbital skin rejuvenation. *J Drugs Dermatol* **6**, 725–9.
30 Smiles K, Walfield M, Yarosh D. (2006) *Remergent barrier repair formula restores many aspects of skin health*. Proprietary Report, AGI Dermatics. Freeport, NY.
31 Rao J, Erhlich M, Goldman M, *et al.* (2004) Facial skin rejuvenation with a novel topical compound containing transforming growth beta and vitamin C. *Cosmet Dermatol* **17**, 705–10.
32 Wu J. (2008) Anti-inflammatory ingredients. *J Drugs Dermatol* **7** (Suppl), 13–6.
33 Skougaard G, Jensen A, Sigler M. (2006) Effect of novel dietary supplement on skin aging in post menopausal women. *Eur J Clin Nutr* **60**, 1201–6.
34 Yarosh D. (2008) *The New Science of Perfect Skin*. New York: Broadway Books, pp. 62–73, 100.
35 Baumann LS. (2007) Botanical ingredients in cosmeceuticals. *J Drugs Dermatol* **6**, 1084–7.
36 Baumann LS. (2005) Advancing the science of naturals. *Cosmet Dermatol Suppl* **18**, 51–8.
37 Baumann LS. (2006) Cosmeceutical Critique Compendium. *Skin Allergy News Suppl* pp. 3–23.
38 Bruno G. (2008) An herbal powerhouse. *Healthy Aging* **Jan/Feb**, 39–41.
39 Lewis W. (2007) Cosmeceuticals roundup. *Plastic Surg Products* **Sept**, 38–42.
40 Saluja R, Yosowitz G, Goldman M. (2007) Evaluation of mineral cosmetics. *Cosmet Dermatol* **20**, 382–7.
41 Jin Y, Lee S, Chung, M. (1999) Aloesin and arbutin via a different action mechanism. *Arch Pharm Res* **22**, 232–6.
42 Viera M, Sadegh M, *et al.* (2008) What's new in natural compounds for photoprotection. *Cosmet Dermatol* **21**, 279–89.

43 Charurin P, Ames J, Del Castillo M. (2007) Antioxidant activity of coffee model systems. *J Agric Food Chem* **50**, 3751–6.
44 Middlekamp-Hup M, Puthak M, Parrado C, *et al.* (2004) Oral Polypodium leukotomos extract decreases ultraviolet induced damage of human skin. *J Am Acad Dermatol* **51**, 910–8.
45 Caccialanza M, Percivalle S, Piccino R, *et al.* (2007) Photoprotective activity of oral Polypodium leukotomos extract in 25 patients with idiopathic photodermatoses. *Photodermatol Photoimmunol Photomed* **23**, 46–7.
46 Baumann LS. (2007) Melasma and its newest therapies. *Cosmet Dermatol* **20**, 349–53.
47 Yamakoshi J, Sano A, Tokutake S, *et al.* (2004) Oral intake of proanthocyanidin-rich extract of grape seeds improves chloasma. *Phytother Res* **18**, 895–9.
48 Zhu W, Gao J. (2008) The use of botanical extracts as topical skin lightening agents for the improvement of skin pigmentation disorders. *J Invest Dermatol* **13**, 20–4.
49 Ni A, Mu Y, Gulati O. (2007) Treatment of melasma with Pycnogenol. *Phytother Res* **16**, 567–71.
50 Wu J. (2006) Treatment of rosacea with herbal ingredients. *J Drugs Dermatol* **5**, 29–32.

Chapter 35: Antioxidants and anti-inflammatories

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BASIC CONCEPTS

- An antioxidant is a molecule that prevents the oxidation of other molecules thereby protecting cells from damage caused by free radicals.
- The most common oxygen radicals in the body are the superoxide anion ($O_2^{\bullet -}$) and the hydroxyl radical (•OH).
- Free radicals cause extensive and irreversible damage to proteins, DNA, and lipids, with serious consequences affecting cell survival, malignant transformation, and the development of disease.
- Antioxidants include vitamin C, vitamin E, curcumin, green tea, carotenoids, and ubiquinone.
- Anti-inflammatories include botanical extracts, corticosteroids, non-steroidal anti-inflammatories, and immunomodulators.
- Endogenous antioxidants and anti-inflammatories are necessary to prevent damage that contributes to both extrinsic and intrinsic aging.

Antioxidants

The use of oral and topical antioxidants to provide protection from and treatments for various diseases, including cancer, and to prevent aging, has gained considerable popularity over the past 25 years. While it is clear that antioxidants such as vitamins C, E, A, and carotenoids can protect cells from free radical damage, it is not clear whether taking large quantities of antioxidants can prevent the occurrence of disease or slow the aging process. Some clinical studies have suggested such a role for antioxidants, while other studies have not provided clear evidence that antioxidant supplements can reduce the risk of cancer, heart disease, or aging [1]. Regardless of clinical study results, the fact that antioxidants can block free radical damage to cells has led to rapidly growing markets for antioxidant nutritional supplements, antioxidant beverages, and has fueled an entire industry focused on finding foods with ever-higher antioxidant potential. Most, if not all, topical skincare products manufactured today contain antioxidants such as vitamin E, vitamin C, and carotenoids. The question of whether the antioxidants in topical skincare products provide any skin benefits will be explored.

Antioxidants and free radicals

An antioxidant is simply a molecule that can prevent the oxidation of other molecules. Their importance in protecting cells from damage results from their ability to block the progression of oxidative damage caused by free radicals.

Free radicals are molecules or atoms with unpaired electrons. Having an unpaired electron leaves an incomplete electron shell and makes the atom or molecule more chemically reactive than those with complete electron shells. Because atoms seek to reach a state of maximum stability, they will try to fill the outer shell by "stealing" an electron from another molecule. When the target molecule loses an electron to the free radical it then, in turn, becomes a free radical and must find a "donor" it can steal an electron from. Thus, a chain reaction begins that causes considerable damage to cellular proteins, lipids, membranes, and DNA. Most free radicals in biological systems are derivatives of oxygen. The most common oxygen radicals in the body are the superoxide anion ($O_2^{\bullet -}$) and the hydroxyl radical (•OH). While free radicals have extremely short half-lives, in the order of nanoseconds or microseconds, this is sufficient time to attack molecules and generate new free radicals. In addition to the above oxygen radicals, there are other reactive oxygen species (ROS) which are not actually radicals, but which are reactive and of biological importance. These include hydrogen peroxide and hypochlorite ion [2].

Free radicals can cause extensive and irreversible damage to proteins, DNA, and lipids, and these can have serious consequences on cell survival, malignant transformation, and the development of disease. One of the most damaging free radical events is lipid peroxidation to membrane lipids that have a key role in cell signaling. In this case a hydroxyl radical may remove a hydrogen atom from the side chain of a fatty acid, thereby converting the fatty acid into a radical. The fatty acid then reacts with oxygen to form a very

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reactive peroxyl radical. A chain reaction begins in which one lipid radical becomes two lipid radicals. Ultimately, the lipid radicals may form covalent cross-links with each other thereby ending the chain reaction. Unfortunately, the result is cross-linked and functionally damaged lipids. A good example of this is the free radical damage to low density lipoprotein (LDL). This damage has been shown to lead to atherosclerosis.

Antioxidants protect cells from free radical damage by either donating an electron to a free radical thereby stabilizing it and halting the chain reaction, or by accepting the one unpaired electron, again stabilizing the free radical and preventing it from interacting with and damaging proteins, DNA, and lipids. By donating an electron to the free radical to stop the chain reaction, the antioxidant itself becomes a free radical. However, because of its structure, the antioxidant is far less reactive than other radicals. If it is relatively large, the effect of the unpaired electron is "diluted" along its structure. The antioxidant "radical" may also be neutralized by another antioxidant or it may be enzymatically restored to its non-free radical form. Glutathione is one antioxidant that can donate a hydrogen atom to a hydroxyl radical thereby neutralizing it. The oxidized glutathione is converted back to its reduced form by glutathione reductase and is then ready to reduce additional free radicals.

An antioxidant's "potency" may be quantified by use of Oxygen Radical Absorbance Capacity (ORAC) assays. ORAC is a method of measuring antioxidant capacities of different foods, vitamins, and compounds [3]. The assay measures the oxidative destruction of a fluorescent molecule (e.g. fluorescein) after it is mixed with a free radical producer that generates peroxyl and hydroxyl radicals. By comparing the change in fluorescence in a reaction tube that contains only the fluorescent molecule and free radical with the change in fluorescence measured in the assay tube containing the antioxidant along with the free radical, a measure of antioxidant potential (ORAC score) can be obtained. Table 35.1 shows the ORAC scores of some representative antioxidants.

Of the many antioxidants that are now being formulated into topical products, two of the most common and most important are vitamins C and E. Vitamin C is the most prominent antioxidant in the aqueous compartment of cells. It can neutralize hydroxyl, alkoxyl, and peroxyl radicals by hydrogen donation and is thus an extremely important antioxidant for biological systems. Further, vitamin C can regenerate oxidized vitamin E and is, in turn, regenerated by glutathione. It is a useful antioxidant to incorporate into topical products, including suncare products because, in the skin, vitamin C neutralizes free radicals generated by either UVA or UVB radiation. Unfortunately, vitamin C needs to be continually replaced because even a low dose of UV radiation (UVR) from the sun can deplete 30–40% of the vitamin C present in the skin [4].

Table 35.1 Oxygen Radical Absorbance Capacity (ORAC) values of some antioxidants.

Antioxidant	ORAC (μmol TE/100 g)
Olive extract	2 700 000
Clove	1 078 700
Quercetin	1 090 000
Resveratrol	620 000
Cinnamon	267 536
Vitamin C	189 000
Vitamin E	135 000
Cocoa	80 000
Acai	38 700
Pomegranate	10 500
Blueberry (raw)	7 700
Lycopene	5 800

Vitamin E is one of nature's most important lipid antioxidants because it associates with membranes and protects the lipid environment by scavenging lipid peroxyl radicals. Vitamin E is found in the stratum corneum where it can act as a "front line" defense against UVR-induced free radicals. The vitamin E radical can be regenerated by vitamin C, and also by glutathione and ubiquinol (coenzyme Q10).

There are many other antioxidants that have been formulated into skincare products, including ferulic acid, CoQ10 (ubiquinone), retinol, idebenone, α-lipoic acid, and epigallocatechin gallate. Some of the skin benefits these antioxidants provide may be the result of actions on cells that go beyond their ability to simply scavenge free radicals.

Effects of antioxidants on cell signaling pathways

Many antioxidants that have been incorporated into topical skincare products have significant anti-inflammatory activities while others up- or downregulate various genes. Vitamin C, for example, not only serves as a co-factor for enzymes involved in collagen and neurotransmitter production, but also stimulates the collagen I and III genes, inhibits the UVR-induced levels of inflammatory hormones including prostaglandin E_2 (PGE-2), and stimulates cell proliferation in dermal fibroblasts [5]. The major lipid-soluble antioxidant, vitamin E, has been shown to alter the expression of cell cycle genes in human T cells and suppress PGE-2 production [6]. This PGE-2 inhibition may explain, in part, vitamin E's ability to protect skin from UVR-induced erythema.

One of the best anti-inflammatory antioxidants produced by nature may be curcumin. While this compound can neu-

tralize free radicals, it can also interfere with cell signaling pathways involved in inflammation. A considerable amount of research has investigated the cellular mechanism of action of curcumin. These studies have shown that one action of curcumin is to block NF-κB transcription, activation, and translocation to the nucleus. This transcription factor is involved in the upregulation of several inflammatory genes including tumor necrosis factor α (TNF-α), interleukin 8 (IL-8), and cyclo-oxygenase 2 (COX-2) [7]. Curcumin also inhibits the activation of the inflammation related genes, intercellular adhesion molecule 1 (ICAM) and IL-12, which are controlled, at least in part, by Jak-STAT signaling pathways. This inhibition is brought about by curcumin's ability to block the phosphorylation and activation of the STAT transcription factor [8]. While curcumin inhibits transcription of pro-inflammatory genes, such as COX-2, it can upregulate the gene for the anti-inflammatory signaling receptor peroxisome proliferator-activated receptor γ (PPAR-γ) [9].

In addition to curcumin, a large number of other phenolic and polyphenolic compounds derived from plants have now been shown to have direct anti-inflammatory effects on cells as well as antioxidant activity: quercetin, luteolin, resveratrol, ferulic acid, eugenol, apigenin, genistein, and epigallocatechin gallate [10–12]. While some reduce inflammatory gene expression through interfering with NF-κB driven genes, others interfere with the JNK cell signaling pathway that leads to the activation of the transcription factor, activator protein 1 (AP-1). By interfering with the ability of AP-1 to activate target genes, these compounds, such as luteolin, prevent the activation of such inflammatory genes as IL-6, COX-2, IL-18, and monocyte chemotactic protein 1 (MCP-1). In regard to skin antiaging benefits, not only can luteolin reduce the expression of inflammatory hormones, but it inhibits hyaluronidases and thus preserves hyaluronic acid levels in the skin [13]. A related polyphenol, genistein, blocks intracellular signaling pathways by inhibiting tyrosine kinases, and the phosphorylation of the epidermal growth factor receptor (EGF-R) [14]. A bar graph showing the effect of several antioxidants on inhibition of IL-1 induced PGE-2 levels in human dermal fibroblasts is shown in Figure 35.1(a), while the effect of luteolin and ascorbyl acetate in inhibiting a variety of inflammatory cytokines in human keratinocytes induced with tissue plasminogen activator (TPA) is shown in Figure 35.1(b). Clearly, the polyphenolic antioxidants as well as simpler antioxidants such as vitamins C and E can reduce inflammation in the skin. However, for these compounds to be effective when topically they must penetrate into the skin at a sufficient concentration to exert their protective effects on both keratinocytes in the epidermis, fibroblasts in the dermis, and immune cells migrating in from the vasculature.

Topical formulation of antioxidants

The development of effective topical formulations that can deliver antioxidants into the skin to protect cells in the epidermis and dermis from free radical attack by UVR, pollutants, and from aging is not a trivial undertaking. Although a number of factors influence the ability of a given molecule to penetrate through the stratum corneum and down to the dermal layer, two important considerations are molecular size and charge. As a rule of thumb, molecules with a molecular weight over 500 Da have a more difficult time penetrating through the stratum corneum along the intercellular lipid route than do smaller molecules. In regard to charge, a molecule that is somewhat hydrophobic has a better chance of penetrating the lipids in the stratum corneum than a water-soluble antioxidant, such as vitamin

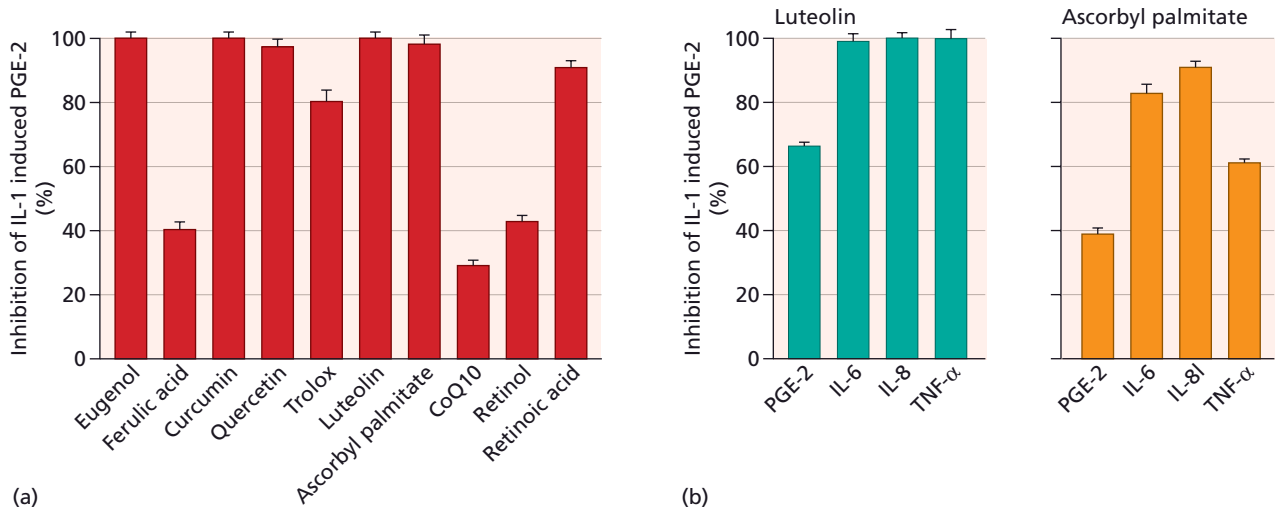

Figure 35.1 Anti-inflammatory properties of antioxidants. (a) Inhibition of the inflammatory mediator prostaglandin E_2 (PGE-2) in human keratinocytes by antioxidants. (b) Inhibition of four important skin inflammatory mediators by luteolin and vitamin C.

C. However, if the compound is too hydrophobic, although it may move into the stratum corneum, it cannot easily enter the aqueous environment of the epidermis and dermis. The likelihood that a given antioxidant will penetrate the skin and thus be useful in a topical formulation can be predicted, somewhat, on its partition coefficient value (logP). This is simply a measure of the antioxidant's solubility in octanol to that in water. Thus, an antioxidant with a logP of 2 is somewhat hydrophobic (it is more soluble in octanol than water). For topical application, antioxidants with logP values of 1–3 have the best chance of moving into the skin and down to the dermal layers, with a logP of about 2.5 being optimal. Curcumin has a molecular weight of 368 Da and a logP of 3.77. Thus, it is somewhat more hydrophobic than desired for a molecule that can penetrate down into the dermal layers but should still be effective when applied topically. In contrast, ubiquinone (CoQ10) has a molecular weight of 863 Da and a logP of 11. Although the molecular weight is not too large for topical application, the logP indicates that this compound is so hydrophobic that it will have little tendency to move from the lipid environment of the stratum corneum to the aqueous environment of the epidermal or dermal layers. Thus, CoQ10 may be useful as a topical antioxidant that neutralizes free radicals at the skin's surface but may not protect cells in the lower layers of the skin. Interestingly, although vitamin E (molecular weight 430 Da) is also extremely hydrophobic with a logP of 10, it has been shown to reach the dermis 24 hours after topical application. Whether it is actually traversing the stratum corneum or penetrating the skin via the appendageal route (hair follicles or sebaceous glands) is not known.

Vitamin C is water-soluble and because of this polarity it will not readily enter the stratum corneum. Various efforts have been taken to increase skin delivery of vitamin C, including lowering the pH to remove the charge on the compound. At a pH of 3.5, vitamin C loses its ionic charge and will penetrate the skin [15]. Vitamin C, like vitamin E, presents formulation challenges relative to the stability of the molecule. Neither are stable in most aqueous emulsions, so non-aqueous "serums" have been developed that are better at maintaining the stability of the vitamins. Alternatively, aqueous-based emulsions can be used if the more stable ester forms of the vitamins are incorporated into the formulation. Vitamin E acetate is fairly stable and penetrates into the skin although its antioxidant activity is less than vitamin E [16]. In regard to vitamin C, ascorbyl palmitate, or more recently tetrahexydecyl ascorbate, both of which are fairly stable, have been used in topical formulations. At least for tetrahexyldecyl ascorbate, this vitamin C derivative has been shown to have not only excellent antioxidant activity, but also to produce the same biologic effects on the skin (e.g. collagen production, increased lipid synthesis) as the un-derivatized vitamin C [17].

To determine how much antioxidant penetrates into the skin from a given topical formulation, a Franz cell is typically used. The device consists of an upper chamber and a lower reservoir. Human skin, either full-thickness or dermatomed skin, is sandwiched between the two chambers. The formulation to be tested is applied to the surface of the skin in the upper chamber and the amount of antioxidant (or other "active") that penetrates the skin and falls into the buffer solution in the lower chamber determined by either high performance liquid chromatography (HPLC) or, if the compound is radiolabeled, by scintillation counting. From this analysis it is possible to determine:

1 How much antioxidant penetrates the skin;
2 How fast it penetrates;
3 How long a finite dose placed on the skin's surface will continue to supply antioxidant to the skin; and
4 The steady state concentration of the antioxidant in the skin.

In conclusion, the incorporation of antioxidants into skincare and topical dermatologic products provides substantial skin benefits. Not only do these compounds protect the skin from free radical damage caused by skin aging and exposure to UVR, but many of them reduce skin inflammation by repressing the activity of inflammatory cytokine and chemokine genes. Further, some, such as vitamin C, have marked antiaging properties by upregulating matrix promoting genes such as collagen I and III genes, while inhibiting matrix-eroding genes such as the those for matrix metalloproteinases (MMP).

Anti-inflammatories

Inflammatory skin disorders are common and range from occasional rashes accompanied by skin itching and redness to more chronic conditions such as atopic dermatitis, rosacea, seborrheic dermatitis, and psoriasis. This discussion provides a brief overview of the inflammation process, reviews current drug topical treatments for several inflammatory diseases, and presents data on new, botanically derived, anti-inflammatory technologies.

Biology of the skin inflammatory process

Skin inflammation, which is characterized by redness, swelling, heat, itching, and pain, can exist in either an acute or chronic form, with acute disease frequently progressing to a more chronic condition. Acute inflammation can result from exposure to UVR, ionizing radiation, allergens, or to contact with chemical irritants (e.g. soaps, hair dyes). Assuming that the triggering stimulus is eliminated, this type of inflammation is typically resolved within 1–2 weeks with little accompanying tissue destruction. A chronic inflammatory condition, however, can last a lifetime, and cause considerable damage to the skin.

Some of the cellular and biochemical events that occur in the skin in response to a triggering stimuli (e.g. UVR, chemical or antigen) and which lead to an inflammatory response are shown in Figure 35.2. Within minutes of exposure of skin to an insult there is a rapid release of inflammatory mediators from keratinocytes and fibroblasts and from afferent neurons. Keratinocytes produce a number of cytokines and chemkines including PGE-2, TNF-α, IL-1, IL-6, and IL-8. Dermal fibroblasts also respond to the insult and to IL-1 produced by keratinocytes by increasing production and secretion of cytokines including IL-1, IL-6, IL-8, as well as PGE-2. PGE-2 increases vasodilatation and vascular permeability, facilitates the degranulation of mast cells, and increases the sensitivity of afferent neuronal endings. Increased vasodilatation and vascular permeability by PGE-2 and histamine leads to increased blood flow and extravasation of fluid from blood vessels, resulting in visible redness and swelling. Increased production of TNF-α and IL-1 leads to the expression of intracellular adhesion molecules, such as VCAM and ICAM, on endothelial cells of the blood vessels [18]. These proteins, as well as P and E selectin, serve as anchoring elements for bloodborne monocytes and neutrophils. The attachment of leukocytes to the adhesion molecules slows their movement through the bloodstream and finally causes their adhesion to the endothelial wall [19]. In the presence of chemokines, particularly, IL-8 produced and released by both keratinocytes and fibroblasts, the adherent leukocytes undergo chemotaxis and migrate from the blood vessel out into the skin where they act to scavenge the area of debris and also produce additional inflammatory mediators. The initial acute response occurs within minutes of the insult to the skin [20]. The subsequent movement of neutrophils and monocytes into the "wounded" area typically takes up to 48 hours to occur. If the triggering stimulus is eliminated, inflammatory mediator production by keratinocytes, fibroblasts, and mast cells ceases, the influx of leukocytes to the "wounded" area decreases and inflammation subsides.

In contrast to acute inflammation, which typically resolves in 1–2 weeks, chronic inflammation results from a sustained

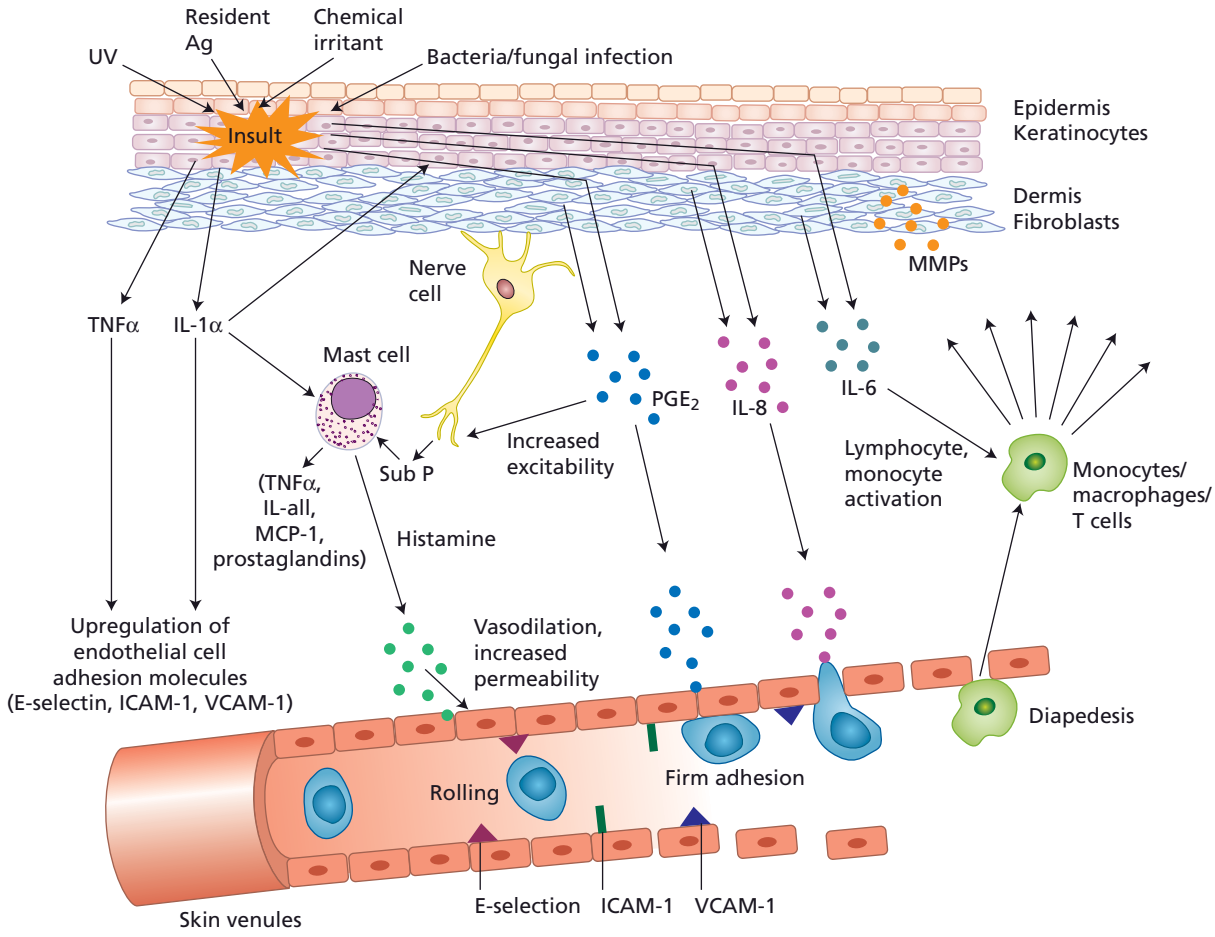

Figure 35.2 Skin inflammation pathway.

immune cell-mediated inflammatory response within the skin itself and is long-lasting. This response involves antigen presenting cells (APC) in the skin, called Langerhans cells in the epidermis and dendritic cells (DC) in the dermis, that, when activated, transport antigens through the lymphatics and to T lymphocytes where the antigen is "presented." The T lymphocytes are activated and travel back to the skin where they proliferate and express a wide range of inflammatory mediators as well as matrix-eroding enzymes (MMP-1; collagenase) [21]. Cytokines produced by T lymphocytes can stimulate fibroblasts and keratinocytes to produce additional cytokines and chemokines, and can also induce the expression of a variety of tissue-destructive enzymes by fibroblasts, including MMP-1 (collagen), MMP-3 (stomelysin-1), and MMP-9 (gelatinase B). As long as the antigen or insult stimulus persists in the skin, the inflammatory response will continue, resulting in significant and serious tissue destruction [22].

Inflammatory processes in the skin, particularly those triggered by long-term exposure to solar radiation, trigger molecular pathways that escalate the aging process. Actinic aging, or photoaging, which occurs following prolonged exposure of the skin to UV light from the sun, results in increased cytokine production with attendant activation of genes in both keratinocytes and fibroblasts that cause erosion of the normal skin structure. MMPs, which break down the skin extracellular matrix causing sagging and wrinkling, are stimulated in sun-exposed skin. Furthermore, dermal fibroblast synthesis and assembly of collagen, which is required to maintain and restore the extracellular matrix, is inhibited while elastin production is overstimulated, leading to elastosis. It is now widely accepted that sun-exposed skin in most individuals remains in a constant state of low level UV-induced inflammation, and that this "smoldering" inflammation is responsible for the signs of skin aging that appear in middle age [23–25].

Prescription medicines for inflammation and mechanism of action

Corticosteroids

Some of the most effective and commonly used prescription drugs for treating inflammation are the corticosteroids, particularly the glucocorticoid-related steroids. They are effective for many forms of eczema, including atopic dermatitis and allergic contact dermatitis, and are fairly effective in ameliorating the symptoms of psoriasis. Corticosteroids can be used topically or orally. Given the efficacy of corticosteroids in treating many different types of skin inflammation and autoimmune-based inflammatory diseases such as rheumatoid arthritis, asthma, lupus erythematosus, and allergic rhinitis, considerable research has been directed toward understanding their mechanism of action.

Corticosteroids act on target cells by binding to the glucocorticoid receptor present primarily in the cytosol. This binding "activates" the receptor resulting in its translocation to the nucleus. The steroid hormone receptor complex then binds, as a homodimer, to DNA regulatory elements along the promoter regions of specific genes. This binding usually results in the upregulation of gene activity but can also cause transcriptional repression of the target gene [26]. The effectiveness of corticosteroids as inhibitors of inflammation stems from the ability of the steroid activated glucocorticoid receptor complex to interfere with the activation of genes regulated primarily by two transcription factors: NF-κB and AP-1 [27,28]. These two transcription factors are largely responsible for the transcriptional activation of a wide variety of pro-inflammatory genes including cytokines IL-1, IL-2, IL-3, IL-4, IL-6, IL-11, IL-12, and IL-13, TNF-α, and granulocyte macrophage colony-stimulating factor (GM-CSF), chemokine genes IL-8, RANTES, MCP-1, adhesion molecules ICAM-1, VCAM-1, and E-selectin, the COX-2 gene, and the MMP gene, MMP-1 [29].

The transcription factors, NF-κB or AP-1, are activated by kinases which, in turn, are activated as a result of a hormone or cytokine binding to, and activation of, a surface receptor. In the case of the NF-κB activation pathway, a kinase, IκK, when activated, phosphorylates an inhibitor protein, IκB. Unphosphorylated, IκB binds to and represses the activity of NF-κB, but when phosphorylated, it dissociates from NF-κB and is degraded. Once freed from the IκB, NF-κB can translocate to the nucleus where it binds to the promoter region of specific genes and activates them [30]. In regard to the AP-1 transcription factor, it is phosphorylated and activated as a result of a kinase "signaling cascade" that begins with the binding of a hormone/cytokine, such as IL-1 or TNF-α, to a surface receptor on target cells [27].

While some genes are regulated only by either NF-κB or AP-1, other inflammatory genes have both an NF-κB and AP-1 binding site in their promoter regions and thus can be regulated by either or both transcription factors.

The anti-inflammatory activity of corticosteroids comes from their ability to repress either the activation or activity of the NF-κB and AP-1 transcription factors, thereby suppressing transcription of genes coding for inflammatory mediators. A model showing one mechanism glucocorticoids use to block the transcriptional activity of NF-κB is shown in Figure 35.3(a). When activated by hormone binding, the glucocorticoid receptor translocates to the nucleus where it can bind to NF-κB and suppress its transcriptional activity, either by preventing its binding to the promoter region of target genes or by preventing NF-κB's ability to activate the transcriptional machinery when bound to the promoter. Thus, inflammatory genes that require NF-κB for activation remained turned off [30–33]. Similarly, the activated glucocorticoid receptor interacts with the AP-1 transcription factor and prevents it from binding to and activating target

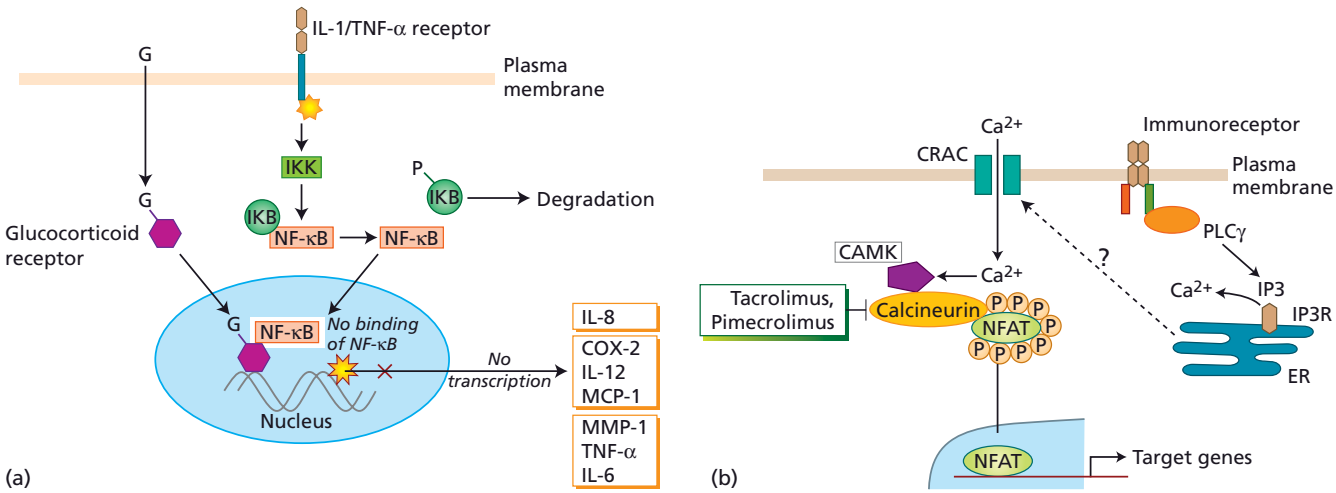

Figure 35.3 Glucocorticoid and immunomodulator inhibition of inflammatory pathways. (a) Mechanism of glucocorticoid inhibition of the NF-κB driven inflammation pathway. (b) Calcineurin and nuclear factor of activated T cells (NFAT) activation and inhibition by tacrolimus/pimecrolimus.

inflammatory genes. Recent evidence also suggests that glucocorticoids may block AP-1 phosphorylation and activation [27].

While the glucocorticoids are very effective in suppressing the activation of pro-inflammatory genes they unfortunately produce a variety of undesirable side effects. First, because of their potent inhibition of genes involved in an immune cell driven inflammatory response, they have an overall immunosuppressive effect. Prolonged use of glucocorticoids leads to a reduction in B and T lymphocyte populations, and a reduced ability to fight skin infections. Further, steroids adversely affect the ability of dermal fibroblasts to synthesize collagen and at high doses they reduce the proliferation rate of these cells. Consequently, long-term use of topical steroids leads to skin thinning and a decrease in the dermal matrix. Other potential negative side effects caused by prolonged use of steroids include altered carbohydrate metabolism, suppression of the hypothalamic-pituitary-adrenal axis, increased osteoporosis, and increased risk of developing cataracts.

Because of undesirable side effects which limit the length of time steroids can be used to treat inflammatory diseases, non-steroidal topical therapeutics have been developed to treat inflammation. One group of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) have been used for many years as oral drugs to control inflammatory responses.

Non-steroidal anti-inflammatory drugs

The most well-known of all the NSAIDs, aspirin, has been used for over 100 years to control various forms of inflammation . NSAIDs are available in over-the-counter (OTC) and prescription forms. Common OTC forms are ibuprofen, naproxen, aspirin, and acetaminophen. Those available with a prescription include celecoxib (Celebrex®, Pfizer, New York), diclofenac (Voltaren®, Novartis, Parsippany, NJ, USA), etodolac (Lodine®, Almirall, Uxbridge, UK), indomethacin (Indocid®, Aspen Pharma, Durban, South Africa), ketoprofen (Orudis®, Sanofi-aventis, Paris, France), and rofecoxib. One topical prescription NSAID that has received Food and Drug Administration (FDA) approval in the USA is diclofenac (SOLARAZE, PharmaDerma, Florham Park, New Jersey) which is indicated for the treatment of actinic keratoses [34].

When one examines the published data on the efficacy of topical NSAIDs in treating various inflammatory symptoms, the results show considerable disparity. A statistical analysis of clinical data from a wide number of trials with various topical NSAID preparations concluded that with long-term use the effectiveness of the NSAID-treated group was not significantly different from the placebo group [35]. Other studies, however, do suggest that topical NSAID treatment for joint pain provides relief beyond that observed with the placebo group [36–38]. Few studies have evaluated topical formulations that contain newer NSAIDs, including the specific COX-2 inhibitors, but it seems likely that a topical preparation of a potent NSAID that delivers adequate levels of an effective COX inhibitor through the skin would likely be effective in treating a variety of inflammatory conditions in which PGE-2 is indicated as a causative factor.

The target for NSAIDS is the enzyme cyclo-oxygenase (COX), which exists in two forms: COX-1 and COX-2. While most older versions of NSAIDs including aspirin, ibuprofen, and acetaminophen are not selective inhibitors of any particular form of COX, newer drugs have been designed to target primarily COX-2 [39].

Because of their ability to lower PGE-2 levels, topical NSAIDs have been evaluated for their ability to reduce the severity of a sunburn, which is largely mediated by PGE-2.

Topical indometacin (1%) if administered immediately after sun exposure is more effective than steroids, being able to block the onset of sunburn, produced by a 6 minimal erythema dose (MED) dose of UVB radiation [40]. Topical application of the COX-2 inhibitor, celecoxib, after UVB irradiation of skin, reduced erythema, edema, PGE-2 levels, the number of sunburn cells, and dermal infiltration of neutrophils [41]. The topical NSAID, diflofenac (Solareze), which is approved for use in the USA to treat actinic keratoses, has been shown to reduce sunburn symptoms when applied within 4 hours of the initial onset of sunburn [42]. Interestingly, several studies implicate PGE-2 as a causative factor in skin cancer, and results from mouse experiments show that topical application of a PGE-2 inhibitor lowers the UVB-induced number of papillomas detectable 12 weeks after UVB dosing [43,44].

Immunomodulators

A newer type of NSAID is represented by the immunomodulators. Two anti-inflammatory drugs that have received FDA approval for topical use are the immunomodulators, tacrolimus and the related drug, pimecrolimus. These drugs, along with ciclosporin, which exerts its effects through the same mechanism of action, had their origin as immunosuppressive agents used to prevent organ rejection after transplant surgery [45]. Both pimecrolimus and tacrolimus have been approved for topical use in treating atopic dermatitis, but not for psoriasis. As is the case with the glucocorticoids, the immunomodulators inhibit the production of inflammatory mediators but, unlike the corticosteroids, both tacrolimus and pimecrolimus are more cell specific in that they target primarily mast cells and T lymphocytes. The drugs have fewer inhibitory effects on Langerhans cells/dendritic cells, fibroblasts and keratinocytes [46]. Thus, the skin thinning complications seen with topical corticosteroids are eliminated [47,48].

Tacrolimus, pimecrolimus, and ciclosporin repress inflammatory genes in target cells through a common mechanism that involves the repression of activity of a ubiquitous calcium-activated phosphatase, calcineurin, which is involved in the activation of specific inflammatory genes [49]. A cartoon showing the calcineurin pathway is shown in Figure 35.3(b). When surface membrane receptors are activated by binding to a hormone or cytokine, there is an increase in intracellular calcium. The increased calcium causes the activation of calmodulin which then binds to the calcium-dependent enzyme, calcineurin, and activates it. The activated calcineurin enzyme is a phosphatase, which can dephosphorylate the cytosolic subunit of a transcription factor, nuclear factor of activated T cells, cytosol (NFATc). The dephosphorylation of the cytosolic NFAT subunit allows it to translocate to the nucleus where it forms a complex with the nuclear subunit of NFAT (NFATn) whose synthesis was induced by signaling cascade initiated by the antigen binding to the T-cell surface receptor. Once the NFAT dimer has formed in the nucleus, it can bind to the promoter region of several inflammatory genes including those for IL-2, IL-3, IL-4, and TNF-α [49].

When the drugs tacrolimus, pimecrolimus, or ciclosporin enter the cell they bind to a cytosol protein, either FKBP for tacrolimus or pimecrolimus or cyclophilin for ciclosporin. Once formed, this complex is able to bind to and inactivate calcineurin. The now inactive calcineurin can no longer dephosphorylate NFATc, which results in the transcription factor remaining unactivated and in the cytosol. Thus, the NFATn protein in the nucleus has no binding partner and cannot bind to and activate inflammatory genes [49]. One of the genes in T cells that is inhibited by tacrolimus is the IL-2 gene, which is necessary for full T-cell activation. Thus, in the presence of these immunomodulators, T lymphocyes do not differentiate in response to antigen stmulation.

While tacrolimus and other calcineurin inhibitors are much more specific than corticosteroids in terms of the types of cells they act on, they still inhibit a wide variety of inflammatory genes and are therefore immunosuppressive. In 2006, the FDA issued a "black box" warning that the use of either Elidel® (Novartis Pharmaceutics, East Hanover, New Jersey) (pimecrolimus) or Protopic (Astellas Pharma, Tokyo, Japan) (tacrolimus) may be linked to an increase risk for skin cancer and lymphoma.

Another class of immunomodulators, called "biologic response modifiers" (BRM) or simply "biologics" because they are made from living organisms, have been developed over the past 5 years [50]. These are essentially "designer" drugs because they target a specific event or mediator involved in inflammation. Most of these are "humanized" monoclonal antibodies that bind to and inactivate various inflammatory cytokines. Anti-inflammatory drugs in this category include the TNF-α inhibitors, Enbrel (Wyeth, Collegeville, PA, USA) (etanercept), Remicade® (Centocor Ortho Biotech, Centocor, Horsham, Pennsylvania), (infliximab), and Humira (Abbott Laboratories, Abbott Park, IL, USA) (adalimumab) [51], a fusion protein that can bind to the CD2 binding site on T lymphocytes and prevent the antigen-mediated activation of the cell (Amevive®, Astellas Pharma, Tokyo, Japan) and finally, an antibody, Raptiva (Genentech, South San Francisco, CA, USA), that prevents leukocytes cells from binding to adhesion molecules on endothelial cells, thereby preventing migration of these cells into the skin.

However, these new protein-based biologic immunomodulators, although effective and useful for treating various dermatologic conditions are not without side effects. Because of their potent immunosuppressive effects, particularly on T lymphocytes, the risk of infection among patients taking these medications is elevated. Additionally, these drugs are

expensive and can only be used by injection and not applied topically.

Anti-inflammatory cosmeceutical "actives"

The demand for effective non-prescription topical products to treat inflammatory diseases such as eczema, atopic dermatitis, seborrheic dermatitis, and even psoriasis has led to the introduction of products based on either novel synthetic chemicals or on botanical "actives" which claim to be effective anti-inflammatory compounds. Some of the many purported botanical anti-inflammatory "active" ingredients in cosmeceutical products include bee pollen, curry extract, jewelweed, green tea extract, aloe, bilberry, tea tree oil, lavender essential oil, *Boswellia*, and willow bark. Given the abundance of botanicals which claim anti-inflammatory activity, is there any scientific evidence to suggest that any actually have inhibitory effects on the production or action of inflammatory mediators in the skin? The answer is yes for a few botanically derived ingredients.

One of the most widely studied botanicals for its anti-inflammatory activity is curcumin, the active ingredient in turmeric. A large number of scientific studies published in peer-reviewed scientific journals over the past 5–10 years have shown remarkable and potent anti-inflammatory activities of curcumin.

Another plant-derived "active" that has been shown through rigorous scientific studies to have anti-inflammatory activity is quercetin, a flavonoid derived from several plants and fruits, including apples. Its efficacy as an antioxidant and anti-inflammatory seems to provide some substantiation for the old expression, "an apple a day keeps the doctor away." Recent studies have shown that quercetin, like curcumin, can block NF-κB driven genes and thus prevent the production of a variety of inflammatory mediators [52,53]. Other plant-derived compounds that have been scientifically shown to have anti-inflammatory activities, at least in cell culture model systems include resveratrol, derived from grapes and knotweed; boswellic acid, derived from *Boswellia*; the polyphenol, epigallocatechin gallate, derived from green tea; and bisabolol, derived from chamomile. All of these compounds have been shown to exert some anti-inflammatory effect on cells in culture, either inhibiting the production of PGE-2, cytokines, chemokines, adhesion molecules, or other molecules involved in the inflammatory process.

Conclusions

Although there are a wide number of topical anti-inflammatories available as prescriptions which are effective in treating skin inflammation, all have some side effects that negatively impact their usefulness. Topical steroids are effective for treating many dermatologic diseases but can lower collagen production in dermal fibroblasts, reduce their proliferation, and cause skin thinning. Topical immunomodulators are immunosuppressive and can lead to increased risk for infection and even cancer. Clearly, there is a continued need for identifying newer anti-inflammatory technologies that effectively treat skin disorders without having such strong immunosuppressive effects. Botanically derived anti-inflammatory compounds as well as newer synthetic drugs, should help meet this need.

References

1 Bardin A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, Erwin PJ, *et al.* (2008) Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: systematic review and meta-analysis. *Mayo Clin Proc* **83**, 23–34.

2 Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. (2007) Trends in oxidative aging theories. *Free Radic Biol Med* **43**, 477–503.

3 Cao G, Alessio H, Cutler R. (1993) Oxygen-radical absorbance capacity assay for antioxidants. *Free Radic Biol Med* **14**, 303–11.

4 Placzek M, Gaub S, Kerkmann U, Gilbertz KP, Herzinger T, Haen E, *et al.* (2005) Ultraviolet B-induced DNA damage in human epidermis is modified by antioxidants Ascorbic acid and d-alpha-tocopherol. *J Invest Dermatol* **124**, 304–7.

5 Tajima S, Pinnel SR. (1996) Ascorbic acid preferentially enhances type I and type III collagen gene transcription in human skin fibroblasts. *J Dermatol Sci* **11**, 250–310.

6 Wu D, Hayek MG, Meydani S. (2001) Vitamin E and macrophage cyclooxygenase regulation in the aged. *J Nutr* **131**, 382S–8S.

7 Aggarwal BB, Shishodia S. (2004) Suppression of the nuclear factor-κB activation pathway by spice-derived phytochemicals: reasoning for seasoning. *Ann N Y Acad Sci* **1030**, 434–41.

8 Kim HY, Park EJ, Joe E-H, Jou I. (2003) Curcumin suppresses Janus kinase-STAT inflammatory signaling through activation of SRC homology 2 domain-containing tyrosine phosphatase 2 in brain microglia. *J Immunol* **171**, 6072–9.

9 Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. (2007) Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-κB-regulated gene products. *Cancer Res* **67**, 3853–61.

10 Boots AW, Haenen GR, Bast A. (2008) Health effects of quercetin: from antioxidant to nutraceutical. *Eur J Pharmacol* **585**, 325–37.

11 Huang YT, Hwang JJ, Lee PP, *et al.* (1999) Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells overexpressing epidermal growth factor receptor. *Br J Pharmacol* **128**, 999–1010.

12 Chen D, Milacic V, Chen MS, Wan SB, Lam WH, Huo C, *et al.* (2008) Tea polyphenols, their biological effects and potential molecular targets. *Histol Histopathol* **23**, 487–96.

13 Kuppusamy UR, Khoo HE, Das NP. (1990) Structure-activity studies of flavonoids as inhibitors of hyaluronidase. *Biochem Pharmacol* **40**, 397–401.
14 Zhang LL, Li L, Wu DP, Fan JH, Li X, Wu KJ, *et al.* (2008) A novel anti-cancer effect of genistein: reversal of epithelial mesenchymal transition in prostate cancer cells. *Acta Pharmacol Sin* **29**, 1060–8.
15 Pinnell SR, Yang HS, Omar M, *et al.* (2001) Topical L-ascorbic acid: percutaneous absorption studies. *Dermatol Surg* **27**, 137–42.
16 Azzi A. (2007) Molecular mechanism of α-topopherol action. *Free Radic Biol Med* **43**, 16–21.
17 Fitzpatrick RE, Rostan EF. (2002) Double-blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg* **28**, 231–6.
18 Shindo Y, Wit E, Han D. (1994) Dose–response effects of acute ultraviolet radiation on antioxidants and molecular markers of oxidation in murine epidermis and dermis. *J Invest Dermatol* **23**, 470–5.
19 Ley K. (2003) The role of selectins in inflammation and disease. *Trends Mol Med* **9**, 263–8.
20 Esche C, de Benedetto A, Beck LA. (2004) Keratinocytes in atopic dermatitis: inflammatory signals. *Curr Allergy Asthma Rep* **4**, 276–84.
21 Kupper TS, Fuhlbrigge RC. (2004) Immune surveillance in the skin: mechanisms and clinical consequences. *Nat Rev Immunol* **4**, 211–22.
22 Nathan C. (2002) Points of control in inflammation. *Nature* **420**, 846–52.
23 Fisher GJ, Choi HC, Bata-Csorgo Z, Shao Y, Datta S, Wang ZQ, *et al.* (2001) Ultraviolet irradiation increases matrix metalloproteinase-8 protein in human skin *in vivo*. *J Invest Dermatol* **117**, 219–26.
24 Jenkins G. (2002) Molecular mechanisms of skin ageing. *Mech Ageing Dev* **123**, 801–10.
25 Ma W, Wlaschek M, Tantcheva-Poor I, Schneider LA, Naderi L, Razi-Wolf Z, *et al.* (2001) Chronological ageing and photoageing of the fibroblasts and the dermal connective tissue. *Clin Exp Dermatol* **26**, 592–9.
26 Dostert A, Heinzel T. (2004) Negative glucocorticoid receptor response elements and their role in glucocorticoid action. *Curr Pharm Des* **10**, 2807–16.
27 De BK, Vanden BW, Haegeman G. (2003) The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: molecular mechanisms for gene repression. *Endocr Rev* **24**, 488–522.
28 Hermoso MA, Cidlowski JA. (2003) Putting the brake on inflammatory responses: the role of glucocorticoids. *IUBMB Life* **55**, 497–504.
29 Tak PP, Firestein GS. (2001) NF-κB: a key role in inflammatory diseases. *J Clin Invest* **107**, 7–11.
30 Almawi WY, Melemedjian OK. (2002) Negative regulation of nuclear factor-κB activation and function by glucocorticoids. *J Mol Endocrinol* **28**, 69–78.
31 Necela BM, Cidlowski JA. (2004) Mechanisms of glucocorticoid receptor action in noninflammatory and inflammatory cells. *Proc Am Thorac Soc* **1**, 239–46.
32 De Bosscher K, Schmitz ML, Vanden Berghe W, Plaisance S, Fiers W, Haegeman G. (1997) Glucocorticoid-mediated repression of nuclear factor-κB dependent transcription involves direct interference with transactivation. *PNAS* **94**, 13504–9.
33 Scholzen TE, Brzoska T, Kalden DH, O'Reilly F, Armstrong CA, Luger TA, *et al.* (1999) Effect of ultraviolet light on the release of neuropeptides and neuroendocrine hormones in the skin: mediators of photodermatitis and cutaneous inflammation. *J Invest Dermatol Symp Proc* **4**, 55–60.
34 Jarvis B, Figgitt DP. (2003) Topical 3% diclofenac in 2.5% hyaluronic acid gel: a review of its use in patients with actinic keratoses. *Am J Clin Dermatol* **4**, 203–13.
35 Lin J, Zhang W, Jones A, Doherty M. (2004) Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *Br Med J* **329**, 324–9.
36 Vaile JH, Davis P. (1998) Topical NSAIDs for musculoskeletal conditions: a review of the literature. *Drugs* **56**, 783–99.
37 Grace D, Rogers J, Skeith K, Anderson K. (1999) Topical diclofenac versus placebo: a double blind, randomized clinical trial in patients with osteoarthritis of the knee. *J Rheumatol* **26**, 2659–63.
38 Roth SH, Shainhouse JZ. (2004) Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled clinical trial. *Arch Intern Med* **164**, 2017–23.
39 Rainsford KD. (2007) Anti-inflammatory drugs in the 21st century. *Subcell Biochem* **42**, 3–27.
40 Kaidbey KH, Kurban AK. (1976) The influence of corticosteroids and topical indomethacin on sunburn erythema. *J Invest Dermatol* **66**, 153–6.
41 Wilgus TA, Ross MS, Parrett ML, Oberyszyn TM. (2000) Topical application of a selective cyclooxygenase inhibitor suppresses UVB mediated cutaneous inflammation. *Prostaglandins Other Lipid Mediat* **62**, 367–84.
42 Nelson C, Rigel D, Smith S, Swanson N, Wolf J. (2004) Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze). *J Drugs Dermatol* **3**, 401–7.
43 Brecher AR. (2002) The role of cyclooxygenase-2 in the pathogenesis of skin cancer. *J Drugs Dermatol* **1**, 44–7.
44 Miyauchi-Hashimoto H, Kuwamoto K, Urade Y, Tanaka K, Horio T. (2001) Carcinogen-induced inflammation and immunosuppression are enhanced in xeroderma pigmentosum group A model mice associated with hyperproduction of prostaglandin E2. *J Immunol* **166**, 5782–91.
45 Nghiem P, Pearson G, Langley RG. (2002) Tacrolimus and pimecrolimus: from clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol* **46**, 228–41.
46 Bos JD. (2003) Non-steroidal topical immunomodulators provide skin-selective, self-limiting treatment in atopic dermatitis. *Eur J Dermatol* **13**, 455–61.
47 Gupta AK, Chow M. (2003) Pimecrolimus: a review. *J Eur Acad Dermatol Venereol* **17**, 493–503.
48 Lazarous MC, Kerdel FA. (2002) Topical tacrolimus protopic. *Drugs Today (Barc)* **38**, 7–15.
49 Hogan PG, Chen L, Nardone J, Rao A. (2003) Transcriptional regulation by calcium, calcineurin, and NFAT. *Genes Dev* **17**, 2205–32.
50 Bohjanen KA, Prawer SE. (2004) New biologic therapies for psoriatic disease. *Minn Med* **87**, 34–6.

51 Fantuzzi F, Del Giglio M, Gisondi P, Girolomoni G. (2008) Targeting tumor necrosis factor alpha in psoriasis and psoriatic arthritis. *Expert Opin Ther* **12**, 1085–96.

52 Middleton E Jr, Kandaswami C, Theoharides TC. (2000) The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev* **52**, 673–751.

53 Udenigwe CC, Ramprasath VR, Aluko RE, Jones PJ. (2008) Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutr Rev* **66**, 445–56.

Chapter 36: Peptides and proteins

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BASIC CONCEPTS

- Amino acids are the building blocks of peptides that link together to from proteins.
- Peptides are biologically active communication tools that direct skin functioning.
- Engineered peptides are a new category of active skin ingredients usually applied in a moisturizing vehicle.
- Gene chip array analysis can be used to evaluate the effect of engineered peptides in fibroblast cultures.

Introduction

Peptides, proteins, and amino acids are often mislabeled and the terms applied as if they were interchangeable, yet they are different in their characteristics, uses, biological activities, and cosmetic potential [1]. After defining peptides and proteins, the first part of the chapter discusses the specificities of these molecules and their physiologic, biological function, particularly in the skin; what can they do, what are the obstacles to their use in cosmetic products and how these obstacles can be overcome. In the second part, concrete examples of peptides and proteins in dermocosmetics, in particular for the "antiaging" sector, are discussed before concluding with an outlook for the future of this ingredient category in skincare.

Definitions

It is important to understand the differences between amino acids, peptides, and proteins.

Amino acids

Amino acids are the building blocks of which peptides and proteins are made. They are small molecules, with a molecular weight of 100–200 Da, characterized by the fact that both an amino group (NH_2) and a carboxylic acid group (COOH) are attached to the central carbon atom which also carries further quite variable structures, known as side chains, by which the different amino acids are distinguished (Figure 36.1).

Of the essentially unlimited theoretical number of amino acids that can be imagined on paper, only 20 (e.g. alanine, proline, tyrosine, histidine, phenylalanine, lysine, glutamine) are incorporated into peptides and proteins via the genetic code. Individually, these amino acids in isolation have no specific intrinsic biological activity. Within cells, they exist in a pool from which they can be called upon to make peptides and proteins or, sometimes, biogenic amines, such as serotonin or dopamine. In the upper layers of the skin, they are part of the natural moisturizing factor (NMF) where they participate in the skin water holding capacity contributing to both osmolytic and hygroscopic properties.

The specific interest in amino acids lies in their ability to function as an acid (pH < 7) and amine (pH > 7) simultaneously and the chemical fact that reacting an acid with an amine leads to the formation of an amide, which is a peptide bond, whereas this linkage is achieved in living cells by enzymatic means. The result of linking two or more amino acids in a linear chain is called a peptide, when the length of the chain is less than approximately 100 amino acids, or a protein when the chain is longer.

Peptides

The general terminology uses prefixes to describe the type of a peptide. For example, when the peptide is made of two amino acids, such as tyrosine and arginine written as Tyr-Arg, it is called a dipeptide. Three amino acid combinations yield a tripeptide, four amino acid combinations yield a tetrapeptide, etc. "Oligo" stands for a "few" so that oligopeptides can have 2–20 amino acids linked in a chain. The term polypeptides is used to mean many amino acids, although these latter distinctions are not strict and not governed by official rules.

The most important characteristic of a peptide, besides its length determined by the number of amino acids in the chain, is its sequence. The sequence is the precise order in which the various amino acids are linked together. Both

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glycyl-histidyl-lysine and glycyl-lysyl-histidine are tripeptides, composed of the three amino acids glycine, histidine, and lysine. However, the fact that these amino acids are linked in the Gly-His-Lys sequence in the former and in Gly-Lys-His sequence in the latter is crucial. The former peptide, usually abbreviated GHK, stimulates collagen synthesis in fibroblasts [2], the latter GKH stimulates lipolysis in adipocytes [3]. The primary function of most peptides is to bring a biochemical message from place A in the body to place B allowing effective communication.

Proteins

A peptide chain of more than approximately 100 amino acids is termed a protein. However, interleukins, cytokines, and interferon are also sometimes referred to as peptides, even though they possess a much higher molecular weight (Figure 36.2). Sometimes the distinction between the two categories relies more on the function of the molecule rather than the size.

Proteins can be categorized by their function, roughly into the following:

- Structural proteins: building tissue, such as collagen, elastin, fibronectin and many others;
- Enzymes: very specific proteins that catalyze biochemical reactions, such as superoxide dismutase (SOD), chymotrypsin, tyrosinase;
- Transport proteins that bind to a specific substrate and carry it along in the body (e.g. hemoglobin as oxygen carrier, ferritin for iron transport, lipoprotein for lipids, including cholesterol);
- Difficult to categorize proteins with highly specific functions: receptors such as protein G, genetic regulators such as peroxisome proliferator-activated receptor (PPAR), antibodies, coagulants, histones.

Proteins with individual molecular mass of hundreds of thousands of Daltons often autoassemble into large complexes of even larger size with very complex mechanisms of activity.

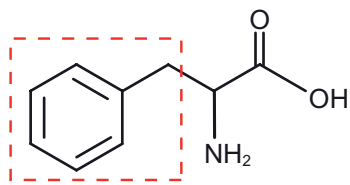


Figure 36.1 Phenylalanine, one of the 20 proteinogenic amino acids. The "side chain" which is characteristic of each amino acid (here a phenyl group) is shown in the box.

Biological functions of peptides and proteins in the skin

Peptides

Single amino acids very seldom have specific biological functions other than being present in the cytoplasmic pool for enzymes to be picked up and processed in one of many ways. Peptides perform many important biologic functions. The word hormone comes from Greek and means messenger. Hormones can be classified as peptide hormones or steroid hormones. Both steroids and peptides act in similar fashion. Some disturbance, either internal or external, leads to the release of a small amount of peptide in a cell, blood, gland, or in some other organ. The peptide then travels in the body until it interacts with a target receptor either on the cellular surface or within the cell nucleus after having penetrated the cell wall. This interaction triggers further

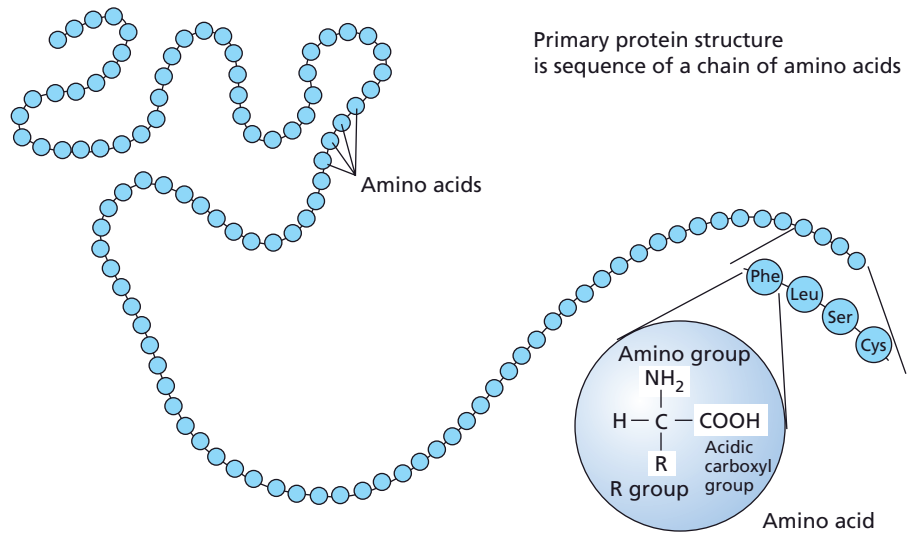


Figure 36.2 A protein chain composed of amino acids.

activity at the site, destined to respond and correct the initial disturbance.

This mechanism of action is usually characterized by three items:

1 Peptides circulate and act at their target sites at extremely low concentration levels, generally in the nanomolar (10^{-9} mol/L) level.

2 Each peptide sequence has, at its rather specific target, a highly specific binding affinity and carries a specific message such that its activity is quite specific. The highly simplified concept of "key" and "lock" (i.e. peptide and receptor) interaction is used to explain this potency and specificity.

3 Peptides have short lifespans in the organism because proteolytic enzymes break them down quickly in order to avoid overload at the target site.

Well-known biological activities of peptides in the human body are, for instance: regulation of blood sugar concentration (insulin); blood pressure regulation (angiotensin, bradykinin, calcitonin gene-related peptide [CGRP]); lactation and birthing (oxytocin); diuresis (vasopressin); pain repression (endorphins, enkephalin); tanning (α-MSH); radical scavenging (glutathione); other peptides include vasointestinal peptide (VIP), substance P, the inflammatory undekapeptide, and hundreds more. The ubiquitous nature of these peptides and their myriad activities clearly indicate their importance.

The relevance of some of the peptides in skin and skincare is of interest. As the term "antiaging" is not defined, it is interpreted here in a rather broad way to represent anything that helps the skin look younger. The rest of this chapter focuses on peptides for antiaging purposes.

Antioxidant peptides

Glutathione (γ-glutamyl-cysteyl-glycine)

This tripeptide GSH is one of the "oldest" members of the peptide family, with respect to its discovery, analysis, and confirmatory synthesis. It contains an –SH bearing, cystein amino acid which confers antioxidant activity to the molecule (Figure 36.3). The level of glutathione concentration in the body decreases notably with age, which may be a cause and a symptom of aging both at the same time [4]. The less GSH that is present, the more damage generated by free radicals; hence less glutathione reductase may be present to regenerate GSH. Besides affording this protective, antioxidant activity, for which there is *in vitro* but very little documented clinical evidence of skin benefits (for a medical study, see [5]), GSH may also have so-called "skin whitening" effects, as described by Villarama and Maibach [6].

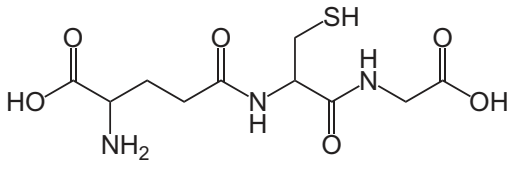


Figure 36.3 Glutathione (γ-Glutamyl-cysteyl-glycine).

Carnosin (β-alanyl-L-histidine)

This dipeptide also contains an unusual structure, in that β-alanine is used instead of the standard α-alanine. The histidine moiety in carnosin is of particular interest. Enzymatic breakdown of this peptide can lead to the production of histamine, a potent inflammatory agent, but also useful and necessary in the preparations for wound healing (see below).

Carnosin has been proven to scavenge reactive oxygen species (ROS) formed from peroxidation of cell membrane fatty acids during oxidative stress. 4-Hydroxy-2-trans-nonenal (4HNE) is one of the toxic end products of lipoperoxidation by free radicals. While the reaction of HNE with glutathione (GSH) is a well-recognized pathway of detoxification in biological systems, the quenching ability of carnosin towards HNE was studied by Aldini *et al*. [7]. Carnosin, although less reactive than GSH, significantly quenched HNE (48.2 ± 0.9% HNE consumption after 1 hour). The results indicate that beside GSH, histidine-containing dipeptides could be involved in the detoxification pathway of reactive species from lipid peroxidation. Carnosin is also shown to be useful to counter the effects of glycation (the non-enzymatic binding of sugars to proteins), leading to cytotoxic advanced glycation end products (AGE).

Nagai *et al*. [8] showed that carnosin may indeed promote wound healing, at least indirectly, as exogenous carnosin is degraded in the body by carnosinase into β-alanine and histidine which is then transformed by histidine decarboxylase to yield histamine. β-Alanine was found to stimulate the biosynthesis of nucleic acids and collagen, whereas histamine is considered to enhance the process of wound healing by stimulating effusion at the initial stage of inflammation.

Neuropeptides

The skin and the brain are derived from the same initial embryonic tissues [9]; thus, it is not surprising that many peptides that are found to exist and possess activities in the brain are also found in the skin.

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) contains 37 amino acids presently known to be the most potent vasodilatating substance. Additionally, other activities were discovered, such as stimulation of cyclic adenosine monophosphate (cAMP) levels and sweating, as the peptide is clearly involved in inflammatory response, and has recently been found to contribute to migraine headaches. It is released from nerve cells, including those of the epidermis. Curiously, atopic dermatitis is inversely correlated with CGRP plasma levels. Certain fragments of the peptide, however, have been

shown to competitively inhibit these activities and may prove to be of interest in skincare applications, such as in anti-redness and antiperspirant products.

Bombesin

Bombesin is a 14 amino acid neuropeptide which activates three different G-protein-coupled receptors known as BBR1, BBR2, and BBR3. With respect to skin-related activity, Baroni *et al*. [10] studied the effect of this neuropeptide on tissue regeneration and wound healing of the skin, on migration, proliferation, and differentiation of keratinocytes in an *in vitro* experimental model, on a mechanically injured human keratinocyte monolayer. Different mediators involved in wound repair, cell proliferation, and motility, and bombesin's direct effect on wound repair by observing the wound closure after mechanical injury, were studied. The data suggest that bombesin may have an important role in skin repair by regulating the expression of healing markers. Bombesin also increased cell growth and migration.

Other neuropeptides of interest include neuropeptides Y (NPY), PYY, and PP which act on a family of protein G receptors. NPY contains 36 amino acids and is present in the central nervous system. Among other (appetite regulating) activities, NPY acts on adipocytes and favors obesity. NPY inhibitors have been used in cellulite treatment whereas stimulation of NPY in facial skin might be of interest in redensifying the hypodermal layers (lipofilling).

Pro-opiomelanocortin

Pro-opiomelanocortin (POMC) should be considered as a protein, given its size of 241 amino acids. It is coded for by a gene found in the anterior pituitary gland. It is also secreted by cells of the hypothalamus, some neurons, and by keratinocytes and melanocytes of the skin and scalp. However, this protein does not seem to have a function of its own. Depending on the cell in which it is produced, it is broken down by endopeptidase enzymes into smaller fragments, or peptides, which have specific functions in the target cells.

The 241 amino acid chain contains the sequences of the immunomodulatory and inflammation mediating peptide adenocorticotropic hormone (ACTH; corticotropin with 39 amino acids), the melanin synthesis stimulating hormone α-MSH (melanocortin, previously called melanocyte-stimulating hormone with 13 amino acids), and its slight variant called β-MSH as well as the lipolytic peptide β-lipotropine (90 amino acids) which contains within its sequence β-endorphin (31 amino acids), and the pentapeptide enkephalin (Tyr-Gly-Gly-Phe-Met) which constitutes the first five amino acids of endorphin.

Of interest in skincare are the fragments α-MSH and its derivatives or analogs, as this peptide may be used to help even out skin tone by either stimulating melanogenesis (tanning) or by reducing the amount of pigmentation (skin "whitening"). β-Endorphin and particularly its N terminal pentapeptide fragment enkephalin may have skin soothing activities, as these molecules can be detected in the epidermis, localized close to nerve endings. A particularly interesting neuropeptide is kyotorphin, which has not yet been detected in the skin, but seems to act in similar ways on the skin as it does in the brain [11, and see below].

Matrikines

The term matrikines is used to describe fragments of matrix macromolecules endowed with stimulatory, tissue repair activity [12]. Katayama *et al*. [13] describe the minimum size fragment of procollagen I still able to induce collagen neosynthesis in human lung fibroblasts; the very hydrophilic pentapeptide Lys-Thr-Thr-Lys-Ser is such a molecule. The tripeptide Gly-His-Lys, found in different parts of broken down collagen and in some serum proteins, also stimulates collagen synthesis in human skin fibroblasts, as found by Maquart *et al*. [2]. The tetrapeptide Arg-Gly-Asp-Ser, a sequence found within the fibronectin structure responsible for the binding affinity of this protein to collagen and to cell membranes, is able to help cells migrate during the wound healing process. In order for this migration to occur, the cells must detach and then move through tissue to where they are needed [14]. This migration is guided by a concentration gradient of peptides, such as Val-Gly-Val-Ala-Pro-Gly, which are fragments of elastin. This migration phenomenon is better known as chemotaxis [15]. Schematically and very simplified, this event is illustrated in Figure 36.4.

Obstacles to peptide use in dermocosmetics

The incorporation of peptides in dermocosmetics can be challenging. Some of the hurdles confronted with peptide formulation include: skin penetration, stability, toxicity, analysis, and cost.

Skin penetration

The stratum corneum is not the primary target for peptides, as they need viable, living skin to receive their message. It is necessary for a peptide to cross the cutaneous barrier in order to reach the viable epidermis (keratinocytes), the basal layer (melanocytes, nerve cell endings), the dermis (fibroblasts), and even the hypodermis (adipocytes). Even small peptide molecules, such as the dipeptide carnosin, are too hydrophilic and electrically charged to penetrate any further than the first or second layer of the stratum corneum. The larger the peptide (beyond six or seven amino acids), the less likely it is to reach the deeper layers of the skin. Thus, the long peptide sequences mentioned above, such as CGRP, POMC, and similar structures, do not function as active ingredients in cosmetic formulas.

Lintner and Peschard [16] have shown that the attachment of a lipophilic chain (fatty acid of sufficient length) to smaller peptides can increase the penetration rate by a factor of 100 or more. Similar effects were confirmed by Leroux

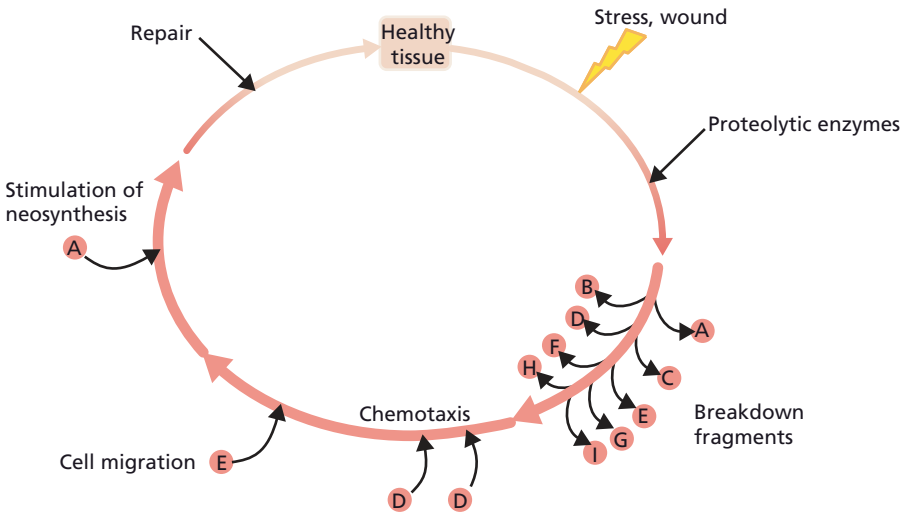


Figure 36.4 A tissue protein (e.g. collagen, elastin, fibronectin) is broken into fragments by enzymatic hydrolysis, either during normal tissue renewal, or as a consequence of induced damages (free radicals, burning, mechanical wound). The breaking up of the protein does not occur randomly, nor sequentially from one or the other end; various pieces of amino acid strings are generated, which when small enough, are readily available to act as "messengers" in the surrounding tissue, and will act as chemoattractants, transport aids, and stimulants to trigger neosynthesis of the necessary tissue molecules to renew/repair the three-dimensional structure.

et al. [3]. This technique of vectorizing the peptides has its limits because the longer the peptide chain, the less penetration the fatty acid will produce. Another limitation is the interference of biologic activity by acylation of the peptide. The N terminal ionic charge may be of importance for triggering effects at the target site or otherwise interfering with the peptide's properties. For example, the antioxidant activity of carnosin turns into pro-oxidant activity when the peptide is modified to become palmitoyl-carnosin (F. Vissac, unpublished results). Alternatively, attaching a poly-arginine chain to the peptide can help molecules penetrate the stratum corneum [17]. Liposome formulations may also help carry the peptide through the barrier, but little if anything has been published in this respect.

Stability

Unfortunately, peptides have limited chemical stability. In aqueous environments, such as those frequently encountered in cosmetic applications, hydrolysis may occur. Experience shows that the longer the peptide, the more fragile it becomes. The choice of excipients and stabilizers can help overcome this obstacle [18]. However, the question of peptide stability, an increasingly important consideration, must be considered.

Analysis

Detecting the presence of a peptide in a formulation 6–12 months after product manufacture can be difficult when the peptide is present in micromolar or less concentrations (p.p.m. level). Special analytical techniques, such as derivatization, mass spectrometry, and fluorescence spectrometry, have to be individually developed for each peptide. This is not always possible and/or very costly and sometimes proves an insurmountable hurdle.

Toxicity

Generally, the smaller the peptide, the less likely it is to show untoward effects. Peptides, in contrast to proteins, are hardly big enough to elicit allergic reactions, but specific undesirable cellular effects may occur with unknown sequences. It is advisable to use peptides with a biomimetic amino acid sequence, as the likelihood of toxicity is close to nil when the peptide is almost identical to human peptides. Nevertheless, proper safety evaluation of newly developed peptides, especially if the peptide is modified by acylation or esterification, is necessary.

Cost

Peptides of defined sequence and high purity (>90%) are expensive to produce; although extraction from some protein hydrolysates is theoretically possible, most peptides used in cosmetic applications are synthetic (i.e. made in a step by step process from the individual amino acid building blocks). It is noteworthy that the amino acids themselves are frequently of natural plant or fermentation origin. However, the very high potency of the peptides compensates for their cost and makes it possible to employ them at efficient level in all types of skincare formulas, because they are used at the p.p.m. level in finished cosmetics. Therefore, in spite of the formulation challenges, peptides have become popular, widely used active ingredients for antiaging skincare products, discussed next.

Examples of concrete applications of peptides in antiaging skincare

Numerous peptides are available for incorporation into cosmetic formulations. This section illustrates the manifold possibilities for using peptides in dermocosmetics.

Matrikines

The best known matrikine peptide used in skin care is the pentapeptide Pal-KTTKS, derived from the Katayama *et al.* [13] discovery discussed above. A DNA array study on this molecule indicated that mostly genes implicated in the wound healing process were upregulated in cells incubated with the peptide. Furthermore, the palmitoylated peptide stimulates not only the synthesis of collagen I, but also of collagen IV, fibronectin, and glycosaminoglycans in monolayer culture of normal and aged human fibroblasts and in full thickness skin (P. Mondon, unpublished data). This peptide was tested in vehicle controlled clinical trials where it proved to thicken the skin, improve the epidermal–dermal junction, and macroscopically reduce fine lines and wrinkles [19–21].

The peptide Pal-Gly-Gln-Pro-Arg (Pal-GQPR), although technically not a matrikine because it is not derived from a matrix macromolecule, is a fragment of the natural circulating protein IgG and stimulates macromolecule synthesis in cell culture demonstrated in Figure 36.5. This peptide also contributes to the reduction of basal and UV-induced IL-6 release in keratinocytes and fibroblasts, as demonstrated in Table 36.1.

The matrikine tripeptide Gly-His-Lys (GHK) has been mentioned as a wound healing and skincare ingredient for dermocosmetic formulas [2], especially when associated with copper ions. In its palmitoylated form (Pal-GHK) it is more active, even in the absence of copper, and can mimic the effects of retinoic acid [16]. The *in vitro* synergy between the tri- and tetrapeptide (Pal-GHK + Pal-GQPR) [22] led to an investigation of the combination in a clinical, vehicle controlled, blind study on 23 panelists (P. Mondon, unpublished data). Twice daily application of an oil-in-water (O/W) emulsion containing 4 p.p.m. of Pal-GHK and 2 p.p.m. of Pal-GQPR against placebo showed significant wrinkle reduction, an increase in skin firmness, and visible smoothing after 1–2 months (Figure 36.6).

In another formulation, the peptide GHK was coupled to biotin, instead of palmitic acid, in order to strengthen the affinity of the peptide to hair keratin. This biotinyl-GHK peptide was then tested on hair growth *in vitro* (Figure 36.7) where 2 p.p.m. of the peptide increased hair length by 58% (identical to minoxidil), and 5 p.p.m. achieved 120% increase.

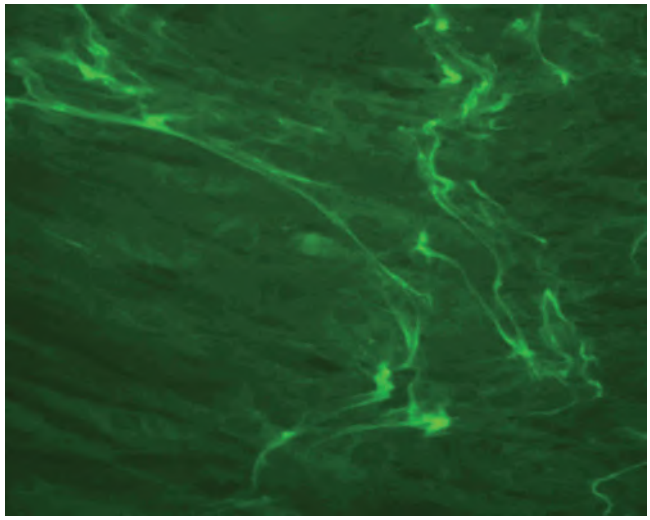
The production of the mitotic marker Ki67 and stimulation of collagen IV and laminin 5 syntheses were also investigated. Confirmation of the improved anchoring of the hair to the follicular infundibulum came from a clinical trial to study hair loss in alopecia patients where a significant

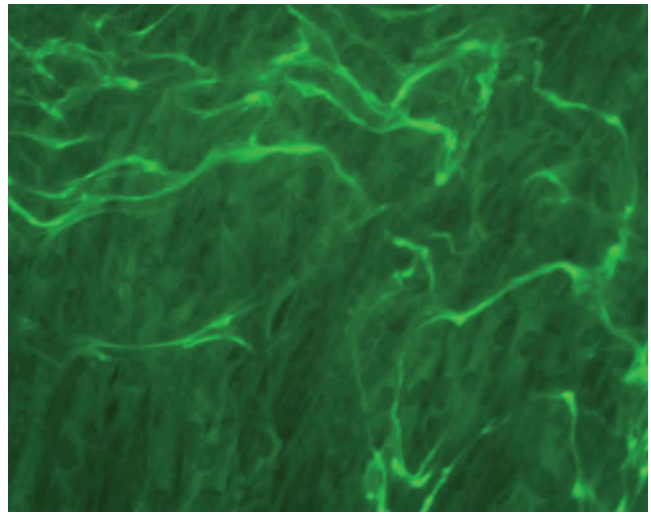
Table 36.1 Variation in IL-6 levels in presence of Pal-GQPR.

Pal-Gly-Gln-Pro-Arg (ppm)	Decrease of basal IL-6 (% of baseline level)	Decrease of UVB-induced IL-6 (% of baseline)
10	–15.6 ± 8.2	–33.2 ± 12.8
15	–20.0 ± 6.6	–37.3 ± 13.0
30	–24.6 ± 17.6	–60.3 ± 8.5
45	NT	–70.6 ± 9.8
65	NT	–85.5*
85	NT	–86.5*

NT, not tested.
* n = 2.

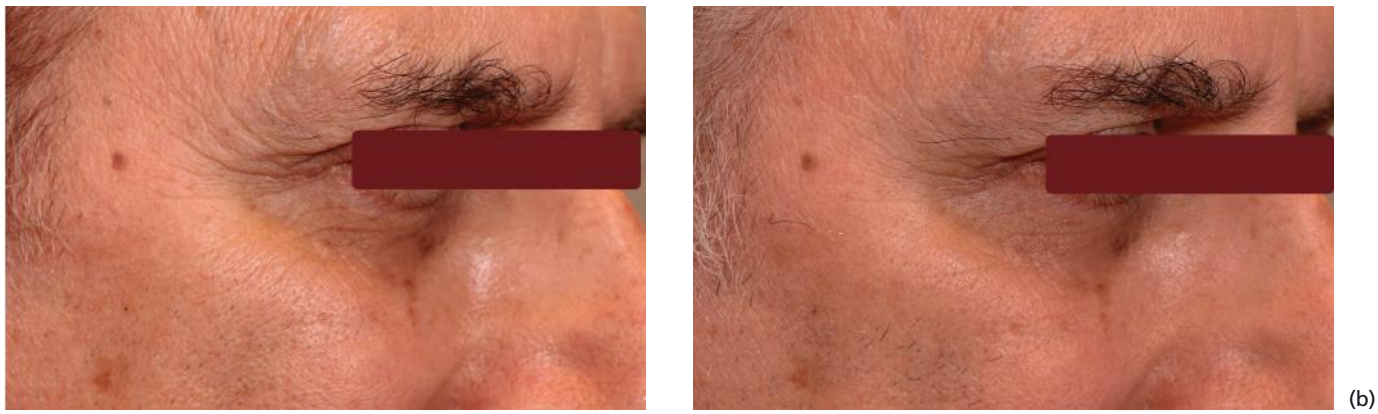
(a)





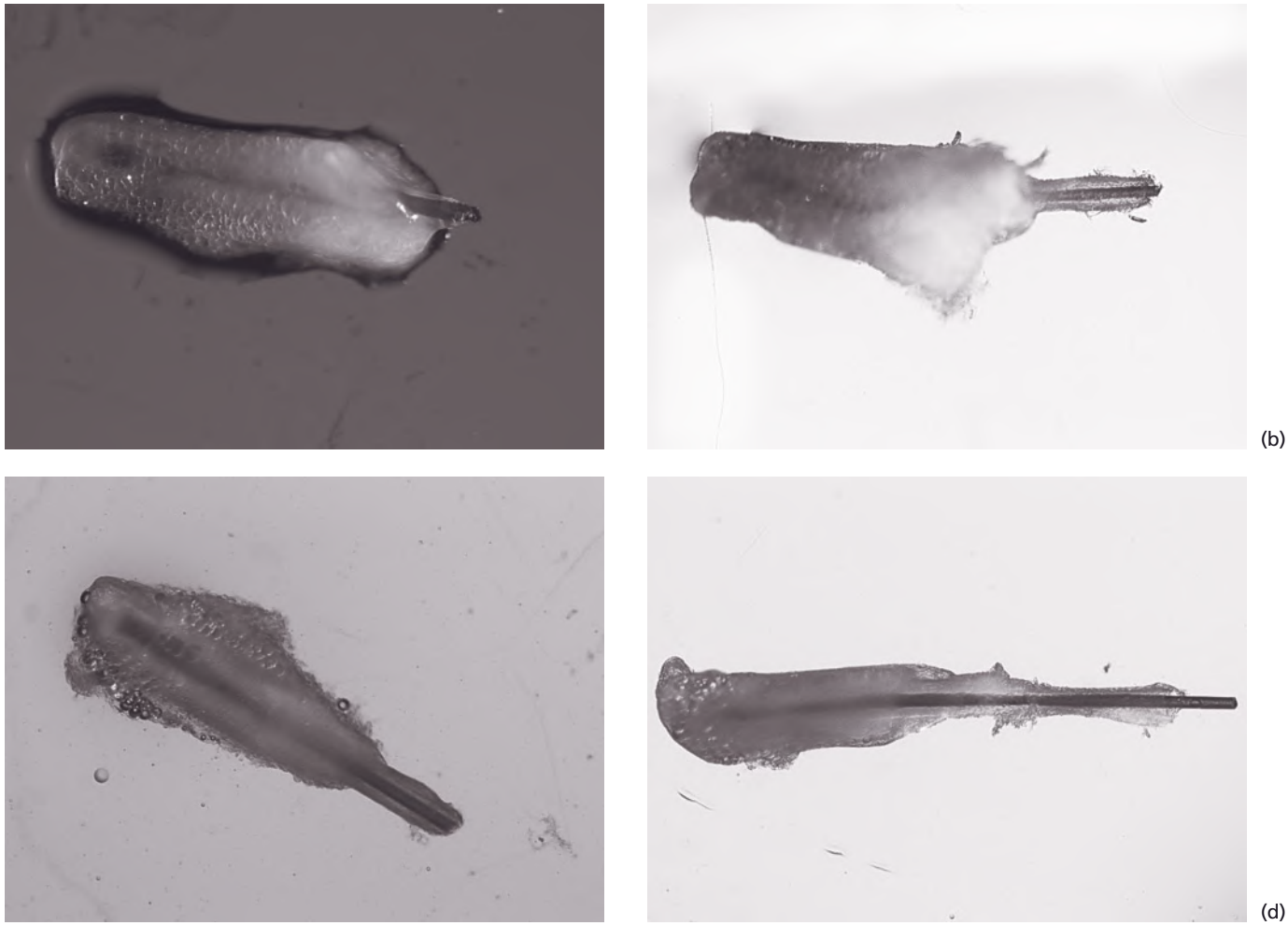
(b)

Figure 36.5 Immunofluorescence staining of collagen I in a normal human skin fibroblast culture after 3-day incubation: (a) control; (b) with 6 p.p.m. of Pal-GQPR.



(a) (b)

Figure 36.6 Wrinkle improvement after 2 months' application (twice daily) of a cream containing 4 p.p.m. Pal-GHK and 2 p.p.m. of Pal-GQPR. (a) Before. (b) After.



(a) (b) (c) (d)

Figure 36.7 Hair follicles in survival medium, incubated 14 days; (a & b) control; (c & d) 5 p.p.m. Biot-GHK.

improvement of the anagen : telogen ratio was observed, in line with histologic observations on plucked hairs from the panelists [23].

Neuropeptides

Neurotensin, VIP, NPY, substance P, and CGRP, although endowed with potent biological activity, are not candidates for cosmetic applications because of their size and irritation potential. This is not the case for the β-endorphin, enkephalin and the kyotorphin peptide complex. The dipeptide Tyr-Arg, which is known as kyotorphin, has been shown to be analgesic via enkephalin release in mouse brain [11]. The modified peptide, also known as *N*-acetyl-tyr-arg-hexadecylester, demonstrates improved skin bioavailability and stimulates the release of β-endorphin in keratinocytes. It is also able to reduce skin sensitivity to external thermal, chemical, and mechanical stress. A double-blind, vehicle controlled study using a lie detector established that this peptide, at 300 p.p.m. in an O/W emulsion, was able to diminish skin electrodynamic response to mechanical trauma induced by wiping the skin with sandpaper [24]. Sensitivity of the skin to thermal trauma induced by a heat probe and chemical trauma induced by topical capsaicin is also decreased after application of the peptide [16]. The peptide also inhibits *in vitro* muscle contraction.

Injections of derivatives of the *Botulinium* neurotoxin have been approved in a number of countries to diminish glabellar wrinkles. To develop a peptide with similar effects, Blanes-Mira *et al.* [25] synthesized the hexapeptide N-Ac-Glu-Glu-Met-Gln-Arg-Arg-NH_2 (N-Ac-EEMQRR-NH_2), a fragment of the SNAP-25 molecule [26]. It is reported to inhibit neurotransmitter release, apparently as a result of interference with the formation and/or stability of the protein complex that is required to drive Ca^{2+}-dependent exocytosis, namely the vesicular fusion known as SNARE complex, similar to what happens with *Botulinium* neurotoxin injections. The authors also claim that the peptide, formulated at the concentration of 10% = 100 000 p.p.m. in an O/W emulsion, reduced wrinkle depth up to 30% upon 30 days treatment on a panel of 10 human female volunteers [25].

Proteins

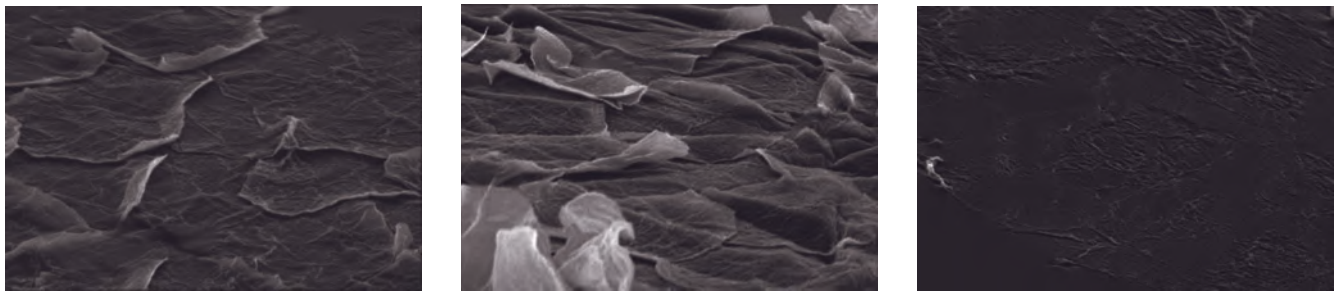
Structural proteins are building blocks for the organs and tissues of the human body. Collagen, one of the most abundant protein families, as well as keratin, elastin, fibronectin, actins, together with glycoproteins and proteoglucans, arrange themselves in finely tuned, three-dimensional structures to form muscles and skin. These proteins undergo a constant renewal process, even in the absence of external disturbances. These structural proteins are in contrast to enzymes, which fulfill an entirely different function. Enzymes speed up biochemical reactions, which would otherwise occur too slowly for the body to function. Enzyme function is highly specific. This specificity results from the precise amino acid sequence, which not only aligns the correct atoms and side chains in the right order, but also directs the precise folding pattern of the enzyme protein, thus guaranteeing its biological function. Enzymes are catalysts acting at low concentrations. The most important families of enzymes are proteolytic, lipolytic, antioxidant, DNA repair, and those involved in protein synthesis and gene regulation. A variety of enzymes have been employed in dermocosmetic products.

Proteolytic enzymes

Proteolytic enzymes are used as an alternative to α-hydroxy acids for superficial peeling of the skin surface, but care must be taken with the dosage. Figure 36.8 illustrates the proteolytic smoothing effect obtained with these enzymes.

T4 endonuclease V

T4 endonuclease V, isolated from *Escherichia coli* infected with T4 bacteriophage, has been shown to repair UV-induced cyclobutane pyrimidine dimers in DNA. Applied topically, liposomes containing T4 endonuclease V reduced the



(a) (b) (c)

Figure 36.8 Scanning electron microscope (SEM) pictures of skin treated with an occlusive patch for 2 hours; (a) control cream pH 7; (b) cream with AHA to pH 3.5; (c) cream with 2% proteolytic enzyme solution (10 proteolytic units/mL).

incidence of basal cell carcinomas by 30% and of actinic keratoses by 68% without adverse effects and no evidence of allergic or irritant contact dermatitis. Although the photoprotective effect of T4N5 has been investigated only in xeroderma pigmentosum patients, it may be also be effective for normal skin [27]. Cosmetic products based on this concept are in the current marketplace.

Superoxide dismutase

Superoxide dismutase, an antioxidant enzyme, is present at the surface of the skin. Adding this enzyme to cosmetic formulations to strengthen the natural defense system is tempting, although the transmutation of the superoxide anion to hydrogen peroxide, without further detoxification of the peroxide, is not necessarily sufficient for protecting the skin. Furthermore, the bovine blood, yeast, or biotechnologically derived SOD does not guarantee sufficient stability to survive manufacturing procedures and shelf life in cosmetic consumer products.

A novel alternative is based on extremozymes (enzymes produced by extremophile bacteria, such as *Thermus thermophilus*). Mas-Chamberlin *et al*. [28] have shown that these enzymes are heat and UV stable, possessing both SOD and catalase mimicking activity protecting the skin against UV-induced free radical damage. A 6-month clinical vehicle controlled blind trial under tropical conditions (Figure 36.9; Tables 36.2 & 36.3) on the island of Mauritius [29] demonstrated the visible and measurable benefits of protecting the skin in preventive manner.

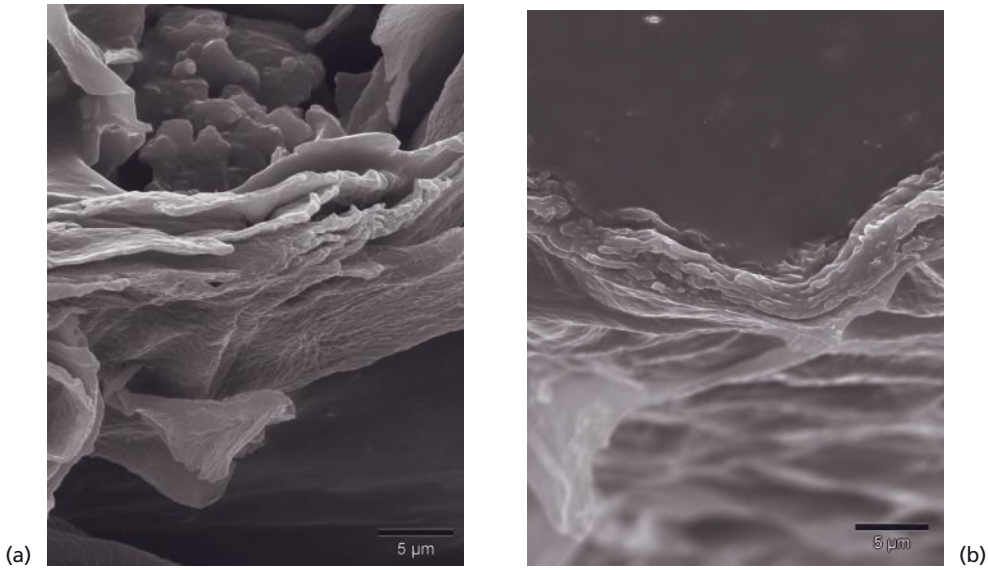


Figure 36.9 Scanning electron microscope (SEM) pictures of stratum corneum strippings: skin exposed to 6 months' tropical climate, treated with moisturizer. (a) Control formula; (b) extremozyme-containing moisturizer. (Reproduced with permission of Soap Perfumery and Cosmetics.)

Table 36.2 Changes in transepidermal water loss (TEWL) after exposure to tropical climate (25 panelists); group treated with extremozyme formula. (Reproduced with permission of Soap Perfumery and Cosmetics.)

Time	Variation ($g/m^{-2}/h^{-1}$) (mean ± SEM)	% Change (mean)	Significance
Week 4 vs. T0	–1.0 ± 0.7	–6%	NS* (p = 0.192)
Week 12 vs. T0	+0.8 ± 0.9	+5%	NS (p = 0.391)
Week 24 vs. T0	+0.2 ± 0.9	+1%	NS (p = 0.855)

* NS, not significant.

Table 36.3 Changes in transepidermal water loss (TEWL) after exposure to tropical climate (25 panelists); group treated with placebo formula; clearly the increase in TEWL indicates damaged skin barrier. (Reproduced with permission of Soap Perfumery and Cosmetics.).

Time	Change ($g/m^{-2}/h^{-1}$) (mean ± SEM)	% Change (mean)	Significance
4 weeks vs. T0	+0.9 ± 0.8	+7%	NS (p = 0.258)
12 weeks vs. T0	+1.3 ± 0.7	+10%	NS (p = 0.081)
24 weeks vs. T0	+1.4 ± 0.7	+11%	Borderline (p = 0.057)

Conclusions

Peptides, more than proteins, have become the "buzz" word of dermocosmetics (sometimes called "cosmeceuticals" or "active" cosmetics) during the last 5 years. This chapter presents some justification for this success. Although the list of peptides naturally occurring in the human body is long, allowing for further biomimetic peptide development for skincare, the possibility to create derivatives, analogs, and other variations on a theme is enormous and exciting. For example, the number of possible pentapeptides based on the 20 proteinogenic amino acids is 20^5 or 3 200 000. As understanding of cellular mechanisms, gene regulation, receptor activity, and metabolic interactions increases, many new peptides may appear in dermocosmetics.

References

1 Lintner K. (2007) Peptides, amino acids and proteins in skin care? *Cosmet Toiletries* **122**, 26–34.

2 Maquart FX, Pickart L, Laurent M, Gillery P, Monboisse JC, Borel JP. (1988) Stimulation of collagen synthesis in fibroblast cultures by the tripeptide-copper complex glycyl-L-histidyl-L-lysine-Cu^{2+}. *FEBS Lett* **238**, 343–46.

3 Leroux R, Peschard O, Mas-Chamberlin C, *et al.* (2000) Shaping up. *Soap Perfum Cosmet* **12**, 22–4.

4 Rizvi SI, Maurya PK. (2007) Markers of oxidative stress in erythrocytes during aging in humans. *Ann N Y Acad Sci* **1100**, 373–82.

5 Enomoto TM, Johnson T, Peterson N, Homer L, Watts D, Johnson N. (2005) Combination glutathione and anthocyanins as an alternative for skin care during external-beam radiation. *Am J Surg* **189**, 627–31.

6 Villarama CD, Maibach HI. (2005) Glutathione as a depigmenting agent: an overview. *Int J Cosmet Sci* **27**, 147–53.

7 Aldini G, Granata P, Carini M. (2002) Detoxification of cytotoxic alpha,beta-unsaturated aldehydes by carnosine: *J Mass Spectrom* **37**, 1219–28.

8 Nagai K, Suda T, Kawasaki K, Mathuura S. (1986) Action of carnosine and beta-alanine on wound healing. *Surgery* **100**, 815–21.

9 Misery L. (2002) Les nerfs à fleur de peau. *Int J Cosmet Sci* **24**(2), 111–6.

10 Baroni A, Perfetto B, Canozo N, Braca A, Farina E, Melito A, *et al.* (2008) Bombesin: a possible role in wound repair. *Exp Dermatol* **17**, 628.

11 Shiomi H, Ueda H, Takagi H. (1981) Isolation and identification of an analgesic opioid dipeptide kyotorphin (Tyr-Arg) from bovine brain. *Neuropharmacology* **20**, 633–8.

12 Maquart FX, Simeon A, Pasco S, Monboisse JC. (1999) Regulation of cell activity by the extracellular matrix: the concept of matrikines. *J Soc Biol* **193**, 423–8.

13 Katayama K, Armendariz-Borunda J, Raghow R, Kang AH, Sayer JM. (1993). A pentapeptide from type I procollagen promotes extracellular matrix production. *J Biol Chem* **268**, 9941–4.

14 Singer II, Kawka DW, Scott S, Mumford RA, Lark MW. (1987) The fibronectin cell attachment sequence Arg-Gly-Asp-Ser promotes focal contact formation during early fibroblast attachment and spreading. *J Cell Biol* **104**, 573–84.

15 Long MM, King VJ, Prasad KU, Freeman BA, Urry DW. (1989) Elastin repeat peptides as chemoattractants for bovine aortic endothelial cells. *J Cell Physiol* **140**, 512–8.

16 Lintner K, Peschard O. (2000) Biologically active peptides: from a lab bench curiosity to a functional skin care product. *Int J Cosmet Sci* **22**, 207–18.

17 Lim JM, Chang MY, Park SG, Kang NG, Song YS, Lee YH, *et al.* (2003) Penetration enhancement in mouse skin and lipolysis in adipocytes by TAT-GKH, a new cosmetic ingredient. *J Cosmet Sci* **54**, 483–91.

18 Ruiz MA, Clares B, Morales ME, Cazalla S, Gallardo V. (2007) Preparation and stability of cosmetic formulations with an anti-aging peptide. *J Cosmet Sci* **58**, 157–71.

19 Mas-Chamberlin C, Lintner K, Basset L, *et al*. (2002) Relevance of antiwrinkle treatment of a peptide: 4 months clinical double blind study *vs* excipient. *Ann Dermatol Venereol* **129**: Proceedings 20th World Congress of Dermatology, Book II, PO 438, Paris.

20 Robinson LR, Fitzgerald NC, Doughty DG, Dawes NC, Berge BA, Bissett DL. (2005) Topical palmitoyl pentapeptide provides improvement in photoaged human facial skin. *Int J Cosmet Sci* **27**, 155–60.

21 Watson RE, Long SP, Bowden JJ, Bastrilles JY, Barton SP, Griffiths CE. (2008) Repair of photoaged dermal matrix by topical application of a cosmetic "antiageing" product. *Br J Dermatol* **158**, 472–7.

22 US Patent US6,974,799 B2.

23 Mas-Chamberlin C, Mondon P, Lamy F, Peschard O, Lintner K. (2005) Reduction of hair-loss: Matrikines and plant molecules to the rescue. In Proceedings of the 7th Scientific Conference of the Asian Society of Cosmetic Chemists, Bangkok, Thailand.

24 Mas-Chamberlin C, Peschard O, Mondon P, Lintner K. (2004) Quantifying skin relaxation and well-being. *Cosmet Toiletries* **119**, 65–70.

25 Blanes-Mira C, Clemente J, Jodas G, Gil A, Fernández-Ballester G, Ponsati B, *et al.* (2002) A synthetic hexapeptide (Argireline) with antiwrinkle activity. *Int J Cosmet Sci* **24**, 303–10.

26 Chen YA, Scheller RH. (2001) SNARE mediated membrane fusion. *Nat Rev Mol Cell Biol* **2**, 98–106.

27 Cafardi JA, Elmets CA. (2008) T4 endonuclease V: review and application to dermatology. *Expert Opin Biol Ther* **8**, 829–38.

28 Mas-Chamberlin C, Lamy F, Mondon P, *et al*. (2002) Heat and UV stable cosmetic enzymes from deep sea bacteria. *Cosmet Toiletries* **117**, 22–30.

29 Mas-Chamberlin C, Mondon P, Lamy F, *et al*. (2006) Potential preventive performance. *Soap Perfum Cosmet* **6**, 34–6.

Chapter 37: Cellular growth factors

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BASIC CONCEPTS

- Skin aging is like a chronic wound that does not completely heal.
- Cellular growth factors have a key role in the wound healing process.
- Cellular growth factors that promote wound healing may accelerate reversal of aging.
- Preliminary clinical studies show efficacy of products containing multiple growth factors and cytokines.

Introduction

This chapter discusses cellular growth factors, which are proteins capable of stimulating cellular growth, proliferation, and cellular differentiation. Growth factors are important for regulating a variety of cellular processes. They have been best studied in wound healing models, but have been adapted as cosmeceuticals for their ability to improve the appearance of aging skin.

Physiology

Skin aging and wound healing

Extensive research on skin aging in the last decade has resulted in an improved understanding of the pathophysiology of intrinsic (age-related) and extrinsic aging (UV-mediated photoaging). Biochemical processes resulting in skin damage following exposure to UV radiation are now being identified and understood [1]. A correlation between biochemical processes following photodamage and creation of wound is emerging. Of specific interest to cosmeceutical manufacturers are the effects of growth factors in the process of wound healing. Figure 37.1 shows the stages of wound healing and role of growth factors in each stage. Growth factors are regulatory proteins that mediate signaling pathways between and within cells. After a wound has been inflicted, a variety of growth factors flood the wound site and interact synergistically to initiate and coordinate each phase of wound healing. They help recruit and activate fibroblast to produce rapid production of extracellular matrix to close the wound followed by stimulation and multiplication of keratinocytes to form new epidermis. The overall process is complex and not completely understood [2].

Following skin damage, a variety of pathways are activated. Formation of a wound or UV damage induces inflammation via several pathways including nuclear factor-κB (NF-κB) mediated activation of tumor necrosis factor-α (TNF-α) and interleukins [3]. Reactive oxygen species (ROS) and proteolytic enzymes are generated as a result of inflammation resulting in degradation of extracellular matrix. ROS increase oxidative phosphorylation of cell surface receptors causing activation transcription factors activator protein 1 (AP-1) and NF-κB, two critical components of mitogen-activated protein (MAP) kinase signaling pathway [4]. ROS therefore have a central role in intrinsic and extrinsic aging. AP-1 stimulates transcription of matrix metalloproteinase (MMP) growth factor genes in fibroblast and keratinocytes, and inhibits type 1 procollagen gene expression in fibroblasts [5]. Multiple studies have shown that activation of the MMP secretion as a result of intrinsic and extrinsic aging produces breakdown of dermal matrix [6].

Different subtypes of MMP have different substrate proteins on which they act to produce a break in their primary sequence. MMP-1 (collagenase) produces cleavage at a single site in central triple helix of fibrillar type I and III collagen. The cleaved subunits are further degraded by MMP-3 (stromelysine 1) and MMP-9 (gelatinase). Tissue inhibitors of metalloproteinase (TIMP) decrease activity of MMPs. ROS inactivates TIMP thereby further increasing MMP activity. AP-1 mediated reduction in synthesis of procollagen appears to result from two mechanisms: interference of AP-1 with type 1 and 3 procollagen gene transcription and blocking the profibrotic effects of TGF-β by impairment of TGF-β type 2 receptor–Smad pathway [3]. Activation of NF-κB stimulates transcriptions of proinflammatory cytokine genes including interleukin 1 (IL-1), TNF-α, IL-6, and IL-8 [4]. Inflammation resulting from these cytokines increases secretion of ROS and more cytokines further enhancing the effect of UV exposure.

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

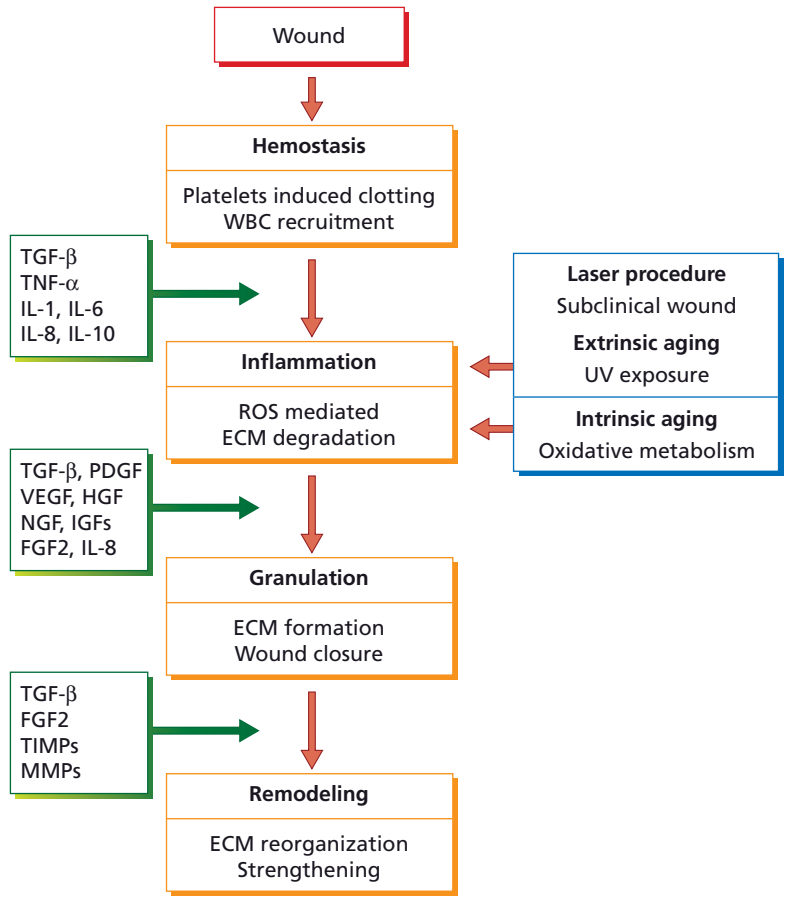


Figure 37.1 Healing and remodeling of skin damaged by the effect of intrinsic aging, extrinsic aging, wound or laser procedures. (From Mehta RC, Fitzpatrick RE. (2007) Endogenous growth factors as cosmeceuticals. *Dermatol Ther* **20**, 350–9.)

Inflammation causes protease-mediated degradation of elastin and UV exposure causes formation of abnormal elastin by fibroblasts. UV light is also an inhibition of leukocyte elastase thereby increasing accumulation of elastotic materials [7]. The accumulation of elastotic materials is accompanied by degeneration of surrounding collagenous network.

The overall effects of these interlinked biochemical activities is reduction of procollagen synthesis, increase of collagen degradation in the dermal extracellular matrix, and increase in irregular elastin deposition. Successful resolution of damage to skin and wound healing requires a balance between development of inflammation and its rapid resolution which includes involvement of growth factors and cytokines such as TGF-β, TNF-α, platelet-derived growth factor (PDGF), IL-1, IL-6, and IL-10 [8]. Intrinsic aging does not show the inflammatory component seen with healing of acute photodamage and wounds; instead, mitochondrial oxidative metabolism produces some of the key mediators of extracellular matrix degradation including ROS [9].

Transition from inflammatory phase of wound healing to granulation phase is mediated by a variety of growth factors and cytokines including PDGF, TGF-α, TGF-β, fibroblast growth factors (FGFs), insulin-like growth factor 1 (IGF-1), cerebrospinal fluid (CSF), interleukins and TNF-α [10]. The growth factors and cytokines are derived from macrophages, epidermal keratinocytes, and fibroblasts. Multiple metabolic pathways lead to formation of new collagen and repair of extracellular matrix during the granulation phase.

The final stage of wound healing after granulation and wound re-epithelialization or peeling of sunburned skin is the beginning of dermal tissue remodeling. During this stage, low strength, unorganized, type 3 collagen and elastin structures produced during the extracellular matrix production phase are replaced by stronger type 1 collagen and structured elastin fibers to provide strength and resiliency to the dermis. This remodeling phase can last for several months and is the key to reversing the visible effects of skin aging [11].

Most studies have evaluated the role of single growth factors in controlled wound-healing environments. These studies demonstrate the importance of growth factors in the repair of damaged tissue, but research into the phases of wound healing has demonstrated that it is the interaction of multiple growth factors that is vital to tissue regeneration.

Cosmeceutical manufacturers have taken notice of the positive results of clinical studies showing accelerated wound healing and have begun to include growth factors in products designed to mitigate damage from chronologic aging and sun exposure [11].

Role of cellular growth factors in skincare

The use of growth factors and cytokines in skin rejuvenation and reversal of photoaging is emerging as a novel antiaging treatment. Table 37.1 lists some important growth factors and cytokines that affect the proliferation of dermal

Table 37.1 Partial list of growth factors and cytokines identified in active gel and their function in skin [12].

Growth factor/cytokine	Skin-related functions
Fibroblast growth factors: bFGF (FGF-2), FGF-4, FGF-6, KGF (FGF-7), FGF-9	Angiogenic and fibroblast mitogen
Hepatocyte growth factor (HGF)	Strong mitogenic activities; three-dimensional tissue regeneration and wound healing
Platelet derived growth factors: PDGF AA, PDGF BB, PDGF Rb	Chemotactic for macrophages, fibroblasts; macrophage activation; fibroblast mitogen, and matrix production
Insulin-like growth factors: IGF1, IGFBP1, IGFBP2, IGFBP3, IGFBP6	Endothelial cell and fibroblast mitogen
Transforming growth factor: TGF-β1, TGF-β2, TGF-β3	Keratinocyte migration; chemotactic for macrophages and fibroblasts
Tissue inhibitor of metalloproteinases: TIMP1 (MPI1), TIMP2 (MPI2)	Prevent enzymatic degradation of collagen and hyaluronic acid
Vascular endothelial growth factor (VEGF)	Influence vascular permeability and angiogenesis to improve tissue nutrition
Placenta growth factor (PLGF)	Promote endothelial cell growth
Bone morphogenetic protein: BMP7	Promote development of nerve cells in developing tissue
Interleukins: IL-1α, IL-1β	Early activators of growth factor expression in macrophages, keratinocytes, and fibroblasts
Interleukin: IL-2	Enhance epithelial wound healing
Interleukin: IL-6	Mediator of acute phase response to wound and has synergistic effect with IL-1
Interleukin: IL-10	Inhibits pro-inflammatory cytokines to reduce inflammation prevents scar formation
Interleukin: IL-4, IL-13	Stimulate production of IL-6
Interleukin: IL-3, IL-4, IL-5	Leukocyte maturation and degranulation during inflammatory phase
Interleukins: IL-7, IL-8, IL-15	Leukocyte activation and proliferation during inflammatory phase
Leptin	Epidermal keratinocyte proliferation during wound healing
Colony stimulating factors: GCSF, GM-CSF, M-CSF	Stimulate the development of neutrophils and macrophages

GCSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; M-CSF, macrophage colony stimulating factor.

fibroblasts and extracellular matrix production [12]. Growth factors, cytokines, and other agents that help rebuild the extracellular matrix are critical in the reversal of the signs of skin aging such as fine lines and wrinkles. Providing a physiologically balanced mixture of these growth factors and cytokines to cells responsible for extracellular matrix production and remodeling may benefit in rejuvenation of aging skin. Several cosmeceutical products containing either a single human growth factor or combination of multiple human growth factors and cytokines are currently marketed for skin rejuvenation. Several clinical studies now show that human growth factors when applied topically provide beneficial effects in reducing the signs of facial skin aging [2].

Unique attributes

Growth factors produce antiaging benefits by virtue of their biologic role to maintain healthy skin structure and function. Together with cytokines, growth factors provide constant communication between cells of the immune system, keratinocytes, and fibroblasts throughout the process of wound healing and skin repair and regeneration. During the final remodeling phase of wound healing, a number of different growth factors and cytokines interact with each other and with the surrounding cells in concert to improve the quality of extracellular matrix. Use of individual growth factors is unlikely to duplicate these complex interactions essential for remodeling of skin. Therefore, a mixture of growth factors and cytokines proven to have a role in skin remodeling should provide superior benefits than individual growth factors. Ideal growth factor products should contain this unique mixture obtained from natural sources.

Advantages and disadvantages

Clinically proven benefits in reversal of skin aging

In one of the first pilot clinical studies with a product containing a natural combination of fibroblast-derived growth factor mixture, 14 patients with Fitzpatrick class II or greater facial photodamage applied TNS Recovery Complex (SkinMedica, Carlsbad, CA, USA) twice daily for 60 days. The results show a statistically significant reduction in fine lines and wrinkles and reduction in periorbital photodamage by clinical grading and by optical profilometry. Figure 37.2 shows an example of a skin biopsy section with increased collagen after treatment with the study product. Measurements of grenz zone collagen and epidermal thickness from the biopsy show a 37% increase in grenz zone collagen and a 30% increase in epidermal thickness [11].

Vehicle controlled studies on cosmeceutical products are very difficult to conduct as topical vehicles can have benefits by virtue of skin hydration, reduced epidermal water loss, or simply providing physical barrier against the environment. Because of these effects, most vehicles cannot be classified as "inactive" and make it more difficult to achieve statistical significance in a vehicle controlled, double-blind study design. In spite of these difficulties, if the product contains any new active combinations, the study must include a reasonably matched vehicle to scientifically validate effects of the new active [13].

In a double-blind study, 60 subjects were randomly assigned to receive either TNS Recovery Complex or vehicle and apply it twice daily for 6 months along with a moisturizing cleanser and sunscreen. Treatment with TNS Recovery Complex for 3 months produced greater reduction in fine

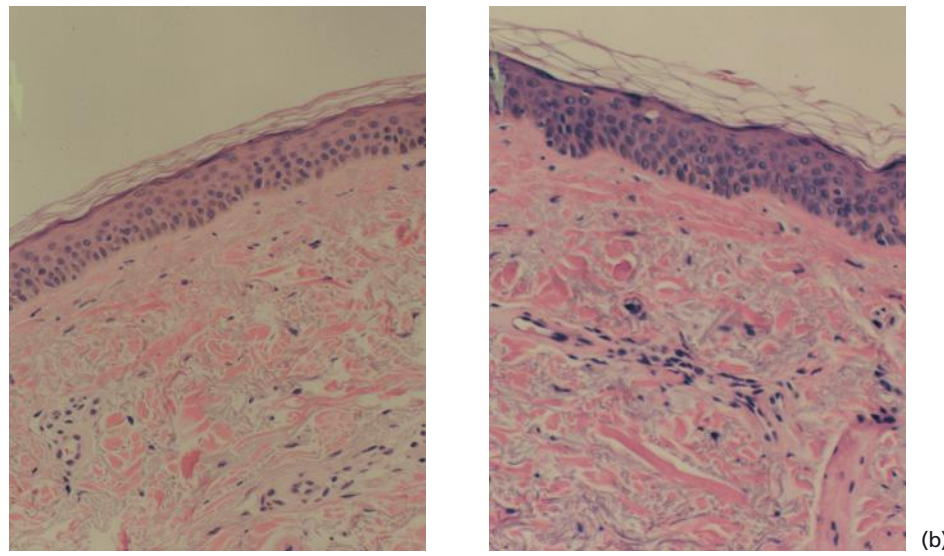


Figure 37.2 Histology of skin before (a) and after 3 months of TNS Recovery Complex (b) showing increase in grenz-zone collagen and epidermal thickness after treatment.

lines and wrinkles than vehicle treatment as measured by optical profilometry and assessment of photographs. The results were either statistically significant ($p \leq 0.05$) or trending towards statistical significance ($p \leq 0.1$). Figure 37.3 shows improvement in facial photodamage observed in this study. The study demonstrates that even when compared with a treatment with a good moisturizer and sunscreen, the product being tested showed significant benefits of reversal of signs and symptoms of skin aging [12].

In another double-blind study, 18 patients with Fitzpatrick class II or greater facial photodamage applied Bio-Restorative Skin Cream (NeoCutis, Inc, San Francisco, CA, USA) twice daily for 60 days. The results showed that while the average facial roughness did not decrease, a significant improvement was seen in several other parameters of facial wrinkles. The measurements were conducted by a novel three-dimensional surface mapping technique [14].

Risks associated with growth factors

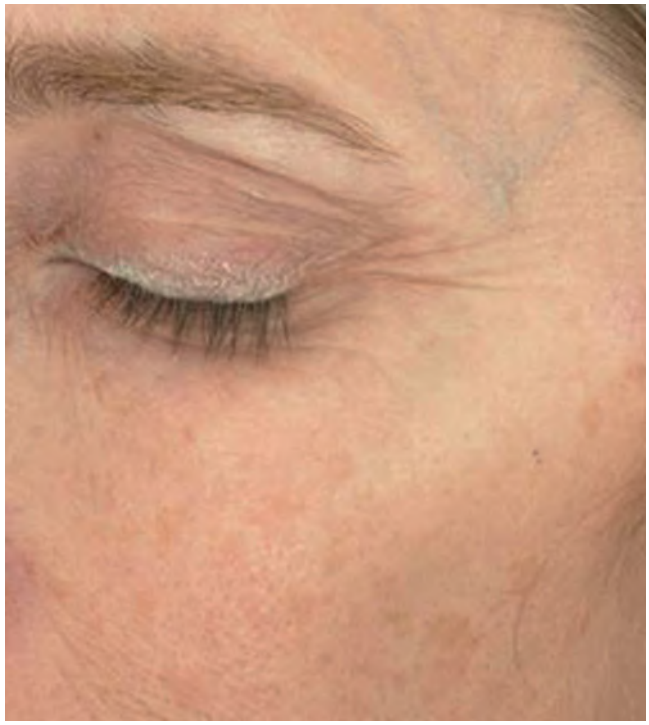
Growth factors are key molecules that affect cellular proliferation and differentiation which, if unregulated, can lead to carcinogenic transformation of cells. Presence of receptors for some growth factors in melanoma cells and expression of certain growth factors by cancerous cells [15] has raised concerns about the potential for topically applied growth factors to stimulate the development of cancer. However, whether presence of receptors or increased expression contributes to tumor growth is uncertain. A recent finding suggests that chronic administration of high concentrations of PDGF directly into debrided diabetic pressure wounds may result in increased mortality from cancer. It is unlikely that growth factors applied topically to intact skin would affect tumor proliferation as the protein molecules are too large to be absorbed in large quantities [12]. In addition, it is unlikely that the levels of growth factors in skin after topical application is significantly higher than those following inflammation-causing event such as chemical peel, lasers, or skin infections.

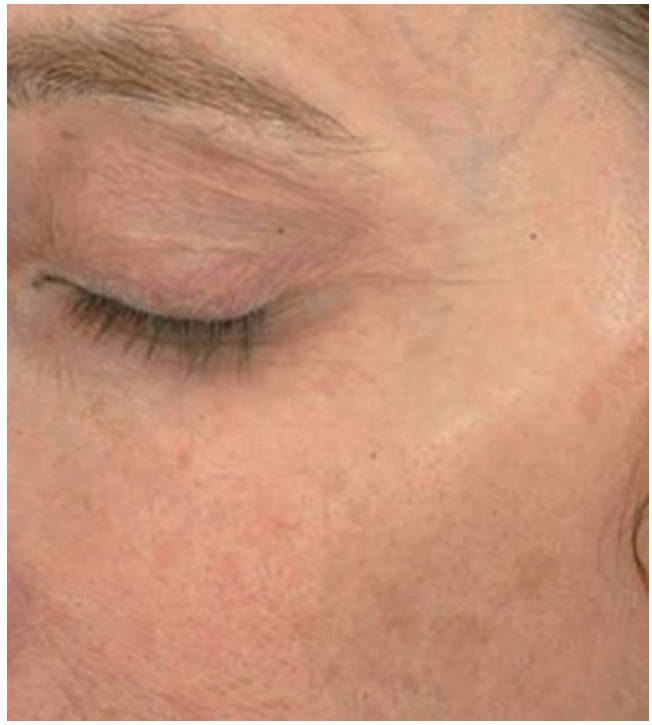
Ingredients

Natural growth factors

Human growth factors may be obtained from two major sources: cultured human cells or genetically engineered microorganisms. Human cells cultured in a three-dimensional network secrete a mixture of a large number of growth factors and other proteins capable of promoting wound healing [16]. The composition of the growth factor mixture varies with cell phenotype and environmental variables. Cells growing under conditions resembling a wound are most likely to produce growth factors, cytokines, and matrix proteins that assist in wound healing.

(a)





(b)

Figure 37.3 Photograph of periorbital and upper cheek area before (a) and after 6 months of TNS Recovery Complex (b) showing reduction in wrinkles and fine lines after treatment.

SkinMedica's NouriCel-MD is collected from a three-dimensional matrix of dermal fibroblasts induced to produce collagen, the same protein they produce during wound healing. The associated combination of growth factors and cytokines naturally secreted during the collagen production phase of the tissue culture therefore represents the most appropriate combination to induce wound healing (Table 37.1). Naturally secreted growth factors can also be obtained from fibroblast and keratinocyte co-cultures. Another method of collecting a mixture of growth factors and cytokines is to lyse fibroblast and collect the intracellular components which include growth factors, cytokines, and other intracellular materials present at the time of cell lysis [17].

Growth factors secreting stem cells

Adipose-derived stem cells, a population of pluripotent cells, have been studied for promotion of wound healing by virtue of their ability to secrete growth factors. Preliminary studies show that intradermal injection of adipose-derived stem cell suspension can produce increased collagen production and reduce signs of skin aging. These preclinical results warrant further evaluation in clinical studies after adequate testing and standardization of methods to obtain autologous adipose-derived stem cells [18].

Synthetic growth factors

Individual growth factors and cytokines can be made via recombinant technology using bacterial or yeast cultures modified to include DNA sequence for growth factors. Many growth factors of cosmeceutical interest are produced by this technique including TGF-β, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), various FGFs, PDGF, and more [19]. Table 37.2 lists various growth factors registered with *International Cosmetic Ingredient Dictionary and Handbook* as cosmetic ingredients. While clinical studies have shown a marginally beneficial effect for some of the individual growth factors, more studies must be carried out to understand the role of combinations of growth factors in skin rejuvenation. Combinations of growth factors that complement each other's effects is likely to be more effective as multiple growth factors are involved in most biochemical processes including wound healing [8].

Table 37.2 Synthetic growth factors registered as cosmetic ingredients [19].

INCI name	Growth factor
Human oligopeptide-1	Epidermal growth factor
Human oligopeptide-2	Insulin-like growth factor-1
Human oligopeptide-3	Basic fibroblast growth factor
Human oligopeptide-5	Keratinocyte growth factor
Human oligopeptide-7	Transforming growth factor-β3
Human oligopeptide-8	Interleukin 10
Human oligopeptide-10	Platelet derived growth factor
Human oligopeptide-11	Vascular endothelial growth factor
Human oligopeptide-12	Fibroblast growth factor 10
Human oligopeptide-13	Acidic fibroblast growth factor
Human oligopeptide-14	Transforming growth factor-α
Human oligopeptide-15	Interleukin 4
Human oligopeptide-19	Nerve growth factor
Human oligopeptide-20	Tissue inhibitor of metalloproteinases

Related products

Phytokinins

Kinetin, a plant-derived growth hormone discovered almost 50 years ago, has been recently used in several cosmeceutical products as an antiaging ingredient [20]. Kinetin is found in the DNA of almost all organisms tested so far, including human cells. In plants, kinetin regulates cellular differentiation by an endocrine pathway with unknown mechanism; however, its function in human cells is not known. Kinetin and other cytokinins are products of oxidative metabolism of the cell. Kinetin is formed in the nucleus by reaction of hydroxyl free radicals with DNA whereas reaction of hydroxyl radical with RNA results in formation of zeatin, another cytokinin used in cosmeceutical products.

A large number of *in vitro* and *in vivo* studies in many species show a number of pharmacologic actions leading to potential antiaging effects of kinetin and other cytokines. However, the effects are not related to the growth factor or hormone related properties but are primarily brought about by their strong intracellular antioxidant properties. A pilot study on 0.1% kinetin showed moisture retention and reduction in appearance of fine wrinkles and pigmentation; however, more controlled studies are required to substantiate the antiaging benefits.

Alternate delivery methods

Mesotherapy is the micro-injection of growth factors or other active molecules into the mesoderm with the premise that the active molecules are directly delivered to the target tissue using fine gauge short needles to a 2–5 mm depth of penetration. Multiple, close spaced injections are made to ensure adequate coverage of the treatment area. There are no clinical studies evaluating the efficacy of the procedures and safety remains a concern because of lack of availability of sterile growth factor solutions.

A variation of mesotherapy is the use of micro-needle devises to create micro-punctures into the stratum corneum

before topical application of growth factors with the assumption that reduced barrier will result in greater efficacy. Again, very little clinical evidence exists to show effectiveness of these procedures.

Product quality considerations

Cosmeceutical products containing mixtures of natural substances such as cellular growth factors are generally difficult to analyze for concentrations of active ingredient. Even products manufactured with single growth factor are not labeled with growth factor content which makes it difficult to compare product strengths. More analytical efforts are needed to ensure that consumers know that the products they are using have reliable quality standards. In addition, growth factors and other biologically active peptides are inherently unstable in non-physiologic environment, unless they are stored frozen at temperatures below −20 °C. Presence of surface active additives, alcohols, and other protein denaturing excipients further decrease product stability and compromise product efficacy during the claimed shelf-life of the product. A recent study shows presence of high levels of growth factors and cytokines in a commercial product stored at room temperature throughout its 2-year shelf-life [12]. If quantitative analysis is not possible because of the complexity of the formulation, measurement of biological activity should be performed using an appropriate technique to ensure product stability throughout the labeled shelf-life.

Conclusions

Studying the role of growth factors in cutaneous wound healing has led to research demonstrating positive cosmetic and clinical outcomes in photodamaged skin. Although the topical use of growth factors is an emerging treatment approach, clinical studies demonstrate that dermal collagen production and clinical improvement in photodamage appearance are significant. Further, the increase in dermal collagen produced by topical growth factors can be measured quantitatively by biopsy. Although the functions of growth factors in the natural wound healing process are complex and incompletely understood, it appears that wound healing is dependent on the synergistic interaction of many growth factors. The most promising research suggests that multiple growth factors used in combination stimulate the growth of collagen, elastin, and glycosaminoglycans leading to reduction in fine lines and wrinkles. The use of a multiple growth factor topical formulation provides a good first line treatment for mild to moderate photodamaged skin.

References

1 Gilchrest BA. (1989) Skin aging and photoaging: an overview. *J Am Acad Dermatol* **21**, 610–3.

2 Mehta RC, Fitzpatrick RE. (2007) Endogenous growth factors as cosmeceuticals. *Dermatol Ther* **20**, 350–9.

3 Quan T, He T, Kang S, Voorhees JJ, Fisher GJ. (2004) Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor-beta type II receptor/Smad signaling. *Am J Pathol* **165**, 741–51.

4 Fisher GJ, Talwar HS, Lin J, Lin P, McPhillips F, Wang Z, *et al.* (1998) Retinoic acid inhibits induction of c-Jun protein by ultraviolet radiation that occurs subsequent to activation of mitogen-activated protein kinase pathways in human skin *in vivo*. *J Clin Invest* **101**, 1432–40.

5 Schwartz E, Cruickshank FA, Christensen CC, Perlish JS, Lebwohl M. (1993) Collagen alterations in chronically sun-damaged human skin. *Photochem Photobiol* **58**, 841–4.

6 Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. (1997) Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* **337**, 1419–28.

7 Martin P. (1997) Wound healing: aiming for perfect skin regeneration. *Science* **276**, 75–81.

8 Eming SA, Krieg T, Davidson JM. (2007) Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* **127**, 514–25.

9 Sohal RS, Weindruch R. (1996) Oxidative stress, caloric restriction, and aging. *Science* **273**, 59–63.

10 Moulin V. (1995) Growth factors in skin wound healing: review article. *Eur J Cell Biol* **68**, 1–7.

11 Fitzpatrick RE, Rostan EF. (2003) Reversal of photodamage with topical growth factors: a pilot study. *J Cosmet Laser Ther* **5**, 25–34.

12 Mehta RC, Smith SR, Grove GL, Ford RO, Canfield W, Donofrio LM, *et al.* (2008) Reduction in facial photodamage by a topical growth factor product. *J Drugs Dermatol* **7**, 864–71.

13 Draelos ZD. (2007) Exploring the pitfalls in clinical cosmeceutical research. *Cosmet Dermatol* **20**, 556–8.

14 Gold MH, Goldman MP, Biron J. (2007) Human growth factor and cytokine skin cream for facial skin rejuvenation as assessed by 3D *in vivo* optical skin imaging. *J Drugs Dermatol* **6**, 1018–23.

15 Liu B, Earl HM, Baban D, Shoaibi M, Fabra A, Kerr DJ, *et al.* (1995) Melanoma cell lines express VEGF receptor KDR and respond to exogenously added VEGF. *Biochem Biophys Res Commun* **217**, 721–7.

16 Mansbridge J, Liu K, Patch R, Symons K, Pinney E. (1998) Three-dimensional fibroblast culture implant for the treatment of diabetic foot ulcers: metabolic activity and therapeutic range. *Tissue Eng* **4**, 403–14.

17 Schütte H, Kula MR. (1990) Pilot- and process-scale techniques for cell disruption. *Biotechnol Appl Biochem* **12**, 599–620.

18 Park BS, Jang KA, Sung JH, Park JS, Kwon YH, Kim KJ, *et al.* (2008) Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. *Dermatol Surg* **34**, 1323–6.

19 Gottscha TE, Bailey JE, eds. (2008) *International Cosmetic Ingredient Dictionary and Handbook*. Washington DC: Toiletry and Fragrance Association, pp. 1170–4.

20 Barciszewski J, Massino F, Clark BF. (2007) Kinetin: a multiactive molecule. *Int J Biol Macromol* **40**, 182–92.

Chapter 38: Retinoids

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BASIC CONCEPTS

- Retinoids define a class of substances comprising vitamin A (retinol) and its naturally and synthetic derivatives.
- Retinoids are lipophilic molecules that diffuse through plasma membranes or cross the cutaneous barrier when applied topically. Inside the cells, retinoids bind to nuclear receptors (RAR-α, -β, -γ, and RXR-α, -β, -γ), then the ligand–receptor complexes bind to a RAR-response element (RARE) DNA sequence, resulting in the modulation of the expression of genes involved in cellular differentiation and proliferation.
- As biologically active agents given to humans, retinoids can be divided into therapeuticals and cosmeceuticals.
- The ranking order of retinoid-like activity following topical application is as follows: retinoic acid > retinaldehyde > retinol >> retinyl esters.

Biologic concepts

Therapeutical and cosmeceutical retinoids

Retinoids define a class of substances comprising vitamin A (retinol) and its natural and synthetic derivatives. Although they were first discovered in the retina as central players of the biology of vision, they function as key regulators of differentiation and proliferation in various tissues. Retinol is produced in the small intestine either by hydrolysis of retinyl esters, or by oxidation of various carotenoids [1]. Retinol can be oxidized into retinaldehyde, and then into retinoic acid, the biologically active form of vitamin A. However, retinol can be esterified with fatty acids to form retinyl esters. Retinoic acid is oxidized to a less active metabolite, 4-oxoretinoic acid, or converted to retinoyl glucuronide, whereas retinol is converted to retinyl glucuronide. Two other vitamin A metabolites, 4-oxoretinol and 4-oxoretinal, are believed to be the products of oxidation of retinol and retinal, respectively, by CYP26-related hydroxylases, although this has not been demonstrated (Figure 38.1) [2,3].

The two predominant endogenous retinoids are retinol and its esters. Retinol and retinyl esters account for more than 99% of total cutaneous retinoids (i.e. approximately 1 nmol/g) [4]. Retinoic acid is catabolized either by phase I or II enzymes, giving rise to retinoyl glucuronide or 4-oxoretinoic acid [5,6]. Although the latter has long been considered an inactive catabolite of retinoic acid, other oxoretinoids (i.e. 4-oxoretinol and 4-oxoretinal) have been shown to be the predominant retinoids in some models of morphogenesis [7–9], and exert some of the retinoid-like activities in mouse *in vivo* [10]. As lipophilic molecules, they can diffuse through plasma membranes or cross the cutaneous barrier when applied topically. Inside the cells, they bind to nuclear receptors (RAR-α, -β, -γ, and RXR-α, -β, -γ), then the ligand–receptor complexes bind to a RARE DNA sequence, resulting in the modulation of the expression of genes involved in cellular differentiation and proliferation (Figure 38.1) [3,11–13].

As biologically active agents given to humans, retinoids can be divided into therapeuticals and cosmeceuticals. Therapeutical retinoids are usually RAR or RXR ligands (except for isotretinoin), and are available on medical prescription to treat diseases such as acne, psoriasis, and actinic keratosis, or oncologic diseases such as acute promyelocytic leukaemia, cutaneous T-cell lymphoma, and squamous or basal cell carcinoma [14]. Endogenous active metabolites of retinol (vitamin A) such as all-*trans*-retinoic acid (tretinoin), 9-*cis*-retinoic acid (alitretinoin), and 13-*cis*-retinoic acid (isotretinoin), as well as the synthetic monoaromatic retinoids acitretin and etretinate, and the arotinoids adapalene, tazarotene, and bexarotene, belong to the therapeutical retinoids (Figure 38.2a) [15,16].

Endogenous precursors of retinoic acids (i.e. retinyl esters, retinol, and retinaldehyde), as well as 4-oxoretinoids (4-oxoretinol, 4-oxoretinal, and 4-oxoretinoic acids), do not bind to nuclear retinoid receptors, are found in many over-the-counter (OTC) products, and constitute the group of topical cosmeceutical retinoids (Figure 38.2b).

Intracrine proligand concept

Chronologic aging and photoaging are not only a question of esthetics which is often accompanied by psychologic problems, they also constitute the background for the

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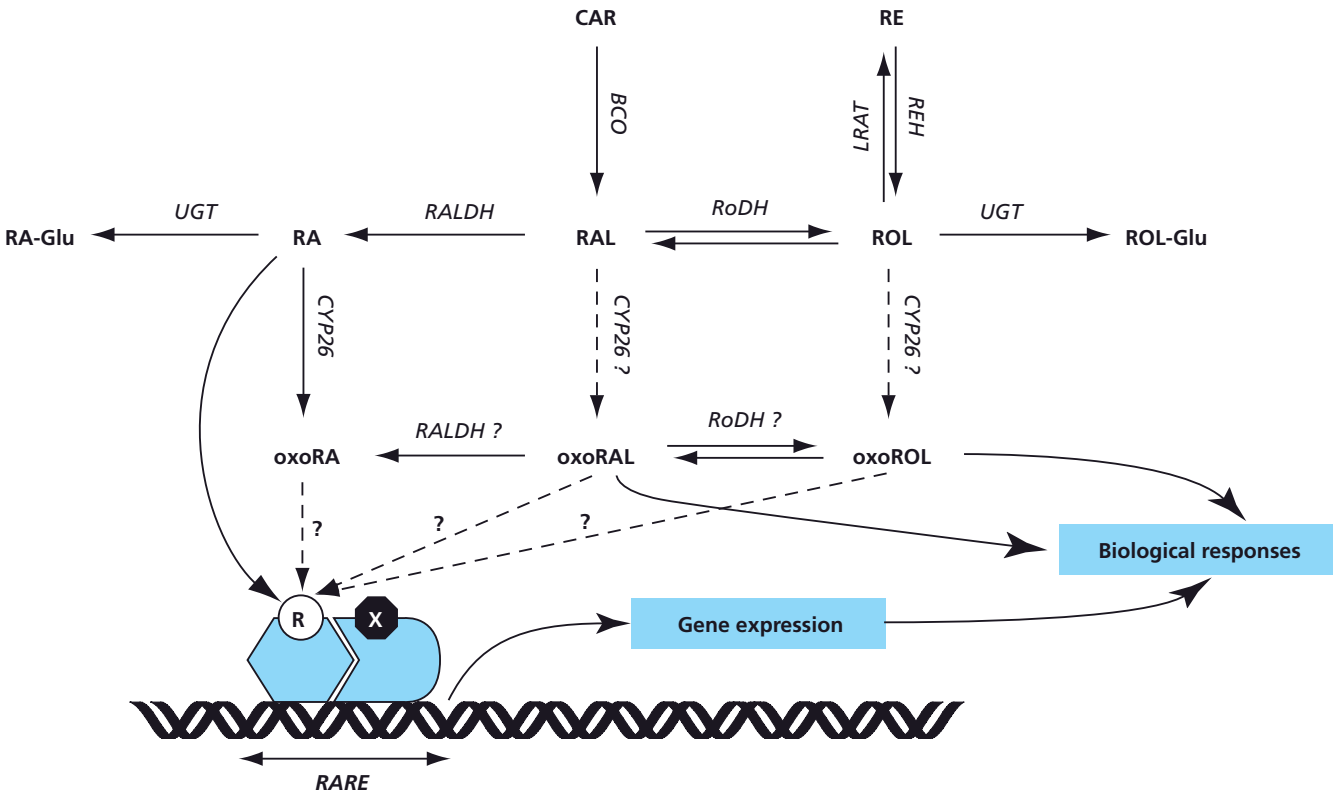

Figure 38.1 Biochemical pathways from dietary provitamins A to gene expression. BCO, beta-carotene-15,15′-monooxygenase; CAR, beta-carotene; CYP26, cytochrome P450 26; LRAT, lecithin–retinol acyltransferase; oxoRA, all-*trans*-4-oxoretinoic acid; oxoRAL, all-*trans*-4-oxoretinal; oxoROL, all-*trans*-4-oxoretinol; RA, all-*trans*-retinoic acid; RA-Glu, all-*trans*-retinoyl-β-D-glucuronide; RAL, all-*trans*-retinaldehyde; RALDH, retinal dehydrogenase; RE, retinyl esters; REH, retinyl ester hydrolase; RoDH, retinol dehydrogenase; ROL, all-*trans*-retinol; ROL-Glu, all-*trans*-retinyl-β-D-glucuronide; UGT, UDP-glucuronosyl transferase.

development of precancerous and cancerous skin lesions, as well as severe functional skin fragility now called dermatoporosis [17,18]. Many clinical studies indicate that certain structural changes induced by excessive sun exposure can be reversed, to some extent, by the use of topical retinoids [19]. Although retinoic acid is widely used for topical therapy of several skin diseases and for improvement of skin aging, it induces irritation of the skin, which precludes its long-term use to treat extrinsic or intrinsic aging.

Irritation might be explained, at least in part, by an overload of the retinoic acid-dependent pathways with supraphysiologic amounts of exogenous retinoic acid in the skin. It is still not established whether all the therapeutic activities of topical retinoids are mediated by nuclear receptors, and whether irritation is necessary for obtaining some of these activities, although most experts now consider that irritation is not mandatory for activity.

To overcome the problems encountered by topical retinoic acid, delivery can be targeted with precursors of biologically active retinoids; these "proligands" are then converted in a controlled process into active ligands [20]. This intracrine concept, in which the active ligand is produced within the targets cells, has been explored to deliver retinoid activity to mouse and human skin topically with natural retinoids such as retinaldehyde that do not bind to nuclear receptors [4,21–25]. This might be a convenient definition of cosmeceutical topical retinoids.

To validate this intracrine concept, the precursor should penetrate easily through the epidermis by topical application and be metabolized into biologically active retinoids, while the latter should be well tolerated and result in biologic effects [4,26–30]. The ranking order of retinoid-like activity following topical application is as follows: retinoic acid > retinaldehyde > retinol ≫ retinyl esters; in other words, this corresponds to the metabolic pathways: retinyl esters are hydrolyzed to retinol, which is oxidized to retinaldehyde, which is in turn oxidized to retinoic acid. However, probably for the same reason, the tolerance ranking order is the opposite: retinyl esters > retinol ≥ retinaldehyde ≫ retinoic acid.

Genomic effects

The genomic effects of topical retinoids are the consequence of the modulation of gene expression following their binding to nuclear RAR or RXR receptors. These effects most probably explain the results obtained in reversing and preventing various hallmarks of skin aging such as the activation of

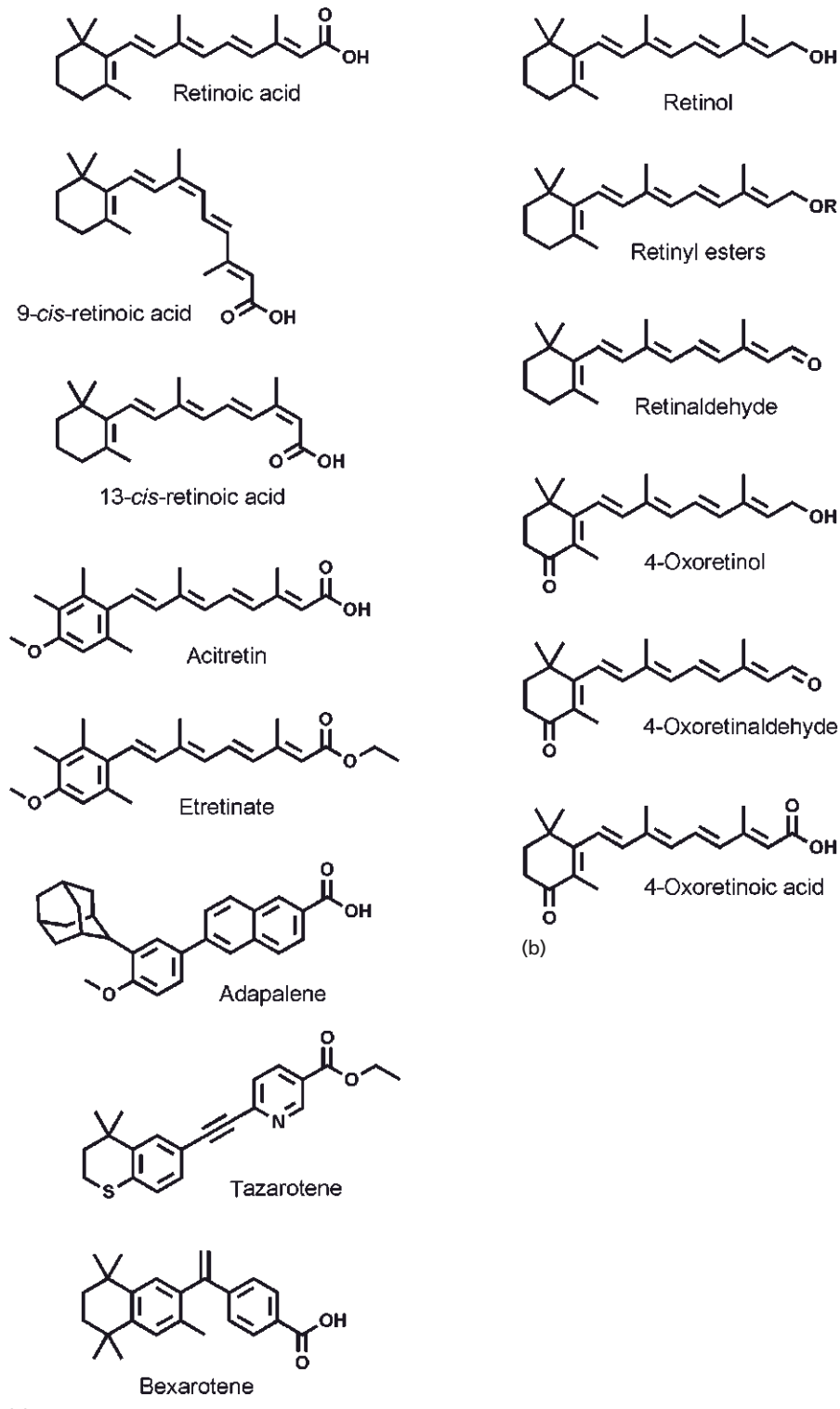

Figure 38.2 Structure of therapeutical (a) and cosmeceutical (b) retinoids. "R" in retinyl esters represents an acyl radical.

matrix metalloproteinase [31,32], oxidative stress, and the degradation of extracellular matrix [33]. In particular, retinoids are known to inhibit keratinocyte differentiation and to stimulate epidermal hyperplasia [10,34,35]. Heparin binding-epidermal growth factor (HB-EGF) activation of keratinocyte ErbB receptors via a RAR-dependent paracrine loop has been proposed to mediate retinoid-induced epidermal hyperplasia [36]. It has been shown that CD44v3, a heparan sulfate-bearing variant of CD44, which is a multifunctional polymorphic proteoglycan and principal cell surface receptor of hyaluronan (HA), recruits active matrix metalloproteinase 7, the precursor of HB-EGF (pro-HB-EGF) and one of its receptors, ErbB4, to form a complex on the surface of murine epithelial cells [37]. We have previously shown that topical application of retinaldehyde increases the expression of CD44 in mouse skin. The increased expression of CD44 accompanying epidermal hyperplasia induced by topical retinaldehyde is associated with an increase in epidermal and dermal HA and with increased expression of the HA synthases 1, 2, and 3 [38]. These observations indicate that the HA system is associated to the HB-EGF paracrine loop, with the transcriptional upregulation of CD44 and HA synthases. Thus, retinaldehyde-induced *in vitro* and *in vivo* proliferative response of keratinocytes is CD44-dependent and requires HB-EGF, its receptor ErbB1, and matrix metalloproteinases [39].

Non-genomic effects

There is some evidence that retinoids might exert a biologic activity independently of their binding to nuclear receptors [10,40], thus confirming the concept of cosmeceutical retinoids. Such indirect effects have been well documented, and clinical manifestations have been observed.

Photobiology of topical retinoids

Owing to their side chain containing multiple double bonds, retinoids strongly absorb UV light, with molar extinction coefficients of approximately 52 000 (M^{-1}/cm^{-1}) at wavelengths ranging from 325 nm for retinol to 385 nm for retinaldehyde. This property is crucial in the retina, where photoisomerization of 11-*cis*-retinaldehyde into all-*trans*-retinaldehyde is the first step in the biochemical cascade leading to the generation of nervous influx from the optic nerve to the visual cortex [41–43]. This property also enables retinoids to act as UV filters when applied topically: topical retinoids have been shown to load the skin with supraphysiologic epidermal concentrations [4,25].

For instance, topical retinyl palmitate 2% was as efficient as a commercial sunscreen with a sun protection factor of 20 to prevent UVB-induced erythema and DNA photodamage in the skin of healthy volunteers [44]. In mice, retinoic acid, retinaldehyde, retinol, and retinyl palmitate were efficient in preventing UVB-induced apoptosis and DNA photodamage [45]. The similar potencies of these retinoids indicate a physical action mediated by their spectral properties rather than a biologic action mediated by the binding to nuclear receptors. This also implies that sun exposure induces significant vitamin A depletion in the epidermis, which significance in term of photoaging has not been fully analyzed.

However, the biologic effects of photodegradation of vitamin A and other retinoids are less well understood and may be important for sun-exposed tissues, such as the skin. Exposure of retinol or its esters to UV light generates free radicals and reactive oxygen species that can damage a number of cellular targets, including proteins, lipids, and DNA [46,47]. The balance between positive, filter-like properties, and possible damage to biomolecules is difficult to assess, and might depend on several factors [48–50]. For this reason, it is still recommended to avoid UV exposure when using topical retinoids.

Antibacterial activity of retinaldehyde

Aldehydes represent an intermediate state of oxidation between alcohols and carboxylic acids [51–54]. Retinaldehyde may thus exert a direct biologic activity by reacting non-enzymatically with many biomolecules on skin surface, as well as on bacterial flora, independently of its conversion to retinoic acid and subsequent activation of nuclear receptors [55].

The putative anti-infective property of vitamin A had already been observed in the 1920s, although its mechanism of action was not understood [56]. Retinoic acid has been shown to protect dendritic cells in mice [57] and topical retinaldehyde, because of its better tolerance profile than retinoic acid, was successfully applied to a long period of time to patients with inflammatory dermatoses [27,28]. Retinaldehyde has been successfully used against Gram-positive bacteria of the cutaneous flora: 2 weeks' treatment with topical retinaldehyde 0.05% displayed a significant decrease in counts of viable *Propionibacterium acnes*, *Staphylococcus aureus*, and *Micrococcus* spp. in healthy volunteers, whereas retinaldehyde showed to be more potent than retinol and retinoic acid when assessing the minimal inhibitory concentration on various bacterial strains [58,59].

Topical cosmeceutical retinoids as antioxidants

Oxidative stress is considered to be the cornerstone of the biochemical pathways leading to both intrinsic (chronologic) and extrinsic aging (photoaging) [13,60–63]. The skin, which is exposed to environmental factors and pollutants, possesses an efficient antioxidant system able to counteract the deleterious effects of occasional oxidative stress of moderate magnitude [64,65]. However, in the case of chronic or severe oxidative stress, this endogenous antioxidant network reaches its limit and irremediable tissue damage is unavoidable [66–70]. According to the free radical theory of aging, oxidative stress increases with age, whereas during the same

time the endogenous antioxidant systems become less efficient [71–74]. It thus seems logical to provide the skin with exogenous antioxidants in order to slow the natural process of skin aging.

Retinoids have been shown to exert a free radical scavenging activity *in vitro* [75–79]. This property is most probably caused by the conjugated double bond structure of the side chain and their cyclohexenyl or aromatic moiety, rather than their ability to bind nuclear retinoid receptors, indicating that topical cosmeceutical retinoids should be as good candidates as therapeutical ones to prevent or improve skin aging. Because the endogenous antioxidants act together in a functional organized network, when supplying any organ with antioxidants, this concept should be followed; this means that if cosmeceutical retinoids have a role in the prevention or improvement of skin aging, they should be considered as partners of other topical antioxidants, rather than as a whole antioxidant system.

In mice, the peroxidation of epidermal lipids induced by topical menadione (vitamin K_3) was completely prevented by a pretreatment with either 0.25% topical α-tocopherol (vitamin E, a known efficient endogenous cutaneous antioxidant) or topical retinaldehyde 0.05% [78]. In human, topical retinol 0.075% provided a better protection of the stratum corneum against physical (UV) and chemical (sodium lauryl sulfate) threat than a cream containing α-tocopherol 1.1% [80].

Effects of topical cosmeceutical retinoids on pigmentation

It has long been observed that retinoic acid has a lightening property on human skin, and for this reason it has been used, alone or in combination with hydroquinone, to treat hyperpigmented lesions [81,82]. The mechanism of this effect is not clear. Depending on the cell culture model, retinoic acid inhibits tyrosinase activity – the rate-limiting step of melanogenesis – inhibits cell proliferation, decreases the melanin content, or has no effect on tyrosinase, melanin content, and cell growth; in particular, in monolayer cultures, there is few or no effect with retinoic acid [83–86]. This suggests that the observed *in vivo* depigmenting effect of retinoic acid, and retinoids in general, may be caused by the increased rate of epidermis "turnover" rather than to a direct effect on melanin content or melanocyte growth [86].

The best depigmenting product containing a retinoid is the formula developed by Kligman and Willis, consisting of 0.1% tretinoin (retinoic acid), 5.0% hydroquinone, and 0.1% dexamethasone, but none of its active ingredients can be used in cosmetic products. Amongst cosmeceutical retinoids, retinaldehyde, the direct precursor of retinoic acid, is well tolerated in human skin and has been shown to have several biologic effects identical to that of retinoic acid [27,28]. In the mouse tail model of depigmentation, topical retinaldehyde 0.05% showed a higher depigmenting effect than retinoic acid 0.05%, indicating that this effect of retinaldehyde was not solely a result of its bioconversion to retinoic acid, but also to a retinoid receptor-independent mechanism [87,88]. A clinical trial in which retinol 10% and lactic acid 7% replaced tretinoin 0.1% and dexamethasone 0.1% in the formula of Kligman and Willis was successfully applied to patients with hyperpigmented lesions on the face. This new formula was shown to be comparable to that of Kligman and Willis, with the advantage of preventing the steroid-induced skin atrophy [89].

Retinyl esters, in particular retinyl palmitate, are widely used in cosmetics. According to the proligand concept discussed above, in order to exert a retinoid-like activity, retinyl esters have first to be hydrolyzed to retinol, and then oxidized to retinoic acid, a process being less effective than retinol and retinaldehyde, because it requires more enzymatic steps [22,25]. If a non-genomic effect is expected, the total retinoid content of the skin would be determinant. However, very few studies aimed at assessing the penetration of retinyl esters through human skin have been reported. In hairless mice, we found that a 3-day treatment with topical retinyl palmitate 0.05% loaded the epidermis with more retinoids than topical retinol 0.05% (119 ± 4.5, 43.3 ± 6.6, and 1.5 ± 0.2 pmol/g for retinyl palmitate, retinol, and vehicle, respectively; unpublished data). Thus, retinyl esters seem to deliver the skin with more retinoids and have less genomic effects than retinol, suggesting that they should have similar depigmenting properties to retinol.

Hyaluronan as a partner for cosmeceutical retinoids

HA is the major component of the extracellular matrix and is found in high quantities in the skin. HA is a high molecular weight, non-sulfated, linear glycosaminoglycan composed of repeating units of D-glucuronic acid and *N*-acetyl-D-glucosamine linked together via alternating β-1,4 and β-1,3 glycosidic bonds. HA chains can have as much as 25 000 disaccharide repeats, corresponding to a molecular mass of approximately 8 MDa. In normal skin, HA is synthesized essentially by dermal fibroblasts and epidermal keratinocytes. Because of its negatively charged residues, HA can accommodate many water molecules, which help to maintain the normal hydration and viscoelasticity of the skin [90–92].

With increasing lifespan, the chronic cutaneous insufficiency syndrome now called dermatoporosis is becoming an emerging clinical problem with significant morbidity, which sometimes results in prolonged hospital stays [17,18,93]. Dermatoporosis is principally caused by chronologic aging and long-term and unprotected sun exposure, but may also result from the chronic use of topical and systemic corticosteroids. Experimental evidence suggests that defective function of CD44, a transmembrane glycoprotein that acts as the main cell surface HA receptor, and the corresponding impaired HA metabolism, are implicated in the pathogenesis

of dermatoporosis, and may be a target for intervention [94]. Cleavage of the high molecular weight HA polymer during tissue remodeling gives rise to lower molecular weight fragments that elicit a variety of CD44-mediated cellular responses, including proliferation, migration, HA synhesis, and cytokine synthesis [91,92]. The cellular responses elicited by topical application of HA, and specifically HA synthesis by keratinocytes, depend on the size of the HA oligosaccharides [95,96].

Topical retinoids are known to stimulate epidermal hyperplasia through the activation of a RAR-dependent HB-EGF paracrine loop [36,97]. HA production is also selectively stimulated by retinoids in mouse and human skin [98,99]. In mouse skin, topical retinaldehyde increases HA content, the expression of CD44 and HA synthases [38], and prevents UV-induced depletion of HA and CD44, an effect also observed with topical retinol and retinoic acid, although to a lesser extent [100]. In humans, topical retinaldehyde has been shown to restore the epidermal thickness and CD44 expression in lichen sclerosus and atrophic lesions [101]. The proliferative response of keratinocytes elicited by either retinaldehyde or intermediate size HA fragments (HAFi) is dependent of CD44 and requires the presence of HB-EGF, its receptor ErbB1, as well as matrix metalloproteinase-7 (MMP-7) [39,102]. In particular, topical application of HAFi in combination with retinaldehyde caused epidermal hyperplasia by specifically stimulating the CD44 platform molecules in the keratinocytes and increased the HA content of epidermis and dermis [103]. Thus, topical retinoids, in particular retinaldehyde, can restore epidermal functions by stimulating HA synthesis and biologic functions.

Specific profiles of cosmeceutical retinoids

Retinol and retinyl esters

Retinol and retinyl esters (mostly retinyl palmitate) have been incorporated into many skin products. Theoretically, these topical endogenous retinoids, which are natural precursors of cutaneous retinaldehyde and retinoic acids [104–106], could also be useful in treating skin conditions for which retinoic acid is active. However, although retinol is widely used in cosmetic formulations to improve photoaging, topical retinol has not been demonstrated to be effective to treat any skin condition, maybe because of its slow oxidation into retinaldehyde and retinoic acid [107]. It seems that the retinol concentrations required to induce a measurable biologic action similar to that of retinoic acid (0.05%) induce a similar irritant dermatitis [89]. Thus, to avoid high concentrations of retinol or retinyl esters in topical formulation, the best way would be to combine them at moderate concentrations with other topical agents such as tocopherols, ascorbate and derivatives, flavonoids, or other biologic antioxidants [108–110].

Another useful property of retinol is its absorption spectrum: it absorbs UV light in shorter wavelengths (325 nm) than retinaldehyde (385 nm) and retinoic acid (345 nm). Therefore, topical retinol could be useful as a filter partner of many cosmetic and cosmeceutical products in the most biologically active solar UV range (290–320 nm), while delivering small amounts of retinoic acid on a relatively long period of time [44,45]. This can be expanded to retinyl esters, which have the same UV spectrum as retinol, have the better tolerance profile among topical retinoids, while being the weaker retinoic acid precursors [22].

Retinaldehyde

Retinaldehyde is much less irritant than retinoic acid, which explains its good compliance, and has been shown to be well tolerated and effective in treating photoaging for long periods of time: in particular, retinaldehyde produced significant improvement in fine and deep wrinkles [28,111]. Retinaldehyde does not bind to nuclear retinoid receptors and selectively delivers low concentrations of retinoic acid at the cellular level [27,97]; this prevents an excess of retinoic acid in the skin, a condition that contributes to cutaneous irritation [4,20] and confers to retinaldehyde the required properties for the intracrine concept discussed above [20].

The association of retinaldehyde and δ-tocopherylglucopyranoside, a vitamin E precursor, improved the protection against the generation of free radicals – a condition leading to aging – as well as the skin elasticity [112]. Retinaldehyde, which possesses an aldehyde functional group, exerts direct receptor-independent biologic actions not shared by other retinoids. This explains the usefulness of topical retinaldehyde 0.05% against *P. acnes* and *Staphylococcus* spp. [58,59]. Retinaldehyde shares with other retinoids a high absorption power in the UVA range, and may decrease the fluence received in this window significantly [45]. Compared with other retinoids, retinaldehyde loads the skin with natural retinoids very efficiently, probably because of its better penetration profile through the skin, and its ability to be reduced to retinol or oxidized to retinoic acid very rapidly [105,113–116]. Retinaldehyde has been shown to reduce the pigmentation when applied to the skin for a couple of weeks or longer; this could be due in part to a melanosomal dilution resulting from an increase of epidermal turnover, an effect attributable to its conversion to retinoic acid. The depigmenting property of retinaldehyde could also be due to its antioxidant power, because the production of small quantities of hydrogen peroxide has been considered to be an essential step of the melanogenesis [117]. Indeed, topical retinaldehyde 0.05% decreases the melanin content by 80% and the density of active melanocytes by 75% in mouse tail skin, whereas an application of retinaldehyde 0.01% to guinea pig ear skin decreases epidermal melanin by 50% and the density of active melanocytes by 40% (unpublished data). Owing to these properties,

retinaldehyde should be considered as a key partner in topical depigmenting preparations.

4-Oxoretinoids

According to Achkar *et al*. [7] and Blumberg *et al*. [8], 4-oxoretinol and 4-oxoretinaldehyde, the least known of endogenous retinoids, exert morphogenic properties and are able to bind and transactivate RARs *in vitro*. In a mouse model of retinoid activity, topical 4-oxoretinaldehyde 0.05% induced a moderate retinoid-like activity compared with topical retinoic acid 0.05%, as assessed by:

1 Epidermal hyperplasia and metaplasia;
2 Cutaneous inflammation (myeloperoxidase activity); and
3 Depigmentation of the tail.

Topical 4-oxoretinol 0.05% was also active, albeit to a lesser extend. Parallel to the action of these 4-oxoretinoids, no retinoic acid could be detected in the skin, indicating that 4-oxoretinoids exerted a direct biologic activity, which was not due to their bioconversion to their non-oxo counterparts [10]. This confirms the *in vitro* studies mentioned above [7,8], which demonstrated a direct biologic action of 4-oxoretinol and 4-oxoretinal, and suggests a potential benefits for their use as cosmeceuticals.

In another study, the 4-oxoderivatives of the biologically active all-*trans*-, 9-*cis*- and 13-*cis*-retinoic acids (although 13-*cis*-retinoic acid does not bind to retinoid receptors) have been shown to display strong and isomer-specific transcriptional regulatory activities in human keratinocytes and fibroblasts *in vitro* [118]. These data revive the interest for these oxidative metabolites of endogenous retinoids. Appropriate clinical trials should be performed to determine whether it is possible to use these the 4-oxoderivatives topically at high concentrations to obtain a better response than retinol and its esters, while retaining a good tolerance. Pilot studies in humans already indicate a good tolerance of 4-oxoretinaldehyde 0.5% (unpublished personal observations). Establishing the spectrum of potential activity of topical 4-oxoderivatives, especially on the pigmentary system also deserves specific clinical trials.

Association with topical hyaluronan fragments

The molecular mechanisms underlying retinoid-induced epidermal hyperplasia are closely related to CD44-dependent pathways in keratinocytes. It is well demonstrated that retinoids synergize with the activities of HAFi on cell renewal and *de novo* HA synthesis [38,103,119]. Accordingly, the topical application of HAFi was found to have repairing action in dermatoporosis [102]. Therefore the combination of HAFi with a retinoid is highly promising as preventive treatment in early phases of dermatoporosis.

High molecular weight HA, which do not show the topical activities of HAFi, has been widely used in cosmetic preparations [120]. Application of high molecular weight HA-containing cosmetic products to the skin is reported to moisturize and restore elasticity [121]. HA-based cosmetic formulations or sunscreens may also be capable of protecting the skin against UV irradiation due to the antioxidant properties of HA [122]. In almost all of these cosmetic formulations, the HA is associated with retinol. Scientific proof that the association of any topical retinoids with high molecular weight HA has some specific synergizing effect is currently lacking.

References

1 Castenmiller JJM, West CE. (1998) Bioavailability and bioconversion of carotenoids. *Annu Rev Nutr* **18**, 19–38.
2 Roos TC, Jugert FK, Merk HF, Bickers DR. (1998) Retinoid metabolism in the skin. *Pharmacol Rev* **50**, 315–33.
3 Sorg O, Antille C, Kaya G, Saurat JH. (2006) Retinoids in cosmeceuticals. *Dermatol Ther* **19**, 289–96.
4 Saurat JH, Sorg O, Didierjean J. (1999) New concepts for delivery of topical retinoid activity to human skin. In: Nau H, Blaner WS, eds. *Retinoids. The Biochemical and Molecular Basis of Vitamin A and Retinoid Action*. Berlin: Springer-Verlag, pp. 521–38.
5 Sass JO, Forster A, Bock KW, Nau H. (1994) Glucuronidation and isomerization of all-*trans*- and 13-*cis*-retinoic acid by liver microsomes of phenobarbital- or 3-methylcholanthrene-treated rats. *Biochem Pharmacol* **47**, 485–92.
6 Taimi M, Helvig C, Wisniewski J, Ramshaw H, White J, Amad M, *et al.* (2004) A novel human cytochrome P450, CYP26C1, involved in metabolism of 9-*cis* and all-*trans* isomers of retinoic acid. *J Biol Chem* **279**, 77–85.
7 Achkar CC, Derguini F, Blumberg B, Levin AA, Speck J, Adams RM, *et al.* (1996) 4-Oxoretinol, a new natural ligand and transactivator of the retinoic acid receptors. *Proc Natl Acad Sci U S A* **93**, 4879–84.
8 Blumberg B, Bolado J Jr, Derguini F, Craig AG, Moreno TA, Chakravarti D, *et al.* (1996) Novel retinoic acid receptor ligands in *Xenopus* embryos. *Proc Natl Acad Sci U S A* **93**, 4873–8.
9 Ross SA, De Luca LM. (1996) A new metabolite of retinol: all-*trans*-4-oxo-retinol as a receptor activator and differentiation agent. *Nutr Rev* **54**, 355–6.
10 Sorg O, Tran C, Carraux P, Grand D, Barraclough C, Arrighi JF, *et al.* (2008) Metabolism and biological activities of topical 4-oxoretinoids in mouse skin. *J Invest Dermatol* **128**, 999–1008.
11 Fisher GJ, Voorhees JJ. (1996) Molecular mechanisms of retinoid actions in skin. *FASEB J* **10**, 1002–13.
12 Napoli JL. (1996) Retinoic acid biosynthesis and metabolism. *FASEB J* **10**, 993–1001.
13 Sorg O, Antille C, Saurat JH. (2004) Retinoids, other topical vitamins, and antioxidants. In: Rigel DS, Weiss RS, Lim HW, *et al*., eds. *Photoaging*. New York: Marcel Dekker, pp. 89–115.
14 Dawson MI. (2004) Synthetic retinoids and their nuclear receptors. *Curr Med Chem Anticancer Agents* **4**, 199–230.
15 Sorg O, Kuenzli S, Saurat JH. (2007) Side effects and pitfalls in retinoid therapy. In: Vahlquist A, Duvic M, eds. *Retinoids and Carotenoids in Dermatology*. New York: Informa Healthcare, pp. 225–48.
16 Kuenzli S, Saurat JH. (2003) Retinoids. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. London: Mosby, pp. 1991–2006.

17 Kaya G, Saurat JH. (2007) Dermatoporosis: a chronic cutaneous insufficiency/fragility syndrome: clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology* **215**, 284–94.

18 Saurat JH. (2007) Dermatoporosis: the functional side of skin aging. *Dermatology* **215**, 271–2.

19 Stratigos AJ, Katsambas AD. (2005) The role of topical retinoids in the treatment of photoaging. *Drugs* **65**, 1061–172.

20 Saurat JH, Sorg O. (1999) Topical natural retinoids: the "proligand-non-ligand" concept. *Dermatology* **199** (Suppl), 1–2.

21 Duell EA, Derguini F, Kang S, Elder JT, Voorhees JH. (1996) Extraction of human epidermis treated with retinol yields retro-retinoids in addition to free retinol and retinyl esters. *J Invest Dermatol* **107**, 178–82.

22 Duell EA, Kang S, Voorhees JJ. (1997) Unoccluded retinol penetrates human skin *in vivo* more effectively than unoccluded retinyl palmitate or retinoic acid. *J Invest Dermatol* **109**, 301–5.

23 Schaefer H. (1993) Penetration and percutaneous absorption of topical retinoids. *Skin Pharmacol* **6** (Suppl. 1), 17–23.

24 Tran C, Kasraee B, Grand D, Carraux P, Didierjean L, Sorg O, *et al.* (2005) Pharmacology of RALGA, a mixture of retinaldehyde and glycolic acid. *Dermatology* **210** (Suppl. 1), 6–13.

25 Tran C, Sorg O, Carraux P, Didierjean L, Seurat JH. (2001) Topical delivery of retinoids counteracts the UVB-induced epidermal vitamin A depletion in hairless mouse. *Photochem Photobiol* **73**, 425–31.

26 Didierjean L, Sass JO, Carraux P, Grand D, Sorg O, Plum C, *et al.* (1999) Topical 9-*cis*-retinaldehyde for delivery of 9-*cis*-retinoic acid in mouse skin. *Exp Dermatol* **8**, 199–203.

27 Didierjean L, Tran C, Sorg O, Seurat JH. (1999) Biological activities of topical natural retinaldehyde. *Dermatology* **199** (Suppl), 19–24.

28 Saurat JH, Didierjean L, Masgrau E, Piletta PA, Jaconi S, Chatellard-Gruaz D, *et al.* (1994) Topical retinaldehyde on human skin: biological effects and tolerance. *J Invest Dermatol* **103**, 770–4.

29 Kang S, Duell EA, Fisher GJ, Datta SC, Wang ZQ, Reddy AP, *et al.* (1995) Application of retinol to human skin *in vivo* induces epidermal hyperplasia and cellular retinoid binding proteins characteristics of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol* **105**, 549–56.

30 Kurlandsky SB, Xiao JH, Duell EA, Voorhees JJ, Fisher GJ. (1994) Biological activity of all-*trans* retinol requires metabolic conversion to all-*trans* retinoic acid and is mediated through activation of nuclear retinoid receptors in human keratinocytes. *J Biol Chem* **269**, 32821–7.

31 Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, *et al.* (1996) Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* **379**, 335–9.

32 Fisher GJ, Wang ZQ, Datta SC, Varani J, Wang S, Voorhees JJ. (1997) Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* **337**, 1419–28.

33 Griffiths CE, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. (1993) Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med* **329**, 530–5.

34 Ponec M, Weerheim A, Havekes L, Boonstra J. (1987) Effects of retinoids on differentiation, lipid metabolism, epidermal growth factor, and low-density lipoprotein binding in squamous carcinoma cells. *Exp Cell Res* **171**, 426–35.

35 Saurat JH. (1988) How do retinoids work on human epidermis? A breakthrough and its implications. *Clin Exp Dermatol* **13**, 350–64.

36 Xiao JH, Feng X, Di W, Peng ZH, Li LA, Chambon P, *et al.* (1999) Identification of heparin-binding EGF-like growth factor as a target in intercellular regulation of epidermal basal cell growth by suprabasal retinoic acid receptors. *EMBO J* **18**, 1539–48.

37 Yu WH, Woessner JF Jr, McNeish JD, Stamenkovic I. (2002) CD44 anchors the assembly of matrilysin/MMP-7 with heparin-binding epidermal growth factor precursor and ErbB4 and regulates female reproductive organ remodeling. *Genes Dev* **16**, 307–23.

38 Kaya G, Grand D, Hotz R, Augsburger E, Carraux P, Didierjean L, *et al.* (2005) Upregulation of CD44 and hyaluronate synthase by topical retinoids in mouse skin. *J Invest Dermatol* **124**, 284–7.

39 Kaya G, Tran C, Sorg O, *et al.* (2005) Retinaldehyde-induced epidermal hyperplasia via heparin binding epidermal growth factor is CD44-dependent. *J Invest Dermatol* **124**, A32.

40 Clifford JL, Menter DG, Wang M, Lotan R, Lippman SM. (1999) Retinoid receptor-dependent and -independent effects of *N*-(4-hydroxyphenyl)retinamide in F9 embryonal carcinoma cells. *Cancer Res* **59**, 14–8.

41 Nakanishi K. (2000) Recent bioorganic studies on rhodopsin and visual transduction. *Chem Pharm Bull (Tokyo)* **48**, 1399–409.

42 Blomhoff R, Blomhoff HK. (2006) Overview of retinoid metabolism and function. *J Neurobiol* **66**, 606–30.

43 Schoenlein RW, Peteanu LA, Mathies RA, Shank CV. (1991) The first step in vision: femtosecond isomerization of rhodopsin. *Science* **254**, 412–5.

44 Antille C, Tran C, Sorg O, Carraux P, Didierjean L, Saurat JH. (2003) Vitamin A exerts a photoprotective action in skin by absorbing UVB radiations. *J Invest Dermatol* **121**, 1163–7.

45 Sorg O, Tran C, Carraux P, Grand D, Hügin A, Didierjean L, *et al.* (2005) Spectral properties of topical retinoids prevent DNA damage and apoptosis after acute UVB exposure in hairless mice. *Photochem Photobiol* **81**, 830–6.

46 Fu PP, Xia Q, Yin JJ, Cherng SH, Yan J, Mei N, *et al.* (2007) Photodecomposition of vitamin A and photobiological implications for the skin. *Photochem Photobiol* **83**, 409–24.

47 Dillon J, Gaillard ER, Bilski P, Chignell CF, Reszka KJ. (1996) The photochemistry of the retinoids as studied by steady-state and pulsed methods. *Photochem Photobiol* **63**, 680–5.

48 Ferguson J, Johnson BE. (1989) Retinoid associated phototoxicity and photosensitivity. *Pharmacol Ther* **40**, 123–35.

49 Fu PP, Cheng SH, Coop L, Xia O, Culp SJ, Tolleson WH, *et al.* (2003) Photoreaction, phototoxicity, and photocarcinogenicity of retinoids. *J Environ Sci Health Part C Environ Carcinog Ecotoxicol Rev* **21**, 165–97.

50 Kligman LH. (1987) Retinoic acid and photocarcinogenesis: a controversy. *Photodermatol* **4**, 88–101.

51 Becker TW, Krieger G, Witte I. (1996) DNA single and double strand breaks induced by aliphatic and aromatic aldehydes in combination with copper (II). *Free Radic Res* **24**, 325–32.

52 Witz G. (1989) Biological interactions of alpha,beta-unsaturated aldehydes. *Free Radic Biol Med* **7**, 333–49.

53 Esterbauer H, Schaur RJ, Zollner H. (1991) Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic Biol Med* **11**, 81–128.

54 Feron VJ, Til HP, de Vrijer F, Wouterson RA, Cassee FR, van Bladeren PJ. (1991) Aldehydes: occurrence, carcinogenic potential, mechanism of action and risk assessment. *Mutat Res* **259**, 363–85.

55 Ambroziak W, Izaguirre G, Pietruszko R. (1999) Metabolism of retinaldehyde and other aldehydes in soluble extracts of human liver and kidney. *J Biol Chem* **274**, 33366–73.

56 Green HN, Mellanby E. (1928) Vitamin A as an anti-infective agent. *Br Med J* **2**, 691–6.

57 Halliday GM, Ho KKL, Barnetson RSC. (1992) Regulation of the skin immune system by retinoids during carcinogenesis. *J Invest Dermatol* **99**, 83S–6S.

58 Péchère M, Germanier L, Siegenthaler G, Péchère JC, Saurat JH. (2002) The antibacterial activity of topical retinoids: the case of retinaldehyde. *Dermatology* **205**, 153–8.

59 Péchère M, Péchère JC, Siegenthaler G, Germanier L, Saurat JH. (1999) Antibacterial activity of retinaldehyde against *Propionibacterium acnes*. *Dermatology* **199** (Suppl 1), 29–31.

60 Wenk J, Brenneisen P, Meewes C, Wlaschek M, Peters T, Blauschun R, *et al.* (2001) UV-induced oxidative stress and photoaging. *Curr Probl Dermatol* **29**, 83–94.

61 Yaar M, Gilchrest BA. (1998) Aging versus photoaging: postulated mechanisms and effectors. *J Investig Dermatol Symp Proc* **3**, 47–51.

62 Pinnell SR. (2003) Cutaneous photodamage, oxidative stress, and topical antioxidant protection. *J Am Acad Dermatol* **48**, 1–19; quiz 20–2.

63 Nishigori C, Hattori Y, Arima Y, Miyachi Y. (2003) Photoaging and oxidative stress. *Exp Dermatol* **12**, 18–21.

64 Sies H, Stahl W. (2004) Nutritional protection against skin damage from sunlight. *Annu Rev Nutr* **24**, 173–200.

65 Thiele JJ, Schroeter C, Hsieh SN, Podda M, Packer L. (2001) The antioxidant network of the stratum corneum. *Curr Probl Dermatol* **29**, 26–42.

66 Halliwell B. (1994) Free radicals and antioxidants: a personal view. *Nutr Rev* **52**, 253–65.

67 Jacob RA, Burri BJ. (1996) Oxidative damage and defense. *Am J Clin Nutr* **63**, 985S–90S.

68 Kohen R, Gati I. (2000) Skin low molecular weight antioxidants and their role in aging and in oxidative stress. *Toxicology* **148**, 149–57.

69 Sorg O. (2004) Oxidative stress: a theoretical model or a biological reality? *C R Biol* **327**, 649–62.

70 Halliwell B, Gutteridge JMC. (1999) *Free Radicals in Biology and Medicine*, 3th edn. Oxford: Oxford University Press.

71 Berr C. (2000) Cognitive impairment and oxidative stress in the elderly: results of epidemiological studies. *Biofactors* **13**, 205–9.

72 Barja G. (2004) Free radicals and aging. *Trends Neurosci* **27**, 595–600.

73 Harman D. (2001) Aging: overview. *Ann N Y Acad Sci* **928**, 1–21.

74 Crastes de Paulet A. (1990) Free radicals and aging. *Ann Biol Clin* **48**, 323–30.

75 Singh DK, Lippman SM. (1998) Cancer chemoprevention. Part 1: Retinoids and carotenoids and other classic antioxidants. *Oncology (Williston Park)* **12**, 1643–53, 57–8; discussion 59–60.

76 Tsuchiya M, Scita G, Freisleben HJ, Kagan VE, Packer L. (1992) Antioxidant radical-scavenging activity of carotenoids and retinoids compared to alpha-tocopherol. *Methods Enzymol* **213**, 460–72.

77 Tesoriere L, D'Arpa D, Re R, Livrea MA. (1997) Antioxidant reactions of all-*trans* retinol in phospholipid bilayers: effect of oxygen partial pressure, radical fluxes, and retinol concentration. *Arch Biochem Biophys* **343**, 13–8.

78 Sorg O, Tran C, Saurat JH. (2001) Cutaneous vitamins A and E in the context of ultraviolet or chemically induced oxidative stress. *Skin Pharmacol Appl Skin Physiol* **14**, 363–72.

79 Sorg O, Kuenzli S, Kaya G, Saurat JH. (2005) Proposed mechanisms of action for retinoid derivatives in the treatment of skin ageing. *J Cosmet Dermatol* **4**, 237–44.

80 Goffin V, Henry F, Piérard-Franchimont C, Piérard GE. (1997) Topical retinol and the stratum corneum response to an environmental threat. *Skin Pharmacol* **10**, 85–9.

81 Kligman AM, Willis I. (1975) A new formula for depigmenting human skin. *Arch Dermatol* **111**, 40–8.

82 Griffiths CE, Finkel LJ, Ditre CM, Hamilton TA, Ellis CN, Voorhees JJ. (1993) Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* **129**, 415–21.

83 Hoal E, Wilson EL, Dowdle EB. (1982) Variable effects of retinoids on two pigmenting human melanoma cell lines. *Cancer Res* **42**, 5191–5.

84 Edward M, Gold JA, MacKie RM. (1988) Different susceptibilities of melanoma cells to retinoic acid-induced changes in melanotic expression. *Biochem Biophys Res Commun* **155**, 773–8.

85 Fligiel SE, Inman DR, Talwar HS, Fisher GJ, Voorhees JJ, Varani J. (1992) Modulation of growth in normal and malignant melanocytic cells by all-*trans* retinoic acid. *J Cutan Pathol* **19**, 27–33.

86 Yoshimura K, Tsukamoto K, Okazaki M, Virador VM, Lei TC, Suzuki Y, *et al.* (2001) Effects of all-*trans* retinoic acid on melanogenesis in pigmented skin equivalents and monolayer culture of melanocytes. *J Dermatol Sci* **27** (Suppl 1), S68–75.

87 Kasraee B, Tran C, Sorg O, Saurat JH. (2005) The depigmenting effect of RALGA in C57BL/6 mice. *Dermatology* **210** (Suppl 1), 30–4.

88 Ortonne JP. (2006) Retinoid therapy of pigmentary disorders. *Dermatol Ther* **19**, 280–8.

89 Yoshimura K, Momosawa A, Aiba E, Sato K, Matsumoto D, Mitoma Y, *et al.* (2003) Clinical trial of bleaching treatment with 10% all-*trans* retinol gel. *Dermatol Surg* **29**, 155–60.

90 Fraser JR, Laurent TC. (1989) Turnover and metabolism of hyaluronan. *Ciba Found Symp* **143**, 41–59.

91 Laurent TC. (1987) Biochemistry of hyaluronan. *Acta Otolaryngol Suppl* **442**, 7–24.

92 Laurent TC, Fraser JR. (1992) Hyaluronan. *FASEB J* **6**, 2397–404.

93 Kaya G, Jacobs F, Prins C, Viero D, Kaya A, Saurat JH. (2008) Deep dissecting hematoma: an emerging severe complication of dermatoporosis. *Arch Dermatol* **144**, 1303–8.

94 Kaya G, Rodriguez I, Jorcano JL, Vassalli P, Stamenkovic I. (1997) Selective suppression of CD44 in keratinocytes of mice bearing an antisense CD44 transgene driven by a tissue-specific promoter disrupts hyaluronate metabolism in the skin and impairs keratinocyte proliferation. *Genes Dev* **11**, 996–1007.

95 Forrester JV, Balazs EA. (1980) Inhibition of phagocytosis by high molecular weight hyaluronate. *Immunology* **40**, 435–46.

96 West DC, Hampson IN, Arnold F, Kumar S. (1985) Angiogenesis induced by degradation products of hyaluronic acid. *Science* **228**, 1324–6.

97 Didierjean L, Carraux P, Grand D, Sass JO, Nau S, Saurat JH. (1996) Topical retinaldehyde increases skin content of retinoic acid and exerts biological activity in mouse skin. *J Invest Dermatol* **107**, 714–9.

98 Margelin D, Medaisko C, Lombard D, Picard J, Fourtanier A. (1996) Hyaluronic acid and dermatan sulfate are selectively stimulated by retinoic acid in irradiated and nonirradiated hairless mouse skin. *J Invest Dermatol* **106**, 505–9.

99 Tammi R, Ripellino JA, Margolis RU, Maibach HI, Tammi M. (1989) Hyaluronate accumulation in human epidermis treated with retinoic acid in skin organ culture. *J Invest Dermatol* **92**, 326–32.

100 Calikoglu E, Sorg O, Tran C, Grand D, Carraux P, Saurat JH, *et al.* (2006) UVA and UVB decrease the expression of CD44 and hyaluronate in mouse epidermis which is counteracted by topical retinoids. *Photochem Photobiol* **82**, 1342–7.

101 Kaya G, Saurat JH. (2005) Restored epidermal CD44 expression in lichen sclerosus et atrophicus and clinical improvement with topical application of retinaldehyde. *Br J Dermatol* **152**, 570–2.

102 Kaya G, Tran C, Sorg O, Hotz R, Grand D, Carraux P, *et al.* (2006) Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med* **3**, e493.

103 Kaya G, Tran C, Sorg O, *et al.* (2006) Synergistic effect of retinaldehyde and hyaluronate fragments in skin hyperplasia. *J Invest Dermatol* **126**, 33.

104 Bailly J, Crettaz M, Schifflers MH, Marty JP. (1998) *In vitro* metabolism by human skin and fibroblasts of retinol, retinal and retinoic acid. *Exp Dermatol* **7**, 27–34.

105 Siegenthaler G, Saurat JH, Ponec M. (1990) Retinol and retinal metabolism: relationship to the state of differentiation of cultured human keratinocytes. *Biochem J* **268**, 371–8.

106 Boehnlein J, Sakr A, Lichtin JL, Bronaugh RL. (1994) Characterization of esterase and alcohol dehydrogenase activity in skin: metabolism of retinyl palmitate to retinol (vitamin A) during percutaneous absorption. *Pharm Res* **11**, 1155–9.

107 Connor MJ. (1988) Oxidation of retinol to retinoic acid as a requirement for biological activity in mouse epidermis. *Cancer Res* **48**, 7038–40.

108 Bruce S. (2008) Cosmeceuticals for the attenuation of extrinsic and intrinsic dermal aging. *J Drugs Dermatol* **7**, S17–22.

109 Burgess C. (2008) Topical vitamins. *J Drugs Dermatol* **7**, S2–6.

110 Picardo M, Carrera M. (2007) New and experimental treatments of cloasma and other hypermelanoses. *Dermatol Clin* **25**, 353–62.

111 Creidi P, Vienne MP, Ochonisky S, Lauze C, Turlier V, Lagarde JM, *et al.* (1998) Profilometric evaluation of photodamage after topical retinaldehyde and retinoic acid treatment. *J Am Acad Dermatol* **39**, 960–5.

112 Boisnic S, Branchet-Gumila MC, Nocera T. (2005) Comparative study of the anti-aging effect of retinaldehyde alone or associated with pretocopheryl in a surviving human skin model submitted to ultraviolet A and B irradiation. *Int J Tissue React* **27**, 91–9.

113 Kishore GS, Boutwell RK. (1980) Enzymatic oxidation and reduction of retinal by mouse epidermis. *Biochem Biophys Res Commun* **94**, 1381–6.

114 Napoli JL, Race KR. (1988) Biogenesis of retinoic acid from beta-carotene. *J Biol Chem* **263**, 17372–7.

115 Raner GM, Vaz AD, Coon MJ. (1996) Metabolism of all-*trans*, 9-*cis*, and 13-*cis* isomers of retinal by purified isozymes of microsomal cytochrome P450 and mechanism-based inhibition of retinoid oxidation by citral. *Mol Pharmacol* **49**, 515–22.

116 Sorg O, Didierjean L, Saurat JH. (1999) Metabolism of topical natural retinoids. *Dermatology* **199** (Suppl), 13–7.

117 Kasraee B. (2002) Peroxidase-mediated mechanisms are involved in the melanocytotoxic and melanogenesis-inhibiting effects of chemical agents. *Dermatology* **205**, 329–39.

118 Baron JM, Heise R, Blaner WS, Neis M, Joussen S, Dreuw A, *et al.* (2005) Retinoic acid and its 4-oxo metabolites are functionally active in human skin cells *in vitro*. *J Invest Dermatol* **125**, 143–53.

119 Tammi R, Pasonen-Seppanen S, Kolehmainen E, Tammi M. (2005) Hyaluronan synthase induction and hyaluronan accumulation in mouse epidermis following skin injury. *J Invest Dermatol* **124**, 898–905.

120 Manuskiatti W, Maibach HI. (1996) Hyaluronic acid and skin: wound healing and aging. *Int J Dermatol* **35**, 539–44.

121 Brown MB, Jones SA. (2005) Hyaluronic acid: a unique topical vehicle for the localized delivery of drugs to the skin. *J Eur Acad Dermatol Venereol* **19**, 308–18.

122 Trommer H, Wartewig S, Bottcher R, Pöppl J, Hoentsch J, Ozegowski JH, *et al.* (2003) The effects of hyaluronan and its fragments on lipid models exposed to UV irradiation. *Int J Pharm* **254**, 223–34.

Chapter 39: Topical vitamins

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BASIC CONCEPTS

- Vitamins are commonly used as active agents in skincare products designed to improve skin appearance.
- The antioxidant vitamins A, C, and E can be safely applied topically.
- Niacinamide (vitamin B_3) and panthenol (vitamin B_5) are of the vitamin B family used in moisturizers to improve skin appearance.
- Careful formulation is required with vitamins to prevent loss of activity through photoinactivation or premature oxidation.

Introduction

Vitamins are organic compounds required in small quantities for normal function and typically obtained from the diet. Many materials are described as vitamins [1]. Some of them have been used in topical cosmetic products, and certainly there is rationale for such use. Because they are essential nutrients, a few of them in a wide array of biochemical processes, they certainly have potential to have beneficial effects across a wide spectrum of skin problems. Also, because they are well studied because of their importance in nutrition, their mechanisms and toxicology are well understood. Additionally, with topical application and subsequent delivery into skin, they are more likely to have local meaningful effects vs. oral intake and the consequent limited delivery via the circulation to the skin site of interest (e.g. facial skin).

Because there are so many vitamins, this review is necessarily selective, focusing on a few, with particular emphasis on those materials for which there is available well-controlled *in vivo* studies to illustrate skincare effects.

Vitamin A

Forms

Several forms of vitamin A are used cosmetically, the most widely utilized ones being retinol, retinyl esters (e.g. retinyl acetate, retinyl propionate, and retinyl palmitate), and retinaldehyde. Through endogenous enzymatic reactions, all are converted ultimately to *trans*-retinoic acid, the active form of vitamin A in skin. Specifically, retinyl esters are converted to retinol via esterase activity. Retinol is then converted to retinaldehyde by retinol dehydrogenase. Finally, retinaldehyde is oxidized to retinoic acid by retinaldehyde oxidase (Figure 39.1).

Mechanisms

Because *trans*-retinoic acid (RA) is the active form of vitamin A in skin, the abundant published literature on the former is applicable to this discussion. RA interacts with nuclear receptor proteins described as retinoic acid receptors (RAR) and retinoid X receptors (RXR), which can form heterodimer complexes. These complexes then interact with specific DNA sequences to affect transcription, to either increase or decrease expression of specific proteins and/or enzymes [2].

Using genomic methodology, work in our laboratories has found that the expression of over 1200 genes is significantly affected by topical retinoid treatment of photoaged human skin (unpublished observations). Many of these changes can be ascribed, at least on some level, as being normalization of the altered skin conditions that occur with aging (induced by both chronologic and environmental influences such as chronic sun exposure). Some specific changes induced by retinoid that are likely relevant to skin antiwrinkle appearance effects are those that result in thicker skin to diminish the appearance of fine lines and wrinkles; for example, increased epidermal proliferation and differentiation (increased epidermal thickness), increased production of epidermal ground substance (glycosaminoglycans [GAGs] which bind water, increasing epidermal hydration and thickness), and increased dermal production of extracellular matrix components such as collagen (increased dermal thickness).

In addition to stimulation of events in skin, retinoids also have an inhibitory effect on other tissue components. For example, retinoids are reported to inhibit production of collagenase. Retinoid will stimulate production of ground

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

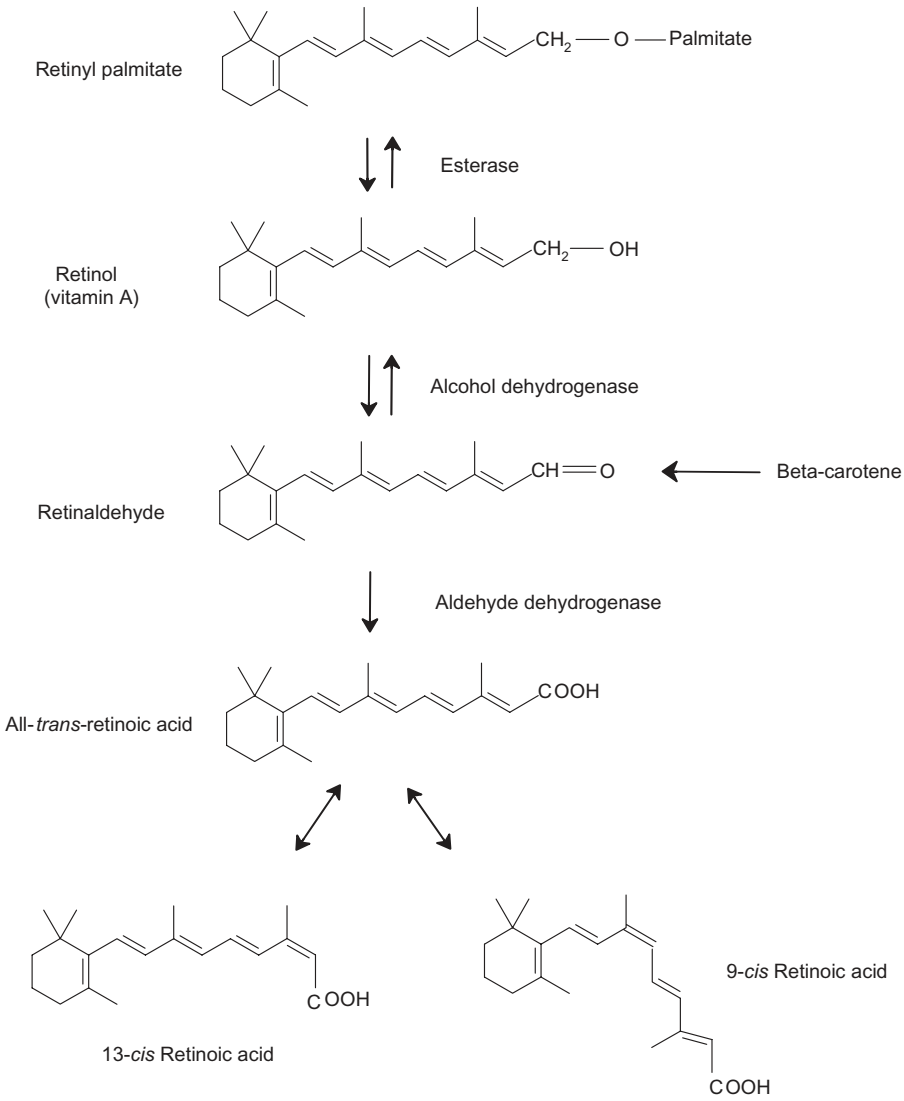

Figure 39.1 Conversion of retinyl ester into *trans*-retinoic acid in the skin.

substance (GAGs) in epidermis, but it will inhibit production of excess ground substance in photoaged dermis. While a low level of GAGs is required in the dermis for normal collagen structure and function, excess dermal GAGs are associated with altered dermal collagen structure and wrinkled skin appearance in the Shar Pei dog and in photoaged skin [3].

Because at least some of the epidermal effects of topical retinoid (e.g. epidermal thickening) occur relatively rapidly (days) after initiation of treatment, some skin effects (e.g. diminution of fine line appearance) can be realized quickly. The dermal effects likely occur on a much longer timeframe (weeks to months) such that reduction in skin problems via this mechanism likely require much longer timeframes (weeks to months).

Topical effects

While much of the substantial literature on the improvement of skin wrinkles by topical retinoids is focused on *trans*-retinoic acid, there are also data available on the vitamin A compounds that are used cosmetically. Because retinoids are irritating to skin, defining skin-tolerated doses clinically is a key step in working effectively with these materials. Retinol is better tolerated by the skin than *trans*-retinoic acid. In our testing we noted that retinyl propionate is milder to skin than retinol and retinyl acetate (Table 39.1).

Because retinoids in general tend to be fairly potent, topical doses of less than 1% are generally sufficient to obtain significant effects. At low doses, in double-blind, split-face, placebo-controlled facial testing (12 weeks' duration), both retinol and retinyl propionate have both been shown to be significantly effective in reducing facial hyperpigmentation and wrinkles across the study (Figure 39.2). Determination of treatment effects was based on quantitative computer image analysis and blinded expert grading of high resolution digital images.

Table 39.1 Cumulative back irritation measures for retinol and its esters (double-blind, vehicle-controlled, randomized study; daily patching for 20 days, under semi-occluded patch, n = 45; 0–3 irritation grading). Equimolar doses and abbreviations used: 0.09% RP (retinyl propionate); 0.086% RA (retinyl acetate); and 0.075% ROH (retinol). RP and RA were significantly less irritating than ROH, and RP was directionally less irritating than RA.

Topical treatment (oil-in-water emulsions)	Expert grader cumulative irritation scores	Significance of expert grader cumulative scores*	Chromameter "a" measure (day 21)	Significance of chromameter "a" measure*
Emulsion control	3.9	a	0.4	a
0.09% RP	24	b	2.7	b
0.086% RA	39	b	3.8	bc
0.075% ROH	164	c	7.6	d

* Treatments with the same letter codes are not significantly different from each other ($p < 0.05$).

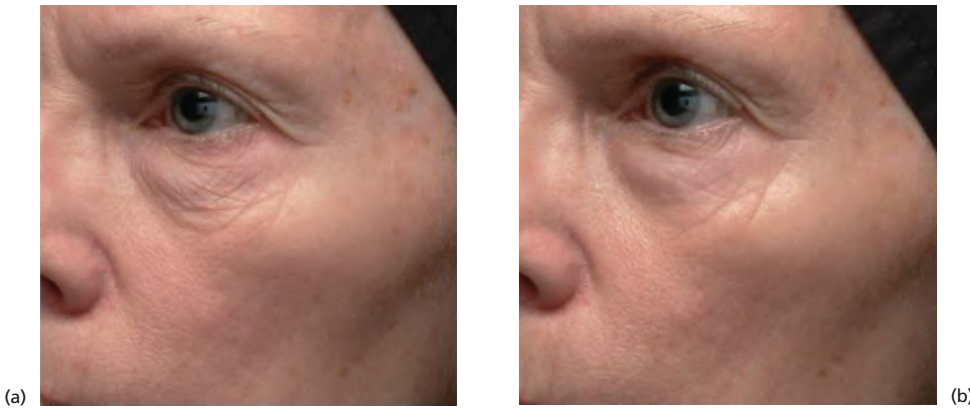

Figure 39.2 Retinyl propionate (RP) reduces the appearance of fine lines and wrinkles. A 0.3% Retinyl propionate in a stable skincare emulsion system was applied twice daily for 8 weeks. (a) Baseline; (b) 8 weeks.

There are also clinical studies published on other retinoids. Retinyl palmitate has very low irritation potential and is effective if tested at a very high dose such as 2%. There are also several studies revealing the clinical efficacy of retinaldehyde, typically at a dose of 0.05%. However, retinaldehyde has irritation potential similar to retinol [4].

Formulation challenges

There are two primary challenges in working with retinoids. One is their tendency to induce skin irritation (as noted above) which negatively affects skin barrier properties. While high doses will provide greater skin aging appearance improvement, the associated irritation tends to define an upper concentration limit where they can be used practically. While the skin may have some capacity to accommodate to retinoid treatment to yield less irritation, it is not completely eliminated even with long-term use, as demonstrated by evaluation of skin barrier function. Mitigation of the irritation may be managed to some extent with appropriate formulation to meter delivery into the skin, use of retinyl esters which are less irritating than retinol (as noted above), or inclusion of other ingredients (e.g. those with anti-irritancy or anti-inflammatory activity) to counter this issue.

The second key issue is instability, especially to oxygen and light. Thus, to ensure stability of retinoid in finished product, formulation and packaging must be carried out in an environment that minimizes exposure to oxygen and light. The final product packaging also ideally needs to be opaque and oxygen impermeable, including use of a small package orifice to reduce oxygen exposure once the container is opened. In addition, a variety of other strategies can be employed (e.g. encapsulation of the retinoid and inclusion of stabilizing antioxidants).

Vitamin B_3

Forms

There are three primary forms of vitamin B_3 that have found utility in skin care products: niacinamide (nicotinamide), nicotinic acid, and nicotinate esters (e.g. myristoyl nicotinate, benzyl nicotinate).

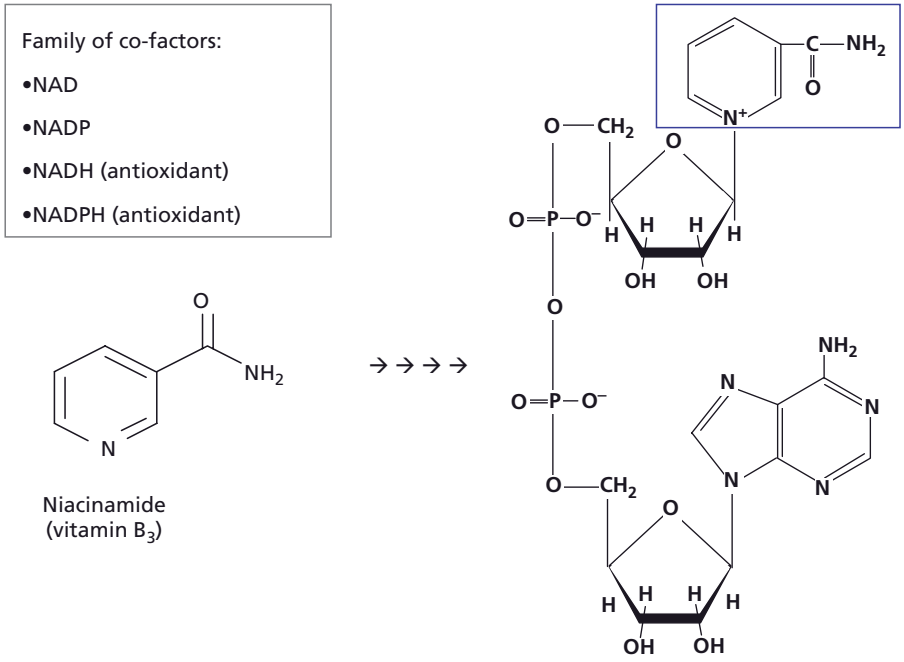

Figure 39.3 Niacinamide as precursor to energy co-factors: nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), and their reduced forms NADH and NADPH.

Mechanisms

Vitamin B_3 serves as a precursor to a family of endogenous enzyme co-factors (Figure 39.3), specifically nicotinamide adenine dinucleotide (NAD), its phosphorylated derivative (NADP), and their reduced forms (NADH, NADPH) which have antioxidant properties. These co-factors are involved in many enzymatic reactions in the skin, and thus have potential to influence many skin processes. This precursor role of vitamin B_3 may thus be the mechanistic basis for the diversity of clinical effects observed for a material such as niacinamide. While precisely how the dinucleotide co-factors might contribute to all these effects has not been elucidated, several specific actions of niacinamide specifically have been described [5,6]. For example, topical niacinamide has the following effects:

- Niacinamide inhibits sebum production, specifically affecting the content of triglycerides and fatty acids. This may contribute to the observed reduction in skin pore size and thus improved skin texture (a component of texture being enlarged pores).
- Niacinamide increases epidermal production of skin barrier lipids (e.g. ceramides) and also skin barrier layer proteins and their precursors (keratin, involucrin, filaggrin), leading to the observed enhancement of barrier function as determined by reduced transepidermal water loss (TEWL). This improved barrier also increases skin resistance to environmental insult from damaging agents such as surfactant and solvent, leading to less irritation, inflammation, and skin redness (e.g. facial red blotchiness). Because inflammation is involved in development of skin aging problems, the barrier improvement may contribute to the antiaging effects of topical niacinamide. The anti-inflammatory and sebum reduction effects of niacinamide likely contribute to the anti-acne effect reported for this material.
- Niacinamide has anti-inflammatory properties (e.g. inhibition of inflammatory cytokines).
- Niacinamide increases production of collagen which may contribute to the observed reduction in the appearance of skin wrinkling.
- Niacinamide reduces the production of excess dermal GAGs. In cell culture testing as noted above for retinyl propionate, 0.5 mmol niacinamide reduced excess GAG production by 15%.
- Niacinamide inhibits melanosome transfer from melanocytes to keratinocytes, leading to reduction in skin hyperpigmentation (e.g. hyperpigmented spots).
- Niacinamide inhibits skin yellowing. A contributing factor to yellowing is protein oxidation (glycation; Maillard reaction) which is a spontaneous oxidative reaction between protein and sugar, resulting in cross-linked proteins (Amedori products) that are yellow–brown in color. These products accumulate in matrix components such as collagen that have long biological half-lives [7]. Niacinamide has antiglycation effects, likely because of its conversion to the antioxidant NAD(P)H.

Because nicotinic acid and its esters are also precursors to NAD(P), they would be expected to provide these same effects to skin. Nicotinic acid and many (if not all) of its esters (following in-skin hydrolysis to free nicotinic acid) also stimulate blood flow, leading to increased skin redness or a flush response. While in some situations this might be a desired effect (e.g. warming sensation for

body skin), it is difficult to manage for the more sensitive facial skin.

Topical effects

As representative for the vitamin B_3 family of compounds, there are several published reports on the diversity of clinical effects of topical niacinamide. These data were obtained from double-blind, placebo-controlled, left–right randomized studies. For example, topical niacinamide has been shown to reduce skin fine lines and wrinkling. The effect increases over time and is significant after 8–12 weeks of treatment. Topical niacinamide also improves other aspects of aging skin, such as reduction in sebaceous lipids (oil control) and pore size, which likely contribute at least in part to improved skin texture. Additionally, niacinamide improves skin elastic properties as demonstrated for two parameters of skin elasticity. Beyond these effects, there is also improvement in appearance of skin color, in particular reduction in the appearance of hyperpigmented spots (Figure 39.4) and also skin yellowing. Fairly high doses (2–5%) of vitamin B_3 have been used to achieve these effects. However, because there is very high tolerance of the skin to niacinamide even with chronic usage, high doses can be used acceptably. In fact, as noted above, because topical niacinamide improves skin barrier, it actually increases the skin's resistance to environmental insult (e.g. from surfactant) and reduces red blotchiness.

Some data on myristoyl-nicotinate have been presented to suggest that a similar broad array of effects occurs with this agent when used topically (1–5% doses). Clinical data for topical nicotinic acid and other esters are not available.

Formulation challenges

The key challenge for working with niacinamide and nicotinate esters on the face is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing) response. While a little skin redness (increased skin "pinkness") may be a desired effect for the face, the flushing response among individuals is highly variable in terms of dose to induce it, time to onset of the response, and duration of response. Additionally, the flushing can also have associated issues such as facial burn, sting, and itch, particularly under cold and/or dry environmental conditions. To avoid hydrolysis, formulating in the pH range of 5–7 is preferred. This flushing issue also requires that the purity of the raw material (e.g. niacinamide) be very high to minimize any contaminating free acid.

For the nicotinate esters, there are many commercial options. Many of them unfortunately are readily hydrolyzed to nicotinic acid on or in the skin such that flushing responses occur rapidly (within seconds to minutes) even at very low concentrations ($\ll$1%). The longer chain esters (e.g. myristoyl-nicotinate) apparently are more resistant to this hydrolysis and thus appear to be more suitable for use topically.

Vitamin B_5

Forms

Pantothenic acid is the active vitamin. A precursor is panthenol or provitamin B_5 which is also known as pantothenol or pantothenyl alcohol. The widely used D optical isomer of panthenol is termed dexpanthenol. Panthenol is water-soluble, stable, and of low molecular weight (readily penetrates the stratum corneum).

Mechanisms

Panthenol has been used topically to treat wounds, bruises, scars, pressure and dermal ulcers, thermal burns, postoperative incisions/distention, and dermatoses [8,9]. The specific

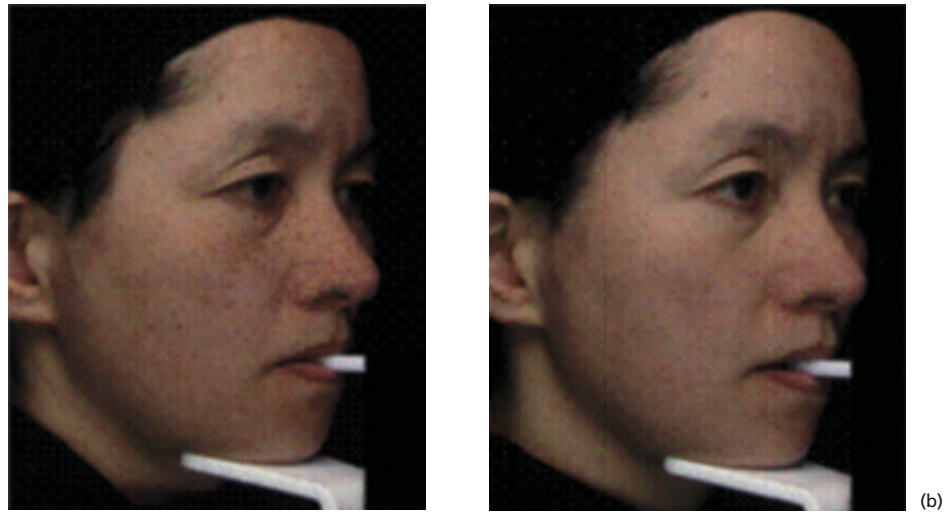

Figure 39.4 Niacinamide reduces pigment spots. (a) Baseline. (b) After 8 weeks.

mechanisms for these effects are not known. However, dexpanthenol is a precursor to pantothenic acid (vitamin B_5). Pantothenic acid is a component of coenzyme A which functions in acyl group transfer during fatty acid biosynthesis and gluconeogenesis. By increasing skin lipid synthesis, improved barrier should occur, resulting in improved wound healing. In addition, panthenol promotes fibroblast proliferation and epidermal re-epithelialization, effects that promote wound healing. Additionally, panthenol has found utility for skin penetration enhancement.

Topical effects

Topical panthenol is extremely well tolerated by the skin, leading to wide topical use of this material and many reported skin effects [8,9]. Among those are hydration and the associated improvement in roughness, scaling, and epidermal elasticity; protection against skin irritation and sodium lauryl sulfate (SLS) induced damage; skin soothing; and anti-inflammatory and antipruritic effects.

Hydration

Panthenol's hydration effect likely derives from its hygroscopic properties. Panthenol is an effective moisturizer of stratum corneum and is even more effective when combined with glycerol. In addition, it improves the dryness, roughness, scaling, pruritus, and erythema associated with a wide variety of skin problems such as atopic dermatitis, ichthyosis, psoriasis, and contact dermatitis [8]. It also reduces the cutaneous side effects associated with retinoid therapy [10]. This hydration effect has further led to its use in haircare, promoting improved elasticity, softening, and easier combing.

Barrier and irritation

Panthenol protects against irritation via improvement in skin barrier function [8,11]. Topical pretreatment with panthenol was observed to increase skin's resistance to visible irritation upon subsequent exposure to the surfactant SLS (Table 39.2). Because panthenol is the precursor to pantothenic acid which is a cofactor in barrier layer lipid biosynthesis, this could account for the noted barrier effect.

Some consumers are sensitive to specific components (e.g. certain preservatives, fragrances, sunscreen actives) in cosmetic formulations, leading to induction of negative kinesthetic irritation effects such as burn, sting, itch, and tingling. Topical panthenol incorporated into such formulations can reduce those negative effects (Table 39.3). The mechanism for this may be related to the reported soothing or anti-inflammatory effect of panthenol [8].

Formulation challenges

Panthenol at high concentrations can yield sticky and/or greasy feeling formulations. Thus, doses of greater than approximately 1% may require appropriate formulation adjustment.

Table 39.2 Prevention of sodium lauryl sulfate (SLS) induced erythema by topical panthenol.

Time point post SLS treatment	Erythema score (0–6 scale) for skin treated with:	
	SLS	Panthenol then SLS
2 days	4.0	2.4
3 days	3.4	1.7
4 days	2.7	1.4

Table 39.3 Reduction in negative kinesthetic effects of formulation containing panthenol vs. formula not containing 1% panthenol.

Visible or kinesthetic attribute	Reduction in attribute by panthenol (0–6 scale)
Redness	–1.4
Burning	–2.4
Tingling	–5.7
Stinging	–4.9
Itching	–4.9
Warming	–5.7

Vitamin C

Forms

Of the many forms of this vitamin, some of the more commonly used are ascorbic acid, ascorbyl phosphate (as the magnesium and sodium salts), and other ascorbate derivatives (e.g. ascorbyl palmitate, ascorbyl glucoside).

Mechanisms

Vitamin C is well known as an antioxidant and has been utilized as a skin lightener (e.g. via tyrosinase inhibition and/or its antioxidant effect). It also has been reported to have anti-inflammatory properties because it reduces the erythema associated with postoperative laser resurfacing [12]. In addition, ascorbic acid also serves as an essential co-factor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for post-translational processing in collagen (types I and III) biosynthesis. Thus, by stimulating these biosynthetic steps, ascorbic acid has the potential to increase the production of collagen which could lead to wrinkle reduction (as discussed above for vitamin A).

While the ascorbic acid derivatives may possess some properties of the free acid (e.g. antioxidant), hydrolysis of the derivatives would be required for the increased collagen production effect because the acid is the active co-factor. Demonstration of the hydrolysis of all these derivatives in skin has not been well documented.

Topical effects

There are several published studies discussing the antiaging effect of ascorbic acid, such as reduced UVA-induced oxidation and reduction in skin aging appearance parameters (skin surface replicas, dermatologist grading, algorithm-based facial image analysis, and histological assessment of biopsy specimens of dermal matrix, such as collagen). For example, topical 5% ascorbic acid for 6 months [13] improved photodamaged forearm and upper chest skin based on dermatologist scores, skin surface replicas, and biopsy specimen analysis (specifically improvements in elastin and collagen fiber appearance).

Formulation challenges

The key challenge with vitamin C compounds in general is stability (oxygen sensitivity), particularly with ascorbic acid. Not only does oxidation lead to loss of the active material, there is also rapid product yellowing (an esthetic negative for the consumer). Various stabilization strategies can be attempted to address the issue, such as exclusion of oxygen during formulation, oxygen impermeable packaging, encapsulation, low pH, minimization of water, and inclusion of other antioxidants. In spite of all those approaches, in general ascorbate stability remains a challenge, and some of these approaches (e.g. very low pH) can lead to unwanted esthetic skin effects such as irritation.

For the ascorbyl phosphates (Mg and Na salts), the resulting high content of salt in product can dramatically impact the thickener system, requiring increased use of thickener ingredients. These ascorbate derivatives are also considerably more expensive than other ascorbate compounds.

Vitamin E

Forms

This vitamin is also commonly known as tocopherol. There are several isomers based, for example, on number and position of substituents on the phenyl ring. Thus, there are α, β, γ, δ, and ε isomers of tocopherol. There are also several esters. A widely used form of vitamin E is α-tocopherol acetate.

Mechanism

Vitamin E is an antioxidant. The active form is free tocopherol, so topical use of esters such as tocopherol acetate would require enzymatic hydrolysis to the free vitamin on or in skin for maximal activity. Because it is lipid-soluble, its site of action is more likely to be in lipid-rich environments (e.g. cell membranes).

Topical effects

While vitamin E is often used as a preservative and/or stabilizer in formulation, at relatively high topical doses it is quite effective in preventing oxidative damage to skin, such as preventing acute and chronic UV radiation damage. For example, in an *in vivo* model of UV radiation damage, topical tocopherol reduced by approximately 50% the visible skin damage (e.g. skin wrinkling) induced by chronic UV exposure [14]. Because antioxidants are the topic of another chapter in this volume (Chapter 35), this discussion has been kept brief.

Formulation challenges

Tocopherol has some oxidative stability concerns, thus esters such as tocopherol acetate are most often used. Both tocopherol and its alkyl esters are oils, so high doses can be greasy/sticky, requiring formulation to address the esthetic impact.

Other vitamins

Vitamin D

There are several vitamin D compounds, and many synthetic variations. The active vitamin is 1,25-dihydroxyvitamin D3. Dehydrocholesterol (provitamin D) is a cosmetically used material which can be converted into active vitamin D upon exposure to UV. As a result of the effects of vitamin D compounds on epidermal growth and differentiation, there has been discussion of their skin barrier and photodamage mitigation activities, as seen in *in vivo* model testing [15,16]. Vitamin D compounds, like vitamin A materials, are often very potent, requiring caution in selecting specific compounds and topical doses.

Vitamin K

There are several forms of vitamin K, such as phylloquinone and menaquinone. Vitamin K compounds function in blood clotting, and there are data showing effects for mitigating bruising [17], along with much speculation about the use of them in improving other skin problems such as under-eye dark circles. However, there do not appear to have been any controlled studies presented to support that latter use. Oxidative stability is a concern with at least some of the vitamin K compounds.

Vitamin P (flavonoids)

This family of plant-derived and synthetically prepared chemicals encompasses a huge variety of compounds, both natural and synthetic. Some of the types of flavonoids are

flavons, isoflavones, flavanones, chalcones, coumarins, and chromones. Activities associated with flavonoids include antioxidant, anti-inflammatory, and phytoestrogen effects [18–20]. They are appearing in cosmetic products, often as components of natural extracts. This is a fertile area for identification of materials active in improving aging skin.

Conclusions

While oral vitamins are well studied because of their importance in nutrition, the entire spectrum of possible effects from topical vitamins has not been thoroughly studied for the potential to improve skin. As the information presented here shows, at least some vitamins used topically can provide appearance-improving effects to aging skin, even in nutritionally normal individuals. With the wide array of vitamin materials, additional effects from their topical use are likely to emerge in the future.

A vitamin alone is not likely to be highly potent, although the high tolerance by skin for some vitamins provides opportunity to use high topical doses to achieve greater effects. A key to achieving that is development of esthetic formulations to provide elegant product forms containing those high levels. Also, combinations of different vitamins or vitamins plus other effective agents have potential to achieve considerably more dramatic effects. For example, combining a vitamin B_3 with a vitamin A or with a peptide leads to greater effects than the individual materials. There is certainly opportunity to continue to explore this avenue.

References

1 Newstrom H. (1993) *Nutrients Catalog*. McFarland & Company, Jefferson, NC.

2 Varani J, Fisher GJ, Kang S, Voorhees JH. (1998) Molecular mechanisms of intrinsic skin aging and retinoid-induced repair and reversal. *J Invest Dermatol Symp Proc* **3**, 57–60.

3 Kligman AM, Baker TJ, Gordon HL. (1975) Long-term histologic follow-up of phenol face peels. *Plast Reconstruct Surg* **75**, 652–9.

4 Fluhr JW, Vienne MP, Lauze C, Dupuy P, Gehring W, Gloor M. (1999) Tolerance profile of retinol, retinaldehyde, and retinoic acid under maximized and long-term clinical conditions. *Dermatology* **199S**, 57–60.

5 Bissett DL, Oblong JE, Saud A, *et al.* (2003) Topical niacinamide provides skin aging appearance benefits while enhancing barrier function. *J Clin Dermatol* **32S**, 9–18.

6 Bissett DL, Miyamoto K, Sun P, Berge CA. (2004) Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci* **26**, 231–8.

7 Odetti P, Pronzato MA, Noberasco G, Cotto L, Traverso N, Cottalasso D, *et al.* (1994) Relationships between glycation and oxidation related fluorescence in rat collagen during aging. *Lab Invest* **70**, 61–7.

8 Ebner F, Heller A, Rippke F, Tausch I. (2002) Topical use of dexpanthenol in skin disorders. *Am J Clin Dermatol* **3**, 427–33.

9 Stozkowska W, Piekos R. (2004) Investigation of some topical formulations containing dexpanthenol. *Acta Polon Pharm* **61**, 433–7.

10 Draelos ZD, Ertel KD, Berge CA. (2006) Facilitating facial retinization through barrier improvement. *Cutis* **78**, 275–81.

11 Biro K, Thaci D, Ochsendorf FR, Kaufmann R, Boehncke WH. (2003) Efficacy of dexpanthenol in skin protection against irritation: a double-blind, placebo-controlled study. *Contact Derm* **49**, 80–4.

12 Alster TS, West TB. (1998) Effect of topical vitamin C on postoperative carbon dioxide laser resurfacing erythema. *Dermatol Surg* **24**, 331–4.

13 Humbert PG, Haftek M, Creidi P, Lapière C, Nusgens B, Richard A, *et al.* (2003) Topical ascorbic acid on photoaged skin: clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol* **12**, 237–44.

14 Bissett DL, Chatterjee R, Hannon DP. (1990) Photoprotective effect of superoxide-scavenging antioxidants against ultraviolet radiation-induced chronic skin damage in the hairless mouse. *Photodermatol Photoimmunol Photomed* **7**, 56–62.

15 Mitani H, Naru E, Yamashita M, Arakane K, Suzuki T, Imanari T. (2004) Ergocalciferol promotes *in vivo* differentiation of keratinocytes and reduces photodamage caused by ultraviolet irradiation in hairless mice. *Photoderm Photoimmun Photomed* **20**, 215–23.

16 Reichrath J, Lehmann B, Carlberg C, Varani J, Zouboulis CC. (2007) Vitamins as hormones. *Hormone Med Res* **39**, 71–84.

17 Shah NS, Lazarus MC, Bugdodel R, Hsia SL, He J, Duncan R, *et al.* (2002) The effects of topical vitamin K on bruising after laser treatment. *J Am Acad Dermatol* **47**, 241–4.

18 Vaya J, Tamir S. (2004) The relation between the chemical structure of flavonoids and their estrogen-like activities. *Curr Med Chem* **11**, 1333–43.

19 Kim HP, Park H, Son KH, Chang HW, Kang SS. (2008) Biochemical pharmacology of biflavonoids: implications for anti-inflammatory action. *Arch Pharm Res* **31**, 265–73.

20 Amic D, Davidovic-Amic D, Beslo D, Rastija V, Lucic B, Trinajstic N. (2007) SAR and QSAR of the antioxidant activity of flavonoids. *Curr Med Chem* **14**, 827–45.

Chapter 40: Clinical uses of hydroxyacids

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BASIC CONCEPTS

- Hydroxyacids are low pH substances that have a keratolytic effect on the skin.
- The hydroxyacids include alpha-hydroxyacids (AHAs), beta-hydroxyacids (BHAs), polyhydroxy acids (PHAs), aldobionic acids (bionic acids), and aromatic hydroxyacids (AMAs).
- Effects of hydroxyacids include increased thickness of epidermis and papillary dermis; improved barrier properties; increased amounts of hyaluronic acid in the dermis and of other dermal glycosaminoglycans which correspond to increased skin thickness measured micrometrically; improved histologic features of dermal collagen; increase in total skin thickness which in turn diminishes clinical wizened appearances; and diminished dyspigmentation.
- Hydroxyacids are effective skin peeling agents.

Introduction

Research on aging today is motivated by the belief that innate degenerative processes of aging, and aging itself, can be modulated, prevented, and perhaps reversed. Even though a complete understanding of the mechanisms of aging may not be known, improvement in clinical appearance and function of the skin with antiaging measures is a signal that modulation of aging and/or degenerative processes has probably occurred.

After many years of research and clinical use, hydroxyacids (HAs) have been shown to have biologic importance and clinical value for both younger skin and older skin with a variety of hyperkeratotic and aging-related conditions. This chapter covers HAs, including alpha-hydroxyacids (AHAs), beta-hydroxyacids (BHAs), polyhydroxy acids (PHAs), aldobionic acids (bionic acids), and aromatic hydroxyacids (AMAs).

Chemical categorization and natural occurrence of hydroxyacids

Hydroxyacids may be divided into five groups based on their chemical structures: AHAs, BHAs, PHAs, bionic acids, and AMAs.

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Alpha-hydroxyacids

The AHAs are the most widely studied and commercialized ingredients within the HA family. They are the simplest of the HAs, consisting of organic carboxylic acids with one hydroxyl group attached to the alpha position of the carboxyl group. Both the hydroxyl and carboxyl groups are directly attached to an aliphatic or alicyclic carbon atom. As a result, the hydroxyl group in the AHA is neutral and only the carboxyl group provides acidity to the molecule, a property that distinguishes the AHAs from aromatic hydroxyacids such as salicylic acid as described below.

Many AHAs are present in foods and fruits, and therefore are called fruit acids (Table 40.1). Glycolic acid, the smallest AHA, occurs in sugar cane and citric acid is found in lemon juice at a concentration of 5–8%. Some AHAs contain a phenyl group as a side chain substituent; this changes the solubility profile of the AHA providing increased lipophilicity over conventional water-soluble AHAs and can be used to target oily and acne-prone skin. Examples include mandelic acid (phenyl glycolic acid) and benzilic acid (diphenyl glycolic acid).

Beta-hydroxyacids

The BHAs are organic carboxylic acids having one hydroxyl group attached to the beta position of the carboxyl group. Both the hydroxyl and carboxyl groups are attached to two different carbon atoms of an aliphatic or alicyclic chain rendering the hydroxyl group neutral in nature. Some BHAs are present in body tissues as metabolic intermediates and energy source. For example, β-hydroxybutanoic acid is produced by the liver and utilized by skeletal and cardiac

Table 40.1 Examples of hydroxyacids.

Category	Example	Occurrence/source	Antioxidant
Alpha-hydroxyacid (AHA)	Glycolic	Sugar cane	No
	Lactic	Sour milk, tomato	No
	Methyllactic	Mango	No
	Citric	Lemon, orange	Yes
	Malic	Apple	Yes
	Tartaric	Grape	Yes
Beta-hydroxyacid (BHA)	Beta-hydroxybutanoic	Urine	No
	Tropic	Plant	No
Polyhydroxy acid (PHA)	Gluconic	Skin, commercially derived from corn	Yes
	Gluconolactone	Skin, commercially derived from corn	Yes
Aldobionic acid (bionic acid)	Lactobionic	Lactose from milk	Yes
	Maltobionic	Maltose from starch	Yes
Aromatic hydroxyacid (AMA)	Salicylic	Ester form in wintergreen leaves	No

muscle as an energy source. In contrast to the water-soluble β-hydroxybutanoic acid, tropic acid is derived from a plant source, and is a lipid-soluble BHA. For the most part, BHAs have yet to be commercialized in skincare mainly because of a lack of commercial supply and high cost.

Some AHAs are also BHAs when the molecule contains two or more than two carboxyl groups. In this case, the hydroxyl group is in the alpha position to one carboxyl group, and at the same time is in the beta position to the other carboxyl group. For example, malic acid (apple acid) containing one hydroxyl and two carboxyl groups is both an AHA and a BHA. In the same manner, citric acid containing one hydroxyl and three carboxyl groups is both an AHA to one carboxyl group and a BHA to the two other carboxyl groups. These ingredients have been commercialized in skincare formulations to adjust pH and to deliver antioxidant and antiaging benefits.

Polyhydroxy acids

The PHAs are organic carboxylic acids that possess two or more hydroxyl groups in the molecule. The hydroxyl and carboxyl groups are attached to the carbon atoms of an aliphatic or alicyclic chain. All the hydroxyl groups in the PHA are neutral, and only the carboxyl group accounts for its acidity. Although hydroxyl groups may be attached to several positions of the carbon chain, in order to be both an AHA and PHA it is essential that at least one hydroxyl group be attached to the alpha position.

Many PHAs are endogenous metabolites or intermediate products from carbohydrate metabolism in body tissues. Both galactonic acid and galactonolactone are derived from galactose, which is an important component of glycosaminoglycans. Gluconic acid and gluconolactone are important metabolites formed in the pentose phosphate pathway from glucose during the biosynthesis of ribose for ribonucleic acid. Gluconolactone is the most widely studied and commercialized skincare ingredient among the PHAs.

Aldobionic acids or bionic acids

The aldobionic acids, also called bionic acids, consist of one carbohydrate monomer chemically linked to a PHA via a stable ether linkage; examples are lactobionic acid (galactose/gluconic acid) and maltobionic acid (glucose/gluconic acid) (Figure 40.1). The bionic acid is commonly obtained from its disaccharide through chemical or enzymatic oxidation. For example, lactobionic acid is obtained from lactose and maltobionic acid from maltose. In general, the bionic acids have a larger molecular size and weight than most PHAs because of the additional sugar unit; however, at 358 Da (lactobionic acid and maltobionic acid) these molecules remain small enough to penetrate skin.

Aromatic hydroxyacids

AMAs such as salicylic acid and gallic acid are derived from benzoic acid, which has been used in combination with sali-

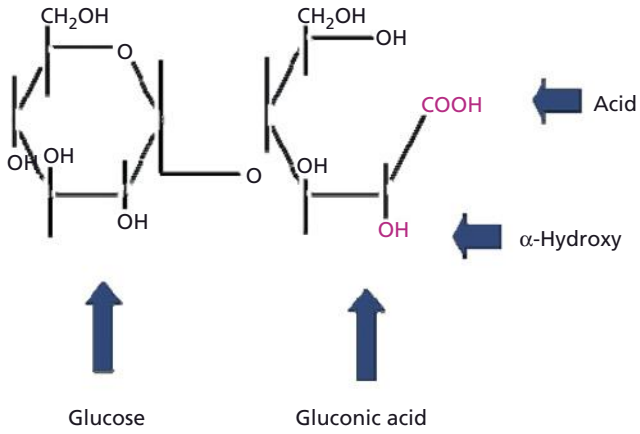


Figure 40.1 Maltobionic acid, a bionic acid.

cylic acid as Whitfield's ointment for hyperkeratotic conditions and fungal infections. Salicylic acid is 2-hydroxybenzoic acid and may be called an HA within a broad definition; however, its effects on skin differ from those of the AHAs, BHAs, PHAs, and bionic acids. Salicylic acid is a conventional keratolytic agent which desquamates corneocytes, layer by layer from the top downward [1]. In contrast, AHAs and BHAs appear to act at the innermost layers of the stratum corneum, the stratum compactum, near the junction with stratum granulosum [2,3]. Moreover, AHAs, PHAs, and bionic acids have been shown to stimulate biosynthesis of dermal components and increase dermal skin thickness upon topical application, whereas salicylic acid has been shown to decrease dermal skin thickness [3–7].

Physicochemical and biological properties distinguishing HAs

As individual compounds, HAs differ broadly in physicochemical properties. Some HAs are very small molecules such as glycolic acid and lactic acid, and some are larger molecules such as lactobionic acid. Most HAs are white crystalline at room temperature such as glycolic acid, malic acid, tartaric acid, citric acid, mandelic acid, and benzilic acid, but a few are liquid such as lactic acid. Most HAs are soluble in water, but some are also soluble in lipid solvents. Some HAs are soluble only in lipid solvents. Certain physicochemical properties of HAs are discussed herein.

Water binding properties/gel matrix formation

In contrast to AHAs and BHAs, PHAs and bionic acids are strongly hygroscopic and can attract and bind water similarly to other polyol compounds such as glycerin. The bionic acids are so strongly hygroscopic that they form a gel matrix when their aqueous solution is evaporated at room temperature. The transparent gel thus obtained retains certain amounts of water, forming a clear gel matrix. The amount of water retention depends on the individual bionic acid. For example, maltobionic acid can form a clear gel film containing 29% water complexed with maltobionic acid molecules. The formation of a gel matrix provides moisturization and may add protective and soothing properties for inflamed skin. PHAs and bionic acids are gentle and non-irritating, and can be used to provide antiaging benefits to sensitive skin, even after cosmetic procedures [8–11].

Antioxidant properties

Most PHAs, bionic acids, and some AHAs and BHAs with one hydroxyl group and two or more vicinal carboxyl groups have been found to be antioxidants. The antioxidant property is readily determined by using any one of the following test methods: prevention or retardation from air oxidation of: (a) anthralin, (b) hydroquinone, or (c) banana peel. A freshly prepared anthralin solution or cream is bright yellow, and an air-oxidized one is brownish or black. A hydroquinone solution or cream is colorless or white color, and an air-oxidized one is brownish or black. A freshly peeled banana peel is light yellow in color, and an oxidized one ranges in color from tan, dark tan, brown to brownish black. Known antioxidants such as vitamin C and N-acetylcysteine may be used as the positive control in these screen tests. Based on these tests, all the PHAs and bionic acids tested are antioxidants, which include ribonolactone, gluconolactone, galactonolactone, lactobionic acid, and maltobionic acid [11]. Among AHAs and BHAs, malic acid, tartaric acid, citric acid, and isocitric acid have been shown to be antioxidants.

Another method to determine antioxidant, free radical scavenging properties utilizes an *in vitro* model of cutaneous photoaging. In this model, compounds are measured for their ability to prevent UV-induced activation of the elastin promoter gene in skin via free radical scavenging activity. An increase in the expression of this gene causes the abnormal production of poorly structured elastin in skin, resulting in the condition known as solar elastosis. Maximum protection by free radical scavengers reduces gene induction by approximately 50%; the remaining 50% of gene activation is reportedly caused by direct UV damage to cells and cellular DNA, and can only be prevented with sunscreens. Results of the study indicate that the PHA gluconolactone provides up to 50% protection against UV radiation. This significant benefit could not be explained by UV screening, and therefore was attributed to gluconolactone's ability to chelate oxidation-promoting metals and possibly via direct free radical scavenging effects [12].

It is interesting to note that lactobionic acid (a bionic acid) is an important antioxidant chelator in organ transplantation preservation solutions and is used to suppress tissue damage caused by hydroxyl radicals during organ storage and reperfusion. Lactobionic acid reportedly inhibits

hydroxyl radical production by forming a complex with Fe(II) [13].

Sun sensitivity

AHAs and PHAs have been evaluated to determine whether daily application alters the sensitivity of normal human skin to UVB radiation. A change in UV sensitivity resulting from enhanced transmission of UVB can be monitored by the formation of sunburn cells (SBCs). Treatment with glycolic acid has been shown to increase the formation of SBCs in skin [14]; this effect can be prevented with use of low level sunscreens [14,15]. Importantly, pretreatment with gluconolactone (PHA) does not lead to an increase in sunburn cells following UVB irradiation, presumably because of its antioxidant effects [12].

Sensory responses

One of the distinguishing benefits of the PHAs and bionic acids is their gentleness on skin. When compared to glycolic acid and lactic acid, PHAs and bionic acids are non-stinging and non-burning. Product use studies have demonstrated compatibility with sensitive skin, even on rosacea and atopic dermatitis [8–10]. PHAs and bionic acids are gentle enough to be applied to the skin immediately following cosmetic procedures such as microdermabrasion and non-ablative laser procedures, providing complementary antiaging benefits while helping to reduce redness [11,16].

MMP inhibition

Matrix metalloproteinase enzymes (MMPs) digest the skin's extracellular matrix. Naturally occurring inhibitors of MMPs protect the skin from excessive degradation caused by these enzymes. With aging and sun exposure, an increase in MMP activity and a decrease in natural inhibitors contributes to excessive MMP activity and the clinical manifestations of wrinkles, skin laxity, and telangiectasia [17]. Previous work has revealed that the bionic acid lactobionate is an inhibitor of (MMPs) enzymes obtained from human liver effluents during organ transplantation procedures [18]. Similarly, topical lactobionic acid has been shown to inhibit MMPs in skin helping to protect skin against photodamage [5].

Effects of HAs on skin – similarities and differences

Clinical and histologic observations on the biofunctionality of HAs, both in connection with therapeutic performance on numerous skin disorders and in the course of investigative studies on normal skin, confirm that AHAs, PHAs, and bionic acids have favorable effects on the stratum corneum, epidermis, and dermis. All these effects appear to modulate form and function toward more normal or optimal states (Table 40.2). Because of these effects such compounds may be categorized as eudermatrophic agents (i.e. agents that nourish the skin toward normalcy).

Stratum corneum and epidermis

The initial response to AHAs on ichthyotic skin is a sheet-like disjunctive desquamation of the thick, compact stratum corneum. With continued daily use of AHA formulations, the stratum corneum becomes histologically more normal in thickness and in appearance, and the hyperplastic acanthotic underlying epidermis returns to more normal thickness [19]. The opposite occurs in the treatment of atrophic skin of the elderly wherein the stratum corneum and epidermis are both thin. After daily applications of AHAs for several weeks, histologic examination reveals both the stratum corneum and keratinocyte layer to have regained more normal thickness [5,20], with a more even distribution of pigmentation [4]. Other studies have shown AHAs to improve barrier function, particularly the PHAs with antioxidant properties [21].

Dermis

Significant dermal remodeling occurs with daily application of AHAs to the skin. In studies on forearm skin where AHAs were applied daily, measurable increases in dermal thickness occurred, which was correlated with increased amounts of hyaluronic acid and other glycosaminoglycans (Figure 40.2) [4,5,7,22], and with qualitative improvements in collagen fibers and improved fibrous quality of elastic fibers [4]. Additionally, the papillary dermis increased in thickness, with increased prominence of dermal papillae. Increased thickness of skin without further topical applications persists for months [23]. Consistent with these clinical histologic findings are *in vivo* and *in vitro* observations of others showing the AHA glycolic acid to increase fibroblast proliferation and production of collagen [24].

Clinical uses of HAs

HA effects on skin morphology and functionality are manifold, spanning all of the skin's layers. As a result, numerous clinical benefits have been observed with use of HAs as described herein.

Dry skin and hyperkeratinization

Previous studies demonstrated that the stratum corneum of xerotic skin was thicker and more compact than that of non-xerotic controls, and the epidermis often atrophic. Topical use of AHA formulations on xerotic skin restored the stratum corneum and epidermis to a more normal state both clinically and histologically. This restoration was accompanied by substantial reduction of clinically evident xerosis, and upon discontinuance of the topical AHA treatment the skin

Table 40.2 Clinical grading results for subjects treated with maltobionic acid 8% cream: baseline versus week 12.

Variable	Grading site	Mean baseline score (n = 28)	Mean 12-week score (n = 28)	Mean change	Standard deviation	Statistical difference ($p < 0.05$)[4]	Change from baseline (%)[5]
Pore size[1]	Cheek	4.77	4.01	–0.76	0.37	↓	–20.2
Roughness[1]	Cheek	4.29	1.51	–2.78	1.08	↓	–65.9
Laxity[1]	Cheek	5.43	4.51	–0.92	0.35	↓	–18.2
Fine lines[1]	Eye	4.57	3.29	–1.29	0.40	↓	–29.7
Coarse wrinkles[1]	Eye	5.22	4.12	–1.11	0.40	↓	–22.0
Mottled Pigmentation[1]	Face	4.54	3.32	–1.22	0.40	↓	–28.1
Sallowness[1]	Face	3.79	2.60	–1.20	0.34	↓	–33.4
Clarity/radiance[1]	Face	3.79	7.13	3.35	0.90	↑	92.4
Pinch recoil[2]	Face	1.66	1.42	–0.24	0.11	↓	–14.2
Erythema[3]	Face	0.18	0.20	0.02	0.32	ns	0.6
Dryness[3]	Face	0.38	0.00	–0.38	0.52	↓	–12.5
Stinging[3]	Face	0.00	0.11	0.11	0.42	ns	3.6

[1] Visually graded by a trained assessor using an anchored 0–10 point scale with 0.25 point increments. 0 = low extreme, 10 = high extreme.
[2] Measurement collected in triplicate by a trained evaluator using a stopwatch in hundreths of a second; a decrease in pinch recoil time indicates an increase in skin firmness.
[3] Visually graded by a trained assessor using an anchored 0–3 point scale (none, mild, moderate, severe) with 0.5-point increments.
[4] Arrow indicates statistically significant increase or decrease from baseline; ns = not significant.
[5] Percent change from baseline, mean calculated on an individual basis and then averaged.

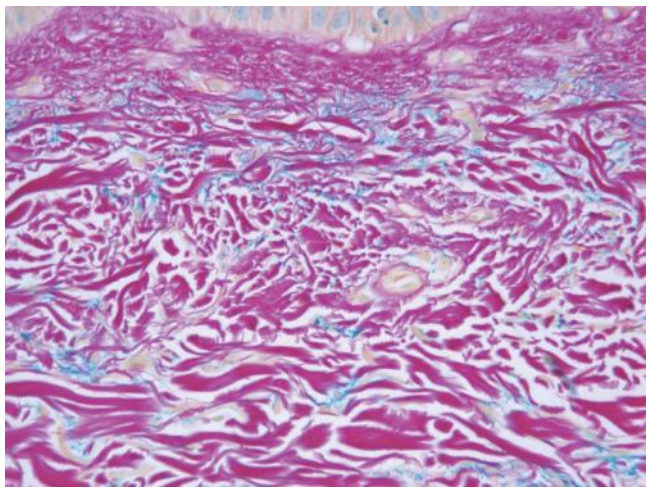
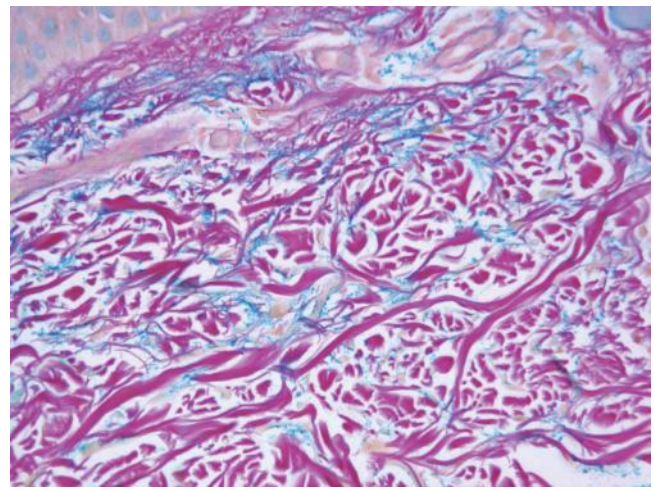
(a)   (b)

Figure 40.2 Histologic staining for acid mucopolysaccharides/glycosaminoglycans (GAGs): ×400. (a) Specimen shows staining of untreated control forearm skin. (b) Specimen shows staining following topical application of 8% maltobionic acid cream (pH 3.8) for 12 weeks. Increased density of blue colloidal iron stain demonstrates an increase in GAGs. (Reproduced by permission of Elsevier. From Green B, Briden ME. PHAs and bionic acids: next generation hydroxy acids. In: Draelos Z, ed. (2009) *Procedures in Cosmetic Dermatology Series: Cosmeceuticals*, 2nd edn, figure 33.9.)

remained relatively normal for up to about 2 weeks when the thick compact stratum corneum again reformed [11].

Today we find that efficacy of HA formulations for problem dry skin conditions is improved by incorporating into the formulation combinations of AHAs, PHAs, and bionic acids selected for their efficiency in restoring and maintaining a more normal stratum corneum and epidermis. The PHAs and bionic acids, because of water-binding capabilities and inherent gentleness to the skin, offer special advantages in this regard. Combination HA formulations are found to have unparalleled efficacy for treating xerosis [25], and for treating otherwise treatment-resistant conditions such as callused fissured plantar and palmar skin (Figure 40.3).

Keratoses and dyspigmentation

Markers of advancing years are a variety of localized hyperkeratotic lesions that include seborrheic keratoses, actinic keratoses, lentigines, age spots, and mottled pigmentation. HAs exfoliate hyperkeratotic pigmentation spots and AHAs have been shown to aid in the even disbursement of melanin [4]. PHAs and bionic acids chelate metals such as copper, an essential co-factor in the production of melanin. HAs can be useful alone or in combination of skin lightening agents to lighten dyspigmentation [2,22].

Wrinkles and photoaging

AHAs, PHAs, and bionic acids are now used widely as topical antiaging substances. They are used for superficial peeling to initiate accelerated epidermal turnover and to initiate dermal regenerative events; they are used in therapeutic formulations under physicians' guidance; and they are used in a multitude of consumer cosmetic formulations. The reason for this wide use is because of what may be their eudermatrophic properties, demonstrated in studies described earlier herein where effective concentrations applied to human skin have been found to normalize photoaged skin (Table 40.2). Such changes include increased thickness of epidermis and papillary dermis; improved barrier properties; increased amounts of hyaluronic acid in the dermis and of other dermal glycosaminoglycans which correspond to increased skin thickness measured micrometrically; improved histologic features of dermal collagen; increase in total skin thickness which in turn diminishes clinical wizened appearances (Figure 40.4); and diminished dyspigmentation [3–5].

Uses as a peeling agent

Several substances have been used to date as peeling agents, these include phenol, trichloroacetic acid (TCA), salicylic acid, and AHAs. Phenol, weakly acidic in aqueous solution is actually phenylic acid and is quite distinct from AHAs, as is TCA. Both phenol and TCA have a long history of use as peeling agents. Both are caustic, corrosive, powerful denaturants. Both cause rapid chemical destruction of skin. Neither are nutritive, and their benefit is the post-injury replacement of destroyed epidermis and upper dermis through

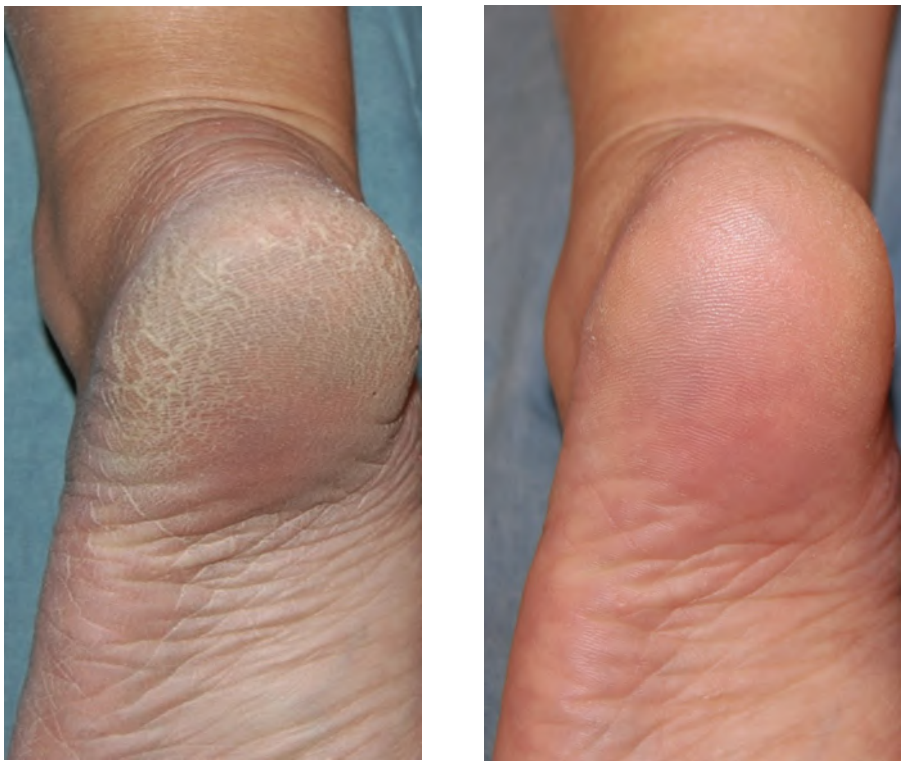


Figure 40.3 Hyperkeratotic feet treated once nightly with a cream containing an AHA/PHA/bionic acid blend (20% total) for 3 weeks. (a) Before treatment. (b) After treatment.

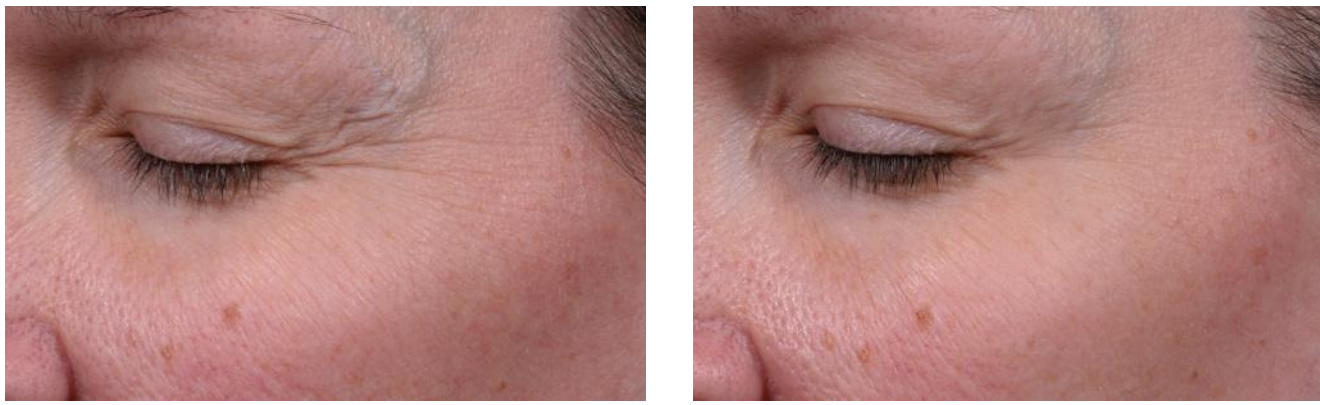


Figure 40.4 Periocular wrinkling is reduced on this 49-year-old female following twice daily application of 8% maltobionic acid cream (pH 3.8) for 12 weeks. (a) Before treatment. (b) After treatment.

mechanisms of wound repair. Salicylic acid (SA), 2-hydroxybenzoic acid, a phenolic acid, is in use today as an agent for superficial peeling mainly for acne.

Of the HAs, lactic acid and glycolic acid are the most common peeling agents. Many of the AHAs are nutritive and physiologic, giving them an advantage over phenol, TCA, and SA. In high concentrations of up to 70% or greater, lactic or glycolic acid can be applied to the skin for short times to achieve substantial desquamation and initiate accelerated epidermal and dermal renewal. To date, AHAs have been used primarily as superficial peeling agents offering the benefit of safety and effectiveness over the course of a series of peels [6]. AHA peels can also be safely combined with other cosmetic procedures to optimize results including nonablative laser, light treatments, and with injectable fillers and botulinum toxin type A [16,26,27].

Synergy with topical drugs

Enhancement of efficacy can be observed in many conditions by the combined presence of AHAs in formulations that contain active drug ingredients for particular treatments. Examples of active ingredients whose efficacy is enhanced include retinoids, antibacterials, antifungals, antipruritics, and corticosteroids. Mechanisms by which HAs complement or amplify the activity of another substance can be suspected in some instances, for example with retinoids and antibacterials in topical treatment of acne where activities of ingredients join to normalize intrafollicular keratinization and allow more efficient access of the antibiotic into the pilosebaceous unit. The HAs also may enhance therapeutic effect of drugs by providing complementary cosmetic effects. For example, concurrent use of the PHA, gluconolactone, with azelaic acid has been shown to improve therapeutic outcomes for rosacea by reducing skin redness and diminishing the appearance of telangiectasia presumably by increasing overall skin thickness, while also improving the tolerability of the medication [28].

Conclusions

In the quest to reverse the clinical signs of aging and improve overall skin health, the HAs (AHA, BHA, PHA, and bionic acids) have emerged as important ingredient technologies owing to their eudermatrophic effects. That is, HAs have the unique ability to nourish the skin towards normalcy, imparting meaningful cosmetic and therapeutic benefits in the process. HAs can be used alone or in combination with other topicals to target symptoms of photoaging and the myriad conditions of hyperkeratosis. HAs continue to be a mainstay in dermatology because they offer significant epidermal and dermal benefits while being safe for skin and the body, even following full body application over long periods of time such as when treating ichthyosis. As time marches forward, it is our expectation that more scientific data will lead to greater uses of HAs alone and in combination with cosmetics, drugs, and devices in dermatology.

References

1 Briden ME, Green BA. (2006) Topical exfoliation: clinical effects and formulating considerations. In: Draelos ZD, Thaman LA, eds. *Cosmetic Formulation of Skin Care Products*. New York: Taylor & Francis Group, pp. 237–50.

2 Van Scott EJ, Yu RJ. (1982) Substances that modify the stratum corneum by modulating its formation. In: Frost P, Horwitz S, eds. *Principles of Cosmetics for the Dermatologist*. St. Louis: CV Mosby, pp. 70–4.

3 Yu RJ, Van Scott EJ. (2005) α-Hydroxyacids, polyhydroxy acids, aldobionic acids and their topical actions. In: Baran R, Maibach HI, eds. *Textbook of Cosmetic Dermatology*, 3rd edn. New York: Taylor & Francis Group, pp. 77–93.

4 Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WB, *et al.* (1996) Effects of alpha-hydroxyacids on photoaged skin: a pilot clinical, histologic and ultrastructural study. *J Am Acad Dermatol* **34**, 187–95.

5 Green BA, Edison BL, Sigler ML. (2008) Antiaging effects of topical lactobionic acid: results of a controlled usage study. *Cosmet Dermatol* **21**, 76–82.

6 Van Scott EJ, Ditre CM, Yu RJ. (1996) Alpha hydroxyacids in the treatment of signs of photoaging. *Clin Dermatol* **14**, 217–26.

7 Bernstein EF, Underhill CB, Lakkakorpi J, Ditre CM, Uitto J, Yu RJ, *et al.* (1997) Citric acid increases viable epidermal thickness and glycosaminoglycan content of sun-damaged skin. *Dermatol Surg* **23**, 689–94.

8 Bernstein EF, Green BA, Edison B, Wildnauer RH. (2001) Poly hydroxy acids (PHAs): clinical uses for the next generation of hydroxy acids. *Skin Aging* **9** (Suppl), 4–11.

9 Rizer R, Turcott A, Edison B, *et al.* (2001) An evaluation of the tolerance profile of a complete line of gluconolactone-containing skincare formulations in atopic individuals. *Skin Aging* **9** (Suppl), 18–21.

10 Rizer R, Turcott A, Edison B, *et al.* (2001) An evaluation of the tolerance profile of gluconolactone-containing skincare formulations in individuals with rosacea. *Skin Aging* **9** (Suppl), 22–5.

11 Briden ME, Green BA. (2005) The next generation hydroxyacids. In: Draelos Z, Dover J, Alam M, eds. *Procedures in Cosmetic Dermatology: Cosmeceuticals*. Philadelphia, PA: Elsevier Saunders, pp. 205–12.

12 Bernstein EF, Brown DB, Schwartz MD, Kaidbey K, Ksenzenko SM. (2004) The polyhydroxy acid gluconolactone protects against ultraviolet radiation in an *in vitro* model of cutaneous photoaging. *Dermatol Surg* **30**, 1–8.

13 Charloux C, Paul M, Loisance D, Astier A. (1995) Inhibition of hydroxyl radical production by lactobionate, adenine, and tempol. *Free Radical Biol Med* **19**, 699–704.

14 (1998) 34th Report of the CIR expert panel: safety of alpha hydroxy acid ingredients. *Int J Toxicol* **17** (Suppl 1).

15 Johnson AW, Stoudemayer T, Kligman AM. (2000) Application of 4% and 8% glycolic acid to human skin in commercial skin creams formulated to CIR guidelines does not thin the stratum corneum or increase sensitivity to UVR. *J Cosmet Sci* **51**, 343–9.

16 Rendon MI, Effron C, Edison BL. (2007) The use of fillers and botulinum toxin type A in combination with superficial glycolic acid (AHA) peels: optimizing injection therapy with the skin-smoothing properties of peels. *Cutis* **79** (Suppl 1), 9–12.

17 Thibodeau A. (2000) Metalloproteinase inhibitors. *Cosmet Toil* **115**, 75–6.

18 Upadhya GA, Strasberg SM. (2000) Glutathione, lactobionate, and histidine: cryptic inhibitors of matrix metalloproteinases contained in University of Wisconsin and histidine/tryptophan/ketoglutarate liver preservation solutions. *Hepatology* **31**, 1115–22.

19 Van Scott EJ, Yu RJ. (1974) Control of keratinization with α-hydroxy acids and related compounds. *Arch Dermatol* **110**, 586–90.

20 Van Scott EJ, Yu RJ. (1984) Hyperkeratinization, corneocyte cohesion, and alpha hydroxyacids. *J Am Acad Dermatol* **11**, 867–79.

21 Berardesca E, Distante F, Vignoli GP, Oresajo C, Green B. (1997) Alpha hydroxyacids modulate stratum corneum barrier function. *Br J Dermatol* **137**, 934–8.

22 Grimes PE, Green BA, Wildnauer RH, Edison BL. (2004) The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* **73** (Suppl 2), 3–13.

23 Van Scott EJ, Yu RJ. (1995) Actions of alpha hydroxy acids on skin compartments. *J Geriat Dermatol* **3** (Suppl A), 19–24.

24 Kim SJ, Park JH, Kim DH, Won YH, Maibach AI. (1998) Increased *in vivo* collagen synthesis and *in vitro* cell proliferative effect of glycolic acid. *Dermatol Surg* **24**, 1054–8.

25 Kempers S, Katz HI, Wildnauer R, Green, B. (1998) An evaluation of the effects of an alpha hydroxy acid-blend skin cream in the cosmetic improvement of symptoms of moderate to severe xerosis, epidermolytic hyperkeratosis, and ichthyosis. *Cutis* **61**, 347–50.

26 Effron C, Briden ME, Green BA. (2007) Enhancing cosmetic outcomes by combining superficial glycolic acid (AHA) peels with nonablative lasers, intense pulsed light, and trichloroacetic acid peels. *Cutis* **79** (Suppl 1), 4–8.

27 Briden E, Jacobsen E, Johnson C. (2007) Combining superficial glycolic acid (AHA) peels with microdermabrasion to maximize treatment results and patient satisfaction. *Cutis* **79** (Suppl 1), 13–6.

28 Draelos ZD, Green BA, Edison BL. (2006) An evaluation of a polyhydroxy acid skincare regimen in combination with azelaic acid 15% gel in rosacea patients. *J Cosmet Dermatol* **5**, 23–9.

Chapter 41: The contribution of dietary nutrients and supplements to skin health

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BASIC CONCEPTS

- Diet and oral supplementation can influence skin appearance.
- Nutrients effective in minimizing UV skin damage include carotenoids, vitamin E (tocopherols), flavonoids, vitamin C (ascorbate) and n-3 fatty acids.
- Selenium, zinc, and copper protect against UV-induced damage.
- Diets containing high amounts of refined sugars may predispose skin to premature aging through the formation of advanced glycation end products (AGEs).

Introduction

The skin is the largest organ in the body and is exposed to many environmental factors affecting its appearance and health. Additionally, there are changes occurring over time in skin, determined by our genes and hormones. It is often said that the appearance of the skin can predict overall health or is a window to health inside of the body and there is much interest in maintaining a healthy skin appearance and function. One approach to achieve an optimal skin appearance is through the use of topical products, such as cosmetics. However, there is now a growing body of research indicating that diet and/or oral supplementation can also influence skin appearance as is reviewed in this chapter.

Historically, dietary deficiency of many of the essential nutrients (e.g. thiamin, zinc, and vitamins A and C) was first noted as a result of disruption of skin integrity or by a change in the skin's appearance [1]. Many nutrients are important co-factors in biochemical processes occurring within skin cells and therefore deficiencies are manifested by changes in the skin. For example, vitamin C was first discovered for its role in preventing scurvy and is an important co-factor for collagen synthesis [2]. Another example is riboflavin, which, when deficient, causes cracks in the corner of the mouth (angular cheilitis) as well as reddening and cracking of the lips, tongue, and mouth. Zinc deficiency may be noted in poor wound healing, and niacin and vitamin A deficiencies can cause dry skin or, in more extreme cases, dermatitis.

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Conversely, published studies seem to show that supplementation of some of these key nutrients can result in an improvement in skin condition and this has fueled the use of vitamins and other nutrients as benefit agents in cosmetic preparations. There is obvious interest in whether dietary supplementation of these key agents can also provide benefit to skin and how this compares with providing these actives via the topical route. For example, higher intakes of vitamin C have been associated with a lower likelihood of a wrinkled appearance and skin dryness, independent of age, race, education, body mass index (BMI), and supplement use [3,4], while use of vitamin C in topical products is fraught with challenges presented by the instability of the vitamin in skincare formulations. Vitamin C has a number of different biologic roles in skin, including participating in collagen synthesis, skin regeneration, and wound healing [5].

Many nutrients are required by the skin for different functions and this chapter aims to describe some of the key nutrients and discusses the data describing the use of these nutrients when provided orally for skin benefits (Table 41.1). Below is a description of several aspects of skin health and studies of nutrients or dietary supplements that have been shown to improve skin health and appearance.

Nutrients and their role in protecting against UV-induced damage

One of the leading consumer skin concerns is skin aging, and products to delay or reverse the signs of aging are in high demand. A major contributing factor to skin aging is UV radiation, mostly from the sun. Both UVA and UVB rays generate harmful free radicals in the skin contributing to

Table 41.1 Nutrients and their skin health benefits.

Nutrient groups	Specific nutrients	
Antioxidants	Vitamin C	Vitamin C is necessary for collagen synthesis, and higher intakes are associated with better skin appearance [3]. Supplemental vitamin C and E for 3 months significantly reduced the sunburn reaction to UVB irradiation and skin DNA damage [44]
	Vitamin E	Vitamin E is a fat-soluble antioxidant that accumulates in skin cells. It protects against free radical damage. However, if cell membranes are oxidized they become more rigid leading to skin wrinkle formation. Studies have shown that supplemental vitamin E reduced levels of malondialdehyde (MDA, a marker of oxidative stress) in the skin upon exposure to UV rays [18]. Skin healing is also affected by supplemental vitamin E. In 57 patients with pressure ulcers, administration of 400 mg/day oral vitamin E promoted faster healing than the placebo [25]
	Beta-carotene	Beta-carotene can be used in the body as a source of vitamin A, which is important for skin maintenance and repair. Several studies have also demonstrated that supplemental carotenoids improve skin health
	Lycopene	Lycopene is depleted from the skin faster than beta-carotene upon UV exposure [4]. Ten weeks of supplementation of tomato paste, high in lycopene, provided protection against erythema formation following UV irradiation [10,11]
	Lutein/zeaxanthin	Supplemental lutein/zeaxanthin has produced decreased UV damage and increased skin hydration and elasticity [16,17]
	Astaxanthin	Subjects given astaxanthin have shown significant improvements in elasticity, moisture content, and fine lines/wrinkles [33], and those consuming astaxanthin and vitamin E exhibited significant reductions in fine wrinkles and pimples, and increased moisture levels, after 4 weeks of supplementation [34]
	CoQ10	An important antioxidant necessary for energy metabolism. Supplementation of 60 mg CoQ10 for 3 months significant reduced wrinkle grade (depth and area of wrinkles) and improved skin properties [38,39]
	α-lipoic acid	A potent antioxidant that has benefit to water-soluble and fat-soluble portions of cells
	Combinations of antioxidants	A number of studies of vitamins E and C have shown additive or synergistic preventive benefits against UVB-induced erythema [45]. Subjects given beta-carotene, lycopene, vitamin E, vitamin C and experienced significant protection from sun damage [46]
Fish oil/omega-3 fatty acids	Eisapentaenoic acid (EPA) and docosahexaenoic acid (DHA)	Dietary consumption of fish oil is known to modulate the lipid inflammatory mediator balance and therefore is valuable in the treatment of inflammatory skin disorders. Consumption of EPA and DHA totaling 3–4 g/day for up to 3 months reduced erythema upon UV exposure in several studies [4]
Polyphenol and flavonoids	Green tea polyphenols	Polyphenols protect against free radical damage. Forty-one women aged 25–75 years given 300 mg (green tea extract containing 97% pure polyphenols) twice daily for 2 years experienced fewer fine wrinkles and telangiectasias and overall less solar damage compared with baseline and the control group [36]
	Grape seed extract and resveratrol	When subjects received 100 mg oligomeric proanthocyanidins along with vitamin C and SiO_2 and were then exposed to UV rays, they experienced less erythema and increased skin hydration [47]
Vitamin D		Vitamin D is a compound that is formed/activated in the skin upon sun exposure [48]. Unfortunately, there have not yet been any studies on skin health and supplementation
Minerals	Zinc	Zinc serves as a co-factor for many important enzymes in the body. Some of the best known are important for skin healing [49]
	Copper	Copper is an important co-factor for elastin, the support structure for skin
	Selenium	Selenium is a component of the antioxidant enzyme glutathione peroxidase. Supplemental selenium and copper have shown significant protection (versus placebo) against UV-induced cell damage [32]
Negative nutritional components	Diet high in fats and carbohydrates	Diets high in fats and carbohydrates have been shown to increase the likelihood of a wrinkled appearance [3]

photodamage, leading to the production of fine lines and wrinkles, and, in extreme cases of sun exposure, sunburn and skin cancers. With sun exposure and no or inadequate sun protection, the skin depends solely on its internal or endogenous defenses such as melanin for protection. Dietary micronutrients which act as antioxidants can help to protect against the free radical formation induced by UV irradiation. Some of the most widely studied nutrients that have been effective in minimizing UV damage occurring within skin include carotenoids, vitamin E (tocopherols), flavonoids, vitamin C (ascorbate), and n-3 fatty acids [6,7].

Currently, there is perhaps the most evidence to support the role of carotenoids in providing skin benefits, especially for UV damage. Topically, vitamin A has been shown to reduce the signs of photodamage and is most effective in the acid form available on prescription as Retin A® (Ortho Dermatologics, USA) (retinoic acid). Beta-carotene, lycopene, lutein, and zeaxanthin are major carotenoids in human blood and tissues, and are highly effective at quenching singlet molecular oxygen formed during photo-oxidative processes. In fact, carotenoids from a normal, unsupplemented diet accumulate in the skin [8] and confer a measurable photoprotective benefit (at least in lightly pigmented Caucasian skin) that is directly linked to tissue concentrations [9]. Dietary intake of tomato paste, which contains a number of carotenoids, including beta-carotene, lycopene, lutein, and zeazanthin, has been shown to provide photoprotective activity [10,11]. Dietary supplementation with 25 mg total carotenoids a day for 12 weeks to healthy volunteers significantly diminished erythema upon UV irradiation given at week 8. This effect was enhanced when the same regimen was given with 335 mg/day (500 IU) RRR-alfa tocopherol [12]. A 12-week supplementation of beta-carotene from *Dunaliella* algae was also effective in suppressing UV-induced erythema given at a dose of 25 mg/day to healthy volunteers [12]. It is thought that other carotenoids such as lycopene act synergistically with beta-carotene to protect the skin from UV irradiation [4]. In humans, it was shown that lycopene is depleted from the skin faster than beta-carotene upon UV exposure [13], suggesting a primary role of lycopene in mitigating oxidative damage in tissues, and an important role in the defense mechanism against adverse effects of UV irradiation on the skin. In fact, when a single UV light exposure of three times minimal erythemal dose (MED) was administered to human skin, lycopene concentrations decreased rapidly but skin beta-carotene concentrations declined slowly.

Lutein and zeaxanthin (LZ) are found in dark, leafy, green and yellow vegetables, and there is evidence that they can provide protection against UV-induced damage. The presence of these carotenoids in the skin following dietary and oral supplementation has been demonstrated [14,15], along with a benefit in reducing UV damage. Forty female subjects aged 25–50 years were assigned to receive one of the following:

1 Oral LZ at 5 and 0.3 mg, respectively, and a topical application of 50 p.p.m. lutein and 2 p.p.m. zeaxanthin;
2 Oral LZ as before and placebo topical application;
3 Placebo oral supplement and active topical application; and
4 Placebo for both treatments, twice daily for 12 weeks.

All active treatments reduced UV-light induced malondialdehyde (MDA: a measure of lipid peroxidation) production, with the topical and oral and topical treatments producing similar results, and the combined treatment producing the greatest reduction. Other benefits were also noticed in this study – there were measurable increases in skin lipids produced by all treatments, with the oral regimen producing significantly greater increases than the topical treatment. Additionally, hydration was increased similarly by oral and topical treatments, and significantly more with the combination treatment. All differences were significant for all treatments at week 12 compared with placebo, and for all time points after week 2 [16,17].

The benefit of tocopherols in photoprotection has also been studied. Vitamin E is commonly associated with protecting cell membranes from oxidative damage and administration of oral 400 IU/day vitamin E significantly reduced MDA production but not other measures of oxidative stress in the skin or sensitivity to UV damage [18]. The production of sebum containing dietary vitamin E by the sebaceous glands was shown to be the primary delivery route for sources of tocopherols to the skin surface [19].

Vitamin C is an important co-factor for the enzymes involved in collagen synthesis and it has also been shown to provide benefit in protecting against signs of photodamage. Boelsma *et al.* [4] reviewed studies that supplemented diet with vitamin C and identified four studies demonstrating a photoprotective effect of vitamin C on skin. Using data from the National Health and Nutrition Examination Survey (NHANES I), associations between dietary nutrient intakes and signs of skin aging in 4025 women aged 40–74 years were compared. High dietary intakes of vitamin C were associated with a lower likelihood of senile skin dryness and a reduced wrinkled appearance. In fact, an increase consumption of vitamin C, by 1 log unit, was associated with an 11% reduction in the odds of a wrinkled appearance and a 7% reduction in the odds of senile dryness, independent of age, race, education, BMI, other supplement use, sun exposure, menopausal status, family income, energy intake, or physical activity [3]. This was an important study as it was the first to directly relate dietary intakes, rather than supplementation, of vitamin C with skin aging and showed that a diet high in foods supplying vitamin C can lead to a lower prevalence of an aged appearance. Other dietary factors were also studied: a lower intake of vitamin A, lower protein, and higher thiamine intakes were also linked to a wrinkled appearance. Conversely, higher intakes of fat and carbohydrates were associated with an increased chance of

wrinkled skin appearance and skin atrophy. Thus, it appears that one's appearance may be an indicator of overall health status because balanced nutrition is essential, not only to prevent chronic diseases such as cardiovascular disease, certain cancers, and diabetes [20], but also to maintain skin health and ensure normal cellular function. It is a bold statement, but this evidence suggests that looking "old for one's age" may also reflect and/or be associated with an increased risk of disease and mortality [21,22].

Researchers have found that supplemental flavanoids for 10–12 weeks in humans protects against UV-induced erythema [23], although this is related to dose, with high doses appearing necessary to provide benefits. In one study, a cocoa supplement with 327 mg total flavanols produced an increased microcirculation in the skin, while the same cocoa drink containing 27 mg/day total flavanols had no benefit. Another study compared two groups of women ingesting either a high (326 mg/day) or low (27 mg/day) flavanol cocoa powder dissolved in 100 mL water for 12 weeks. The production of erythema following a 1.25 MED UV ray dose was reduced significantly by 15% and 25% at 6 and 12 weeks, respectively, in the high dose supplemented group. No such benefit was observed for the group receiving the lower dose of flavanols. In addition, in the high dose group, but not the low-flavanol group, increases in blood flow to cutaneous and subcutaneous tissues were observed, as well as increases in skin thickness, skin density, and skin hydration, along with a significant decrease in skin roughness and scaling [24].

Antioxidant combinations can provide added protection beyond single antioxidants alone in preventing UV damage. For example, in healthy volunteers given a carotenoid blend (25 mg/day) for 12 weeks there was a significant decrease in skin reddening following blue light exposure to the skin, whereas combining this with 500 IU vitamin E had an even more dramatic decrease after only 8 weeks of consumption [7]. Interestingly, in healthy individuals on a normal diet, little benefit was shown with individual antioxidants like vitamin E in preventing UV-induced skin damage [25]. Data show that a combination of supplemental antioxidants that most closely mimics a diet rich in antioxidants can provide a photoprotective effect against sun damage [26]. Administration of 1 g vitamin C and 500 mg vitamin E (as δ-alfa tocopherol) for 3 months to human volunteers significantly reduced the sunburn reaction to UVB irradiation as measured by a reduction in thymine dimer formation by 43% indicating a reduction in skin DNA damage, and an increased in MED by 41% [27].

Oral intake of lipids and lipid-soluble vitamins have long proved beneficial for skin. One study observed a photoprotective effect of a diet higher in olive oil on the skin [28]. Some evidence suggests that n-3 fatty acids (FA) may also be effective in protection against UV-induced skin cancers and photoaging, in part brought about by the reduction of UV-induced release of cytokines and other inflammatory mediators in a variety of skin cell types [29,30]. In humans, supplemental omega-3 FA have been shown to significantly increase the UVR-mediated erythema threshold and reduce the level of proinflammatory, immunosuppressive prostaglandin E_2 levels from UVB irradiation [31]. Fish oil supplements, which provide eicosapentanoic and docosahexanoic acid, have also shown a photoprotective effect [4,6].

Selenium, zinc, and copper have also been shown to provide benefit and protect against UV-induced damage. This could be because these nutrients are critical components for the activity of several enzymes associated with skin repair following UV irradiation (e.g. matrix metalloproteinase) [32]. A combination of 200 µg selenium and 4 mg copper alone, or with 14 mg vitamin E, 3.6 mg niacin, 0.4 mg pyridoxine, 0.12 mg thiamine, 0.08 mg riboflavin plus 9000 IU retinol per day during meals for 3 weeks gave significant protection (versus placebo) against UV-induced cell damage in the form of sunburn cells, but did not reduce UV-induced erythema. This study was performed on 16 healthy Caucasian subjects aged 20–37 years and the combined supplements gave the strongest effect [32].

Nutrients and their role in improving skin appearance

The benefit of nutrients in protecting the skin from damage was discussed in the previous section [3–32]. Cumulative photodamage results in the appearance of fine lines and wrinkles on the face, as well as changes in pigmentation and skin dryness and roughness. There is also evidence to support the use of oral nutrients in improving the signs of photodamage, once formed, and in improving overall skin condition.

The carotenoid astaxanthin is found in plants and algae and provides pink–orange color to shellfish and salmon. Supplementation of astaxanthin produced significant improvements in pre-existing fine lines and wrinkles, and also improved skin elasticity scores and moisture content [33]. Another study with 16 female subjects (mean age 40 years) with dry skin conditions were given either 2 mg astaxanthin (as 40 mg AstaReal®, Fuji, Toyama, Japan) and 4 mg natural tocotrienols or a control supplement for 4 weeks. Treated subjects exhibited significant reductions in fine wrinkles and pimples, and had increased skin moisture levels. These parameters contributed to the individual assessments that reported reduced swelling under the eyes, improved elasticity, and "better skin feel." Subjects on the placebo did not improve and generally worsened during this time [34].

Similarly, soy isoflavones have been shown to provide a significant improvement in fine wrinkles and skin elasticity, compared with a placebo group [35] after 12 weeks' supplementation. This study showed that the benefits were

evident in women in their late thirties and early forties. Another study examined the effect of green tea on skin condition. Forty-one women aged 25–75 years were given 300 mg of a proprietary green tea extract containing 97% tea polyphenols or a placebo twice daily for 2 years. At 24 months, fine wrinkles were significantly reduced compared to baseline, and at 12 months, telangiectasias were significantly reduced in the green tea supplemented group, but not the placebo group. At 24 months compared with 12 months, overall solar damage was reduced over time for the green tea supplemented group but not in the placebo group [36].

Sun damage to skin does not need to have been severe for it to respond to oral supplements within a relatively short period of time. Eight weeks is common for topical treatments to produce a noticeable difference in skin condition, which includes an improvement in moderate photodamage with 8 weeks' supplementation with key nutrients. For example, one study investigated 30 dry-skinned women aged 48–59 years with moderate xerosis and photoaging. The group was randomized to receive either a topical nanocolloidal gel containing 0.5 mg α-lipoic acid and 15 mg melatonin/emblica along with a nutritional supplement containing 3 mg lutein, 2.5 mg α-lipoic acid, 45 mg ascorbic acid, and 5 mg tocopherol. All treatments were given twice daily for 2 months. Dietary supplements, but not the placebo, significantly reduced blood free radical activity compared with baseline. Skin hydration was significantly increased in all groups compared with baseline and placebo. An increase in superficial skin lipids was found for the treatments, with all being significantly different from baseline. Significantly greater effects were seen with the combined versus individual treatments, and all treatments than the placebo. Lipid peroxidation at weeks 2, 4, and 8 on the skin was significantly greater with the control group [37].

A study of topical application of coenzyme Q10 (CoQ10) for 3 months showed reduced depth and area of wrinkles around the eye area of 20 elderly volunteers, compared with the vehicle, which was applied around the opposite eye. There was a 27% reduction in mean peak to valley depth of the skin and a 26% reduction in Rq values measured on the PRIMOS, compared with controls [38]. Similar findings were reported following daily oral supplementation of 60 mg CoQ10 for 3 months [39].

Diets containing high amounts of refined sugars may predispose skin to premature aging through the formation of advanced glycation end products (AGEs). Glycation is a non-enzymatic reaction between amino groups on proteins (i.e. lysine) and reducing sugars (i.e. fructose). This reaction creates cross-links in the skin and once these reactions occur they disrupt normal function and predispose skin to oxidation or premature aging in the extracellular matrix of the dermis. For example the cross-linkages between dermal molecules cause the loss of elasticity or other properties of the dermis observed during aging. Some preclinical studies have shown that supplemental nutrients such as α-lipoic acid may prevent the detrimental effects AGEs to the skin. Interestingly, some researchers have shown that AGEs may actually be photosensitizers to cause more severe DNA damage to the skin from phototoxicity which ultimately causes accelerated skin aging and increased risk of skin cancer. Future studies will help establish nutritional strategies to prevent the formation and detrimental effects of AGEs.

In summary, there is a growing body of literature that demonstrates that oral nutrients not only protect the skin from UV damage and reduce free radical damage, but also can improve skin condition after the effects of sun damage has formed.

Nutrients shown to provide additional skin benefits

As well as protecting from UV and improving photodamage, data exist to show that diet and nutritional supplementation can provide many other benefits for skin. Ingestion of 5 mg lutein and 0.3 mg zeaxanthin twice daily for 12 weeks was shown to improve skin moisture and elasticity [16,17] and this may have resulted from an increase in skin lipids which was demonstrated during the study. Increases in skin lipids and improvements in skin smoothness and elasticity have been reported from previous studies of orally ingested antioxidants [37,40].

A combination of nutrients was also found to provide significant skin changes. Thirty-nine healthy people with normal skin were divided into three groups and given 3 mg lycopene, 3 mg lutein, 4.8 mg beta-carotene, 10 mg α-tocopherol, and 75 μg selenium per day, a similar supplement with double the amount of lycopene without lutein, or a placebo. A significant increase of skin density and thickness, as determined by ultrasound, along with improved skin surface of decreased roughness and skin scaling (evaluated by Visioscan) was found for both antioxidant groups but not the placebo [7].

Nutrients and their potential in improving dermatologic disorders and wound healing

Skin disorders that have an inflammatory component (e.g. psoriasis and eczema) and are manifested by dry and flaky skin have responded to topical omega-3 polyunsaturated fatty acid supplementation [41] and these nutrients may therefore offer a therapeutic benefit when given orally.

There is also evidence to show that oral supplementation can assist in healing. In 57 patients with pressure ulcers, administration of 400 mg/day vitamin E provided faster healing of the ulcer compared with placebo. When 10 females with lichen sclerosis took 300–1200 IU/day vitamin

E, five improved markedly, two moderately, and three slightly [25]. Zinc deficiency has been associated with delayed wound healing and roughness of the skin [26,42]. Mixtures of tocopherol and CoQ10 have proved to be beneficial for skin healing [43].

Conclusions

An individual's appearance has been regarded as an indicator of overall health, well-being, and age. In fact, it might perhaps be an indicator of life expectancy [21,22]. Nutrients provided in the diet or through dietary supplements can provide benefits to overall skin health and appearance, and in some cases can reverse a wrinkled or aged appearance. There is also evidence that providing several nutrients together is more beneficial than providing single nutrients in isolation. The benefits of nutrients, such as carotenoids, flavonoids, CoQ10, α-lipoic acid, minerals, and omega-3 fatty acids are related to their antioxidant potential, but significant other benefits are also provided, for example nutrients often serve as co-factors for key metabolic enzymes in skin (e.g. vitamin C and collagen production).

References

1 Boelsma E, van de Vijver LP, Goldbohm RA, Klopping-Ketelaars IA, Hendriks HF, Roza L. (2003) Human skin condition and its associations with nutrient concentrations in serum and diet. *Am J Clin Nutr* **77**, 348–55.

2 Miller SJ. (1989) Nutritional deficiencies and the skin. *J Am Acad Dermatol* **21**, 1–30.

3 Cosgrove MC, Franco OH, Granger SP, Murray PG, Mayes AE. (2007) Dietary nutrient intakes and skin-aging appearance among middle-aged American women. *Am J Clin Nutr* **86**, 1225–31.

4 Boelsma E, Hendriks HF, Roza L. (2001) Nutritional skin care: health effects of micronutrients and fatty acids. *Am J Clin Nutr* **73**, 853–64.

5 Catani MV, Savini I, Rossi A, Melino G, Avigliano L. (2005) Biological role of vitamin C in keratinocytes. *Nutr Rev* **63**, 81–90.

6 Sies H, Stahl W. (2004) Nutritional protection against skin damage from sunlight. *Annu Rev Nutr* **24**, 173–200.

7 Heinrich U, Tronnier H, Stahl W, Bejot M, Maurette JM. (2006) Antioxidant supplements improve parameters related to skin structure in humans. *Skin Pharmacol Physiol* **19**, 224–31.

8 Darvin, ME, Patzelt A, Blume-Peytavi U, Sterry W, Lademann J. (2008) One-year study on the variation of carotenoid antioxidant substances in living human skin: influence of dietary supplementation and stress factors. *J Biomed Optics* **13**, 44028.

9 Stahl W, Heinrich U, Aust O, Tronnier H, Sies H. (2006) Lycopene-rich products and dietary photoprotection. *Photochem Photobiol Sci* **5**, 238–42.

10 Stahl W, Heinrich U, Wiseman S, Eichler O, Sies H, Tronnier H. (2002) Dietary tomato paste protects against ultraviolet light-induced erythema in humans. *J Nutr* **132**, 399–403.

11 Sies H, Stahl W. (2003) Non-nutritive bioactive constituents of plants: lycopene, lutein and zeaxanthin. *Int J Vitam Nutr Res* **73**, 95–100.

12 Stahl W, Heinrich U, Jungmann H, Sies H, Tronnier H. (2000) Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am J Clin Nutr* **71**, 795–8.

13 Ribaya-Mercado JD, Garmyn M, Gilchrest BA, Russell RM. (1995) Skin lycopene is destroyed preferentially over beta-carotene during ultraviolet irradiation in humans. *J Nutr* **125**, 1854–9.

14 Wingerath T, Sies H, Stahl W. (1998) Xanthophyll esters in human skin. *Arch Biochem Biophys* **355**, 271–4.

15 Lee EH, Faulhaber D, Hanson KM, Ding W, Peters S, Kodali S, *et al.* (2004) Dietary lutein reduces ultraviolet radiation-induced inflammation and immunosuppression. *J Invest Dermatol* **122**, 510–7.

16 Palombo P, Fabrizi G, Ruocco V, Ruocco E, Fluhr J, Roberts R, *et al.* (2007) Beneficial long-term effects of combined oral/topical antioxidant treatment with the carotenoids lutein and zeaxanthin on human skin: a double-blind, placebo-controlled study. *Skin Pharmacol Physiol* **20**, 199–210.

17 Roberts RL, Green J, Lewis B. (2009) Lutein and zeaxanthin in eye and skin health. *Clin Dermatol* **27**, 195–201.

18 Thiele JJ, Ekanayake-Mudiyanselage S. (2007) Vitamin E in human skin: organ-specific physiology and considerations for its use in dermatology. *Mol Aspects Med* **28**, 646–67.

19 Thiele JJ, Weber SU, Packer L. (1999) Sebaceous gland secretion is a major physiologic route of vitamin E to skin. *J Invest Dermatol* **113**, 1006–10.

20 Willett WC. (2002) Balancing life-style and genomics for disease prevention. *Science* **296**, 695–8.

21 Purba MB, Kouris-Blazos, Wattanapenpaiboon N, Lukito W, Rothenberg E, Steen B, e*t al.* (2001) Can skin wrinkling in a site that has received sun exposure be used as a marker of skin health and biological age. *Age Aging* **30**, 227–34.

22 Christensen K, Iachina M, Rexbye H, Tomassini C, Frederiksen H, McGue M, e*t al.* (2004) Looking old for your age: genetics and mortality. *Epidemiology* **15**, 251–2.

23 Stahl W, Sies H. (2007) Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight. *Mol Biotechnol* **37**, 26–30.

24 Neukam K, Stahl W, Tronnier H, Sies H, Heinrich U. (2007) Consumption of flavanol-rich cocoa acutely increases microcirculation in human skin. *Eur J Nutr* **46**, 53–6.

25 Tebbe B. (2001) Relevance of oral supplementation with antioxidants for prevention and treatment of skin disorders. *Skin Pharmacol Appl Skin Physiol* **14**, 296–302.

26 Richelle M, Sabatier M, Steiling H, Williamson G. (2006) Skin bioavailability of dietary vitamin E, carotenoids, polyphenols, vitamin C, zinc and selenium. *Br J Nutr* **96**, 227–38.

27 Placzek M, Gaube S, Kerkmann U, Gilbertz KP, Herzinger T, Haen E, e*t al.* (2005) Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol. *J Invest Dermatol* **124**, 304–7.

28 Purba MB, Kouris-Blazos, Wattanapenpaiboon N, Lukito W, Rothenberg EM, Steen B, e*t al.* (2001) Skin wrinkling: can food make a difference. *J Am Coll Nutr* **20**, 71–80.

29 Jackson MJ, Jackson MJ, McArdle F, Storey A, Jones SA, McArdle A, e*t al.* (2002) Effects of micronutrient supplements on UV-induced skin damage. *Proc Nutr Soc* **61**, 187–9.
30 Rhodes LE, Durham BH, Fraser WD, Friedmann PS. (1995) Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol* **105**, 532–5.
31 Black HS, Rhodes LE. (2006) The potential of omega-3 fatty acids in the prevention of non-melanoma skin cancer. *Cancer Detect Prev* **30**, 224-32.
32 La Ruche G, Cesarini JP. (1991) Protective effect of oral selenium plus copper associated with vitamin complex on sunburn cell formation in human skin. *Photodermatol Photoimmunol Photomed* **8**, 232–5.
33 Geria NM. (2007) Beauty and the beach: wonders from the sea. *Happi December.*
34 Yamashita E. (2002) Cosmetic benefit of dietary supplements containing astaxanthin and tocotrienol on human skin. *Food Style* **216**, 112–7.
35 Izumi T, Saito M, Obata A, Arii M, Yamaguchi H, Matsuyama A. (2007) Oral intake of soy isoflavone aglycone improves the aged skin of adult women. *J Nutr Sci Vitaminol (Tokyo)* **53**, 57–62.
36 Janjua R, Munoz C, Gorell E, *et al*. (2009) A two-year, double-blind, randomized placebo-controlled trial of oral green tea polyphenols on the long-term clinical and histologic appearance of photoaging skin. *Dermatol Surg* **35**(7), 1057–65.
37 Morganti P, Bruno C, Guarneri F, Cardillo A, Del Ciotto P, Valenzano F. (2002) Role of topical and nutritional supplement to modify oxidative stress. *Int J Cosmet Sci* **24**, 331–9.
38 Hoppe U, Bergemann J, Diembeck W, Ennen J, Gohla S, Harris I, et *al. (*1999) Coenzyme Q10, a cutaneous antioxidant and energizer. *BioFactors* **9**, 371–8.
39 Morre DM, Morre DJ, Rehmus W, Kern D. (2008) Supplementation with CoQ10 lowers age-related arNOX levels in healthy subjects. *Biofactors* **32**, 221–30.
40 Segger D, Shonlau F. (2004) Supplementation with Evelle improves skin smoothness and elasticity in a double blind placebo-controlled study with 62 women. *J Dermatol Treat* **15**, 222–6.
41 Henneicke-von Zepelin HH, Mrowietz U, Farber L, Bruck-Borchers K, Schober C, Huber J, et *al. (*1993) Highly purified omega-3-polyunsaturated fatty acids for topical treatment of psoriasis: results of a double-blind, placebo-controlled multicentre study. *Br J Dermatol* **129**, 713–7.
42 Lansdown AB, Mirastschijski U, Stubbs N, Scanlon E, Agren MS. (2007) Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Repair Regen* **15**, 2–16.
43 De Luca C, Deeva I, Mikhal Chik E, Korkina L. (2007) Beneficial effects of pro-/antioxidant-based nutraceuticals in the skin rejuvenation techniques. *Cell Mol Biol* **53**, 94–101.
44 Placzek M, Gaube S, Kerkmann U, et *al. (*2005) Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol. *J Invest Dermatol* **124**, 304–7.
45 Cesarini JP, Michel L, Maurette JM, Adhoute H, Bejot M. (2003) Immediate effects of UV radiation on the skin: modification by an antioxidant complex containing carotenoids. *Photodermatol Photoimmunol Photomed* **19**, 182–9.
46 Masaki T, Yoshimatsu H, Chiba S, Sakata T. (2000) Impaired response of UCP family to cold exposure in diabetic (db/db) mice. *Am J Physiol Regul Integr Comp Physiol* **279**, R1305–9.
47 Hughes-Formella B, Wunderlich O, Williams R. (2007) Anti-inflammatory and skin-hydrating properties of a dietary supplement and topical formulations containing oligomeric proanthocyanidins. *Skin Pharmacol Physiol* **20**, 43–9.
48 Holick MF, Chen TC, Lu Z, Sauter E. (2007) Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res* **22**, V28–33.
49 Rostan EF, DeBuys HV, Madey DL, Pinnell SR. (2002) Evidence supporting zinc as an important antioxidant for skin. *Int J Dermatol* **41**, 606–11.

Part 2: Injectable Antiaging Techniques

Chapter 42: Botulinum toxins

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BASIC CONCEPTS

- Botulinum toxins are high molecular weight protein complexes that are secreted by clostridial bacteria. This substance exacts its effects by binding to and cleaving specific proteins in the presynaptic nerve terminus, thus preventing release of acetylcholine and focally preventing nerve conduction.
- Currently only one type A botulinum toxin, Botox®, is approved in the USA for cosmetic use, specifically for the glabella. Botox is also approved for the treatment of axillary hyperhidrosis as well as other medical indications.
- In many other areas, Botox has a favorable safety profile and is effective in treating the upper, mid, and lower face, as well as several regions of focal hyperhidrosis (axillary, palmar, plantar, facial).
- Injection-related complications can largely be avoided with good technique and a detailed understanding of the regional anatomy.

Introduction

Botulinum toxins are produced by the Gram-positive, spore-forming anaerobe *Clostridium botulinum*, and cause chemical denervation by suppressing the release of the neurotransmitter acetylcholine from the axon terminals of peripheral nerves. There are seven distinct subtypes of botulinum toxin (A–G), with types A and B being the only clinically relevant subtypes at this time. Currently, there is one botulinum neurotoxin type A (BoNTA) and one botulinum neurotoxin B (BoNTB) toxin available for human use in the USA. Botox® (Allergan, Inc., Irvine, CA, USA) is the type A toxin, and it is currently US Food and Drug Administration (FDA) approved for several therapeutic indications (including blepharospasm and strabismus). Myobloc® (Solstice Pharmaceuticals, South San Francisco, CA, USA) is currently only approved for the therapeutic treatment of cervical dystonia.

Relevant to this chapter, Botox is approved for cosmetic use in the glabella (but is used off-label in various other facial sites as well), and is also approved for axillary hyperhidrosis (but is used off-label for hyperhidrosis of the palms, soles, face, and scalp). Treatment doses are not interchangeable for any of the botulinum products (even among other strains of type A toxin) and all references to BoNTA unless otherwise stated in this chapter refer to Botox.

Clostridial bacteria secrete high molecular weight protein complexes that include three key proteins: a 150-kDa toxin, a non-toxin hemagglutinin protein, and a non-toxin non-hemagglutinin protein. The non-toxin proteins may provide the toxin complex protection against temperature or enzymatic denaturation [1]. The 150-kDa toxin is cleaved by bacterial proteases to form a di-chain composed of a 100-kDa heavy chain and a 50-kDa light chain. Disulfide and non-covalent bonds link the heavy and light chains, and both chains are required for neurotoxicity [1].

In 1987, Canadian ophthalmologist Jean Carruthers recognized the cosmetic potential of BoNTA. While treating patients for benign essential blepharospasm, Dr. Carruthers noted that several patients treated for blepharospasm had significant improvement of dynamic rhytides in the periocular region. Following this observation, the husband and wife team of Drs. Alastair and Jean Carruthers began more systematic studies of BoNTA for cosmetic indications. In 1991, the Carruthers reported their initial findings of cosmetic treatment with BoNTA at North American Dermatology and Ophthalmology meetings. After initiating clinical trials, their first publication on this topic was in 1992, demonstrating the safe and effective treatment of dynamic rhytids in the glabella with BoNTA [2]. After over a decade of off-label cosmetic use in the USA, in 2003 BoNTA (Botox) was

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

approved specifically for the treatment of glabellar rhytids. Currently, off-label cosmetic uses continue to expand with regions of treatment encompassing not only the forehead and lateral canthus, but also the lower face and neck.

Botox and other BoNTA are also widely used worldwide for medical and therapeutic purposes including the treatment of hyperhidrosis, headaches, spasticity disorders, and depression. This chapter highlights both traditional and newer cosmetic applications of BoNTA.

Mechanism of action

The process of chemical denervation requires that the neurotoxin heavy chain bind a specific receptor on the presynaptic nerve terminal. This process leads to toxin–receptor complex endocytosis, and then subsequently to toxin light chain release through vesicle lysis [3]. While binding sites for each toxin have not been clearly defined, all toxins cause chemical denervation by suppressing the release of acetylcholine from the axon terminals of peripheral motor nerves. After vesicle lysis occurs within the axon terminus, toxin light chains ultimately prevent neurotransmission by cleaving specific protein isoforms necessary for the docking, fusion, and release of acetylcholine from this nerve terminus. Toxins A, C, and E cleave synaptosomal associated protein (SNAP-25) and toxins B, D, F, and G cleave vesicle associated membrane protein (VAMP, also known as synaptobrevin) [1]. Muscle paralysis occurs within approximately 3–7 days, and synaptic regeneration reverses the paralytic effect within 3–6 months [3].

Neurotoxin physical characteristics

The complex size of Botox is approximately 900 kDa and one vial contains 5 ng (100 units) of toxin. One unit (U) is standardized to equal the median amount necessary to kill 50% of female Swiss-Webster mice after intraperitoneal injection (LD_{50}) [3–5]. Botox is a vacuum-dried product and in addition to 100 U of toxin, each vial contains 500 µg albumin and 900 µg sodium chloride [1,5]. Typical cosmetic doses of Botox range from 10 to 60 units, depending on the number of areas treated in one session. Product characteristics of Botox compared with some of the other neurotoxins used throughout the world are provided in Table 42.1.

Product stability

Once a vial of Botox is reconstituted, the package insert indicates viability for 4 hours (refrigerated), but recent studies suggest that product is viable for much longer when properly handled. A double-blind, randomized study of 30 patients showed no significant difference in the treatment of canthal lines between those treated with Botox reconstituted with sterile, non-preserved saline immediately prior to injection compared with toxin reconstituted 1 week prior to injection [6]. Further, in one study product reconstitution at times ranging 1–6 weeks prior to injection produced statistically similar results in patients treated for glabellar rhytides compared with product reconstitution 1 day prior to injection [7].

Table 42.1 Botulinum toxin comparison.[1]

	Botox[3]	Dysport[4]	Myobloc[5]
Serotype	A	A	B
Molecular weight (kDa)	900	500–900	700
FDA[2] approved for cosmetic use?	Yes	No, pending	No
Protein weight per vial (ng)	5	5	25, 50, or 100
Units per vial (U/mL)	100	500	5000
pH	7	7	5.6
Target	SNAP-25[6]	SNAP-25	VAMP[7]

[1] Dosages are not equivalent between products.
[2] Food and Drug Administration.
[3] Allergan, Inc., Irvine, CA, USA.
[4] Ipsen Ltd, Slough, UK. (This product may be marketed as Reloxin in the USA.)
[5] Solstice Pharmaceuticals, South San Francisco, CA, USA. Marketed as Neurobloc outside of the USA.
[6] Synaptosomal associated protein (SNAP-25).
[7] Vesicle-associated membrane protein (synaptobrevin).

Advantages and disadvantages

Botox is a drug with a large margin of safety (LD_{50} in humans approximately 40 U/kg), making its cosmetic use a relatively safe endeavor [8]. Care should be taken to use the necessary dosing ranges in a given region in order to optimize patient satisfaction and preserve a natural result. Injectors should possess excellent knowledge of facial anatomy, especially considering the close proximity of adjacent musculature that may not be part of the intended area of treatment.

Indications

At the present time, the glabella is the only FDA-approved site for the cosmetic injection of Botox, although it is also used extensively off-label for other facial esthetic areas. The

Table 42.2 Precautions and contraindications.

Precaution	Mechanism
Ciclosporin	Has been reported to cause neuromuscular blockade, possibly through calcium channel blockade
Aminoglycoside antibiotics	Large doses can prevent release of acetylcholine from neurons
D-penicillamine	May cause formation of antibodies targeting acetylcholine receptor
Contraindication	
Myasthenia gravis	Autoantibodies targeting acetylcholine receptor
Lambert–Eaton syndrome	Paraneoplastic, antibodies targeting calcium channels
ALS	Neurodegenerative disease
Pregnancy or breastfeeding	Insufficient safety data
Allergy to any constituent of BoNTA	Potential for anaphylaxis

ALS, amyotrophic lateral sclerosis.

glabellar region is also the most common site of esthetic BoNTA treatment worldwide, and is a good starting point for the novice injector. Treatment of the glabellar complex frequently results in a high degree of patient satisfaction, and often patient follow-up for additional treatments in this and other areas. Aside from the glabella, other muscle groups in the upper, mid, and lower face and neck can be successfully treated "off-label" with Botox. Contraindications to BoNTA are few and are listed in Table 42.2 along with several precautionary medications [9].

Standard injection techniques

General pretreatment tips

Prior to treatment, patients should be informed that the typical duration of efficacy is likely to be 3–4 months, and potential side effects should be discussed. The fact that treatment of areas other than the glabella constitutes "off-label" use of Botox in the USA at the present time should be included in the consent. Consent should be in the form of an oral discussion as well as a signed, written document. Pretreatment asymmetries and scars should always be discussed, documented, and photographed prior to treatment.

Treatment of the upper face

Photodamage and overactive musculature can cause changes in the upper face that convey a fatigued or angry look that is often discordant with reality. Treatment of the upper face

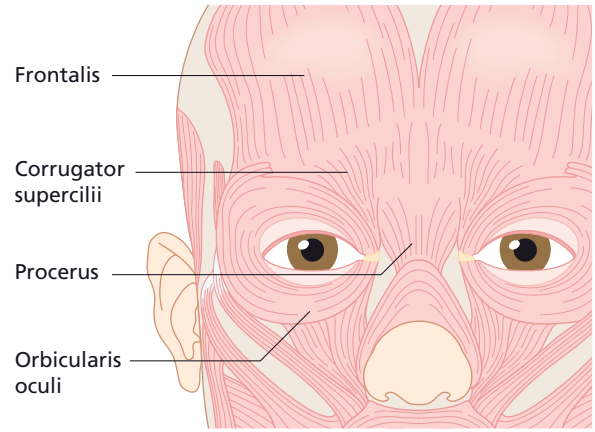


Figure 42.1 Relevant musculature of the upper face. (Adapted from Sommer B, Sattler G, eds. (2001) *Botulinum Toxin in Aesthetic Medicine*. Blackwell Science, Boston, MA.)

with BoNTA can lead to a more youthful, relaxed, and rested appearance [10,11]. Data also support the use of BoNTA in multiple areas of the upper face in a single treatment session [12].

Forehead

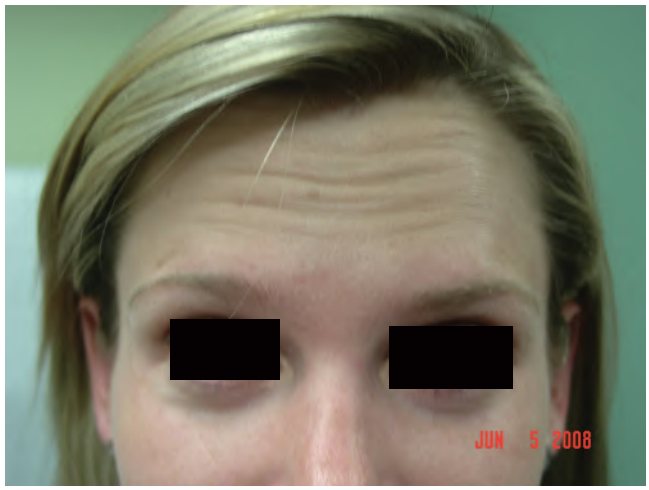
The frontalis muscle is contiguous with the galea aponeurotica of the scalp superiorly, and inserts inferiorly into the skin of the brow. Its configuration varies between individuals but it is generally considered to be either a uniform band across the forehead or V-shaped with a relative absence of fibers medially (Figure 42.1). Fibers of the frontalis are oriented vertically, and thus when they contract the brows elevate and horizontal forehead lines become imprinted in the skin over time. The lateral fibers of the orbicularis oculi muscle pull down on the lateral brow, and thus directly oppose the upward forces of the frontalis. This muscular interaction allows for the creation of a neurotoxin lateral brow lift (discussed below).

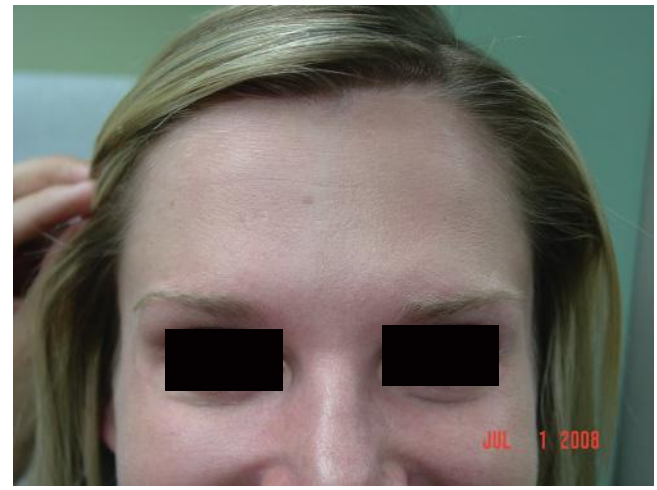
A recent consensus article addressed treatment of horizontal forehead lines caused by the frontalis [13]. Authors recommended ranges of 6–15 U and 6 to >15 U BoNTA for females and males, respectively (Table 42.3), and agreed that doses over 20 U are more likely to lead to complications or patient dissatisfaction (e.g. eyebrow ptosis and patient complaints of immobility and unnatural appearance). Forehead injections of BoNTA are generally placed over 4–9 injection sites. In order to avoid eyebrow ptosis, the injections should generally not be placed any closer than 1–1.5 cm above the bony orbital rim (Figure 42.2). Patients with tall foreheads may benefit from two rows of injections, and patients with wider foreheads may also require more injection sites. Attention to the shape and positioning of the patients baseline brow is essential, and often injection sites in women are performed in an arch to try to preserve the arch of the brow below. Patients with dermatochalasis or

Table 42.3 Treatment recommendations by site.

Treatment site	Muscles	Typical number of injection points	Typical total units of BoNTA*	
			Women	Men
Upper face				
Horizontal forehead lines	Frontalis	4–9	6–15	6 to >15
Glabellar complex	Procerus, depressor supercilii, orbicularis oculi	5–7	10–30	20–40
Crow's feet	Orbicularis oculi	2–5 per side	10–30	20–30
Narrow palpebral aperture	Pretarsal fibers of orbicularis oculi	1 per side	2	2
Lateral brow lift	Superolateral fibers of orbicularis oculi	1–2 per side	8–12	8–12
Mid face				
Bunny lines	Nasalis	1 per side	3–5	3–5
Gummy smile	Levator labii superioris alaeque nasi	1 per side	1–2	1–2
Lower face				
Perioral lines	Orbicularis oris	4–6 per lip	4–12	4–12
Dimpled chin	Mentalis	1–2	4–8	4–8
Downturned smile	Depressor anguli oris	1–2	6–8	6–8
Platysmal bands	Platysma	2–12 per band	20–35	20–35
Nerfertiti lift	Platysma	7 per side	28–42	28–42
Masseter hypertrophy	Masseter	5–6 per side	50–60	50–60

*BoNTA represents the type A botulinum toxin approved in the USA for cosmetics, Botox. All sites other than glabellar complex are "off-label" currently in the USA.

(a) 



(b)

Figure 42.2 Horizontal forehead lines before (a) and after (b) Botox injection.

low-set brows should be evaluated carefully prior to injection as they represent the population most at risk of significant eyebrow ptosis and/or complaints of "heaviness" after treatment. Patients with significant etched-in lines immediately superior to their lateral brows are also patients who may frequently be advised not to have BoNTA treatment as they depend on the baseline action of the lower frontalis fibers to hoist the brow upward and away from their eyelid.

Glabella

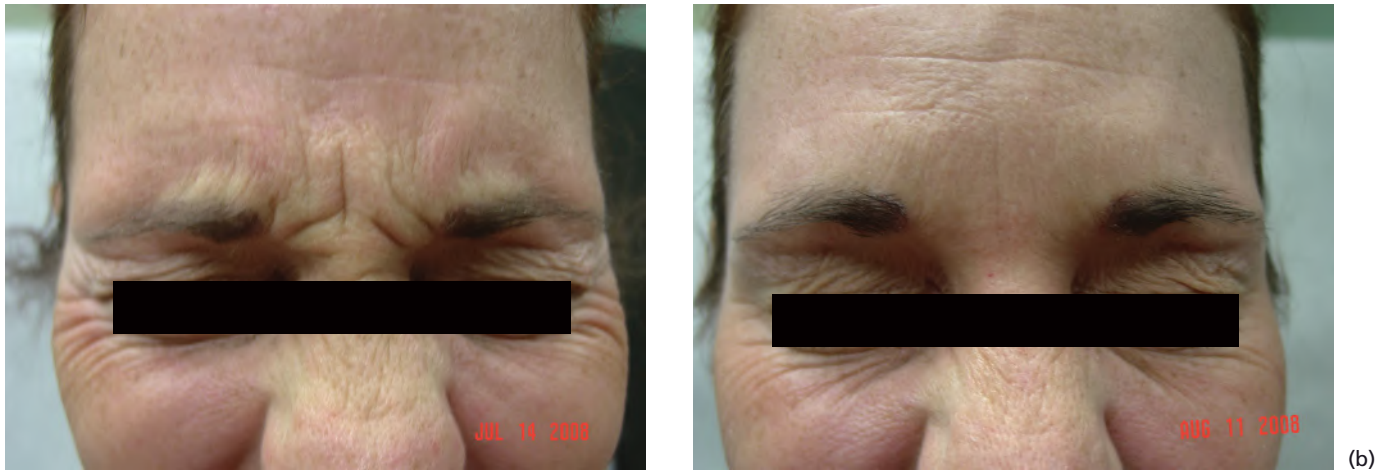
The glabellar complex (Figure 42.1) represents the site most commonly treated with BoNTA. In the USA, it is the only cosmetic site for which Botox has FDA approval. It is one of the easiest sites to treat and a good place for novice injectors to begin. Both the corrugator supercilii and the depressor supercilii originate on the nose and insert into the mid-brow. These muscles draw the brow medially and downward, and thus create vertical lines in the glabella. Treatment of these brow depressors leads to relaxation of these muscles, which usually results in a medial lift of the brow to some extent. The procerus muscle originates on the nasal bridge and inserts into skin of the mid-glabella. Contraction of the procerus also pulls the medial brow down, but with the pure vertical orientation of this muscle a horizontal line becomes etched in the skin with contraction over time.

Glabellar doses of Botox typically range 10–30 U in women and 20–40 U in men. Injections are most commonly placed in five specific sites: one injection in the procerus, one in each of the medial corrugators, and one in each of the lateral corrugators (Figure 42.3). Sometimes, in patients who display significant medial recruitment above the mid-brow, 1–2 additional injection sites can be helpful to avoid this central pulling. Toxin should generally not be placed any closer than 1–1.5 cm above the bony orbital rim in the mid-pupillary line in order to try to avoid lid ptosis. Lid ptosis can occur from migration of the toxin through the orbital septum to the levator palpebrae superioris muscle (which functions to elevate the lid upwards).

Periorbital

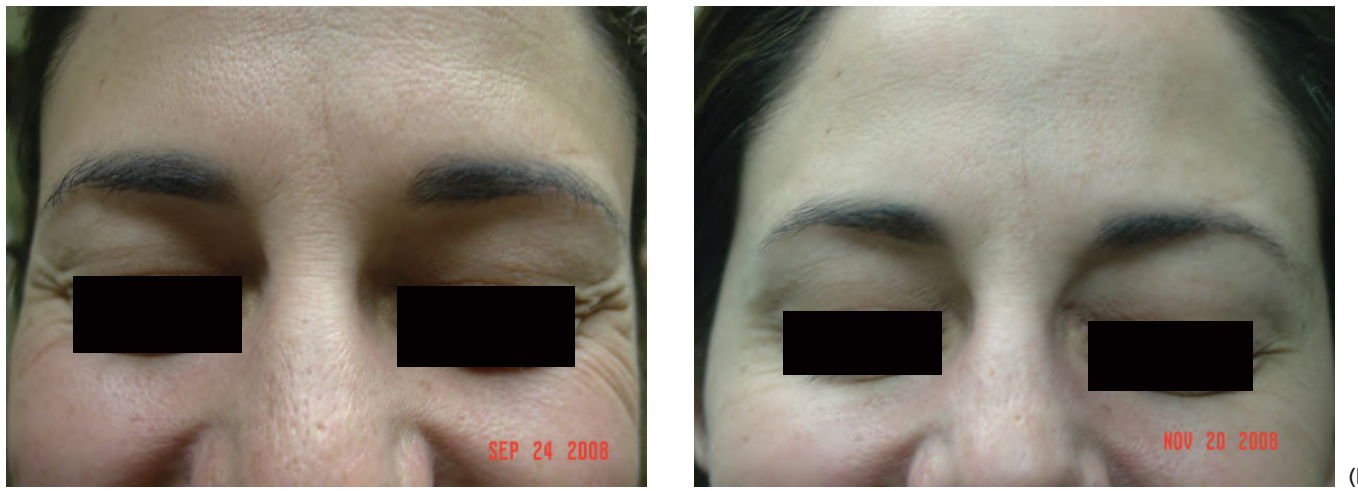
The orbicularis oculi muscle is a circular, sphincter-like muscle that surrounds the eye and functions in eyelid closure. The circularity of this muscle creates an anatomical structure composed of fibers running in multiple directions. The muscular diversity of the orbicularis oculi creates functional diversity in animation of the periorbital area. For example, the lateral and superolateral fibers of the orbicularis oculi immediately below the brow function as brow depressors. Treatment of the lateral canthal rhytides (commonly described as crow's feet) is often satisfying for the novice injector and the patient. Because of the presence of many small vessels in the lateral periocular area, it is often recommended to place BoNTA injections superficially (even intradermally) in this region, usually creating a wheal at the injection site. For treatment of lateral, canthal rhytides, the injector typically chooses 2–5 injection points per side, depending on the prominence of the musculature of the area. The reality is that orbicularis oculi muscle prominence varies between patients, making individual assessment of anatomy and patterns of dynamic muscular lines helpful prior to treatment of each patient [14]. Typically, 5–15 units of BoNTA are injected into each side (Figure 42.4). Care should be taken to inject no closer than 0.5–1 cm to the lateral orbital rim in order to avoid migration of toxin causing unintended paralysis of ocular muscles.

In a small minority of patients, pretarsal bands of the orbicularis oculi muscle can be hypertrophic at the lower lid. A hyperfunctional, pretarsal orbicularis oculi muscle can cause unsightly bands around the lower eyelid and narrow-



(a) (b)

Figure 42.3 Glabellar frown lines before (a) and after (b) Botox injection.



(a) (b)

Figure 42.4 "Crow's feet" before (a) and after (b) Botox injection.

ing of the palpebral aperture. If treating this infraorbital, hyperfunctional musculature, it is recommended to first evaluate lower lid laxity with a "snap-test" to ensure lid competency after the muscle is weakened. Typically, 1–2 units of BoNTA are used in this pretarsal area for patients who complain of significant muscle prominence of this area, or those who desire changing the shape of their eye from an almond-type shape to that of a more rounded eye with a widened palpebral aperture. Injections are placed carefully from a lateral approach subdermally, about 3 mm below the ciliary margin in the mid-pupillary line [13]. A lateral approach in this area helps to ensure a superficial injection, and to allow the non-injecting hand to pull down the lower lid and protect the patient from movement.

Lateral brow lift

In patients with downturned or ptotic lateral brows, either from dermatochalasis, overactive lateral orbicularis oculi activity pulling down on the tail of the brow, or inadvertent paralysis of the most inferior fibers of the frontalis after aggressive forehead BoNTA treatment, partial correction can sometimes be achieved with a BoNTA chemical brow lift. This lateral brow lift can be obtained by injection into the superolateral fibers of the orbicularis oculi muscle. This technique relaxes the specific aspect of the orbicularis oculi that is pulling the lateral brow downward, and carefully tries to avoid some of the adjacent inferolateral frontalis fibers just superior to the brow – as these frontalis fibers can be helpful to try to pull the lateral brow upward. To accomplish this effect the injector places 4–6 units of BoNTA in a specific spot just below the lateral infrabrow [15]. Identification of this injection site requires that the patient first elevate their brows to find the lateral margin of the frontalis muscle (known as the temporal fusion plane). Second, the patient must close their eyes forcefully in order to localize the area where the orbicularis oculi exerts maximal medial and

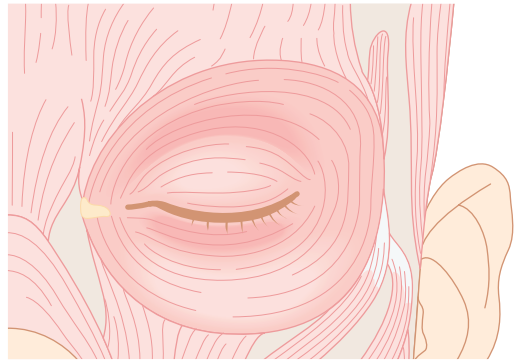


Figure 42.5 The lateral bow lift can be obtained by injection into the superolateral fibers of the orbicularis oculi muscle. This technique relaxes the specific aspect of the orbicularis oculi that is pulling the lateral brow downward. (Adapted from Sommer B, Sattler G, eds. (2001) *Botulinum Toxin in Aesthetic Medicine*. Blackwell Science, Boston, MA.)

downward pull on the lateral brow. The proper injection point is just inferior to the point of maximal pull downward on the brow, but making sure this site is at least 1–1.5 cm inferior to the most lateral fibers of the frontalis muscle (Figure 42.5). Avoiding these trailing lateral frontalis fibers allows for the preservation of the lift the lateral frontalis normally provides at baseline. Patients with more significant brow redundancy can sometimes be improved with a combination of BoNTA in conjunction with small volumes of fillers (e.g. 0.1–0.2 mL of a hyaluronic acid product) placed just below the lateral brow, but clearly those with more severe dermatochalasis can really only be effectively treated with surgical intervention.

Treatment of the mid-face

Bunny lines

Contraction of the nasalis muscle creates diagonal lines along the proximal nasal sidewall. This area is becoming a more common area of BoNTA treatment. Patients seeking

treatment of these lines often have experienced the benefits of BoNTA softening the forehead, glabella, and crow's feet and are looking to extend a more relaxed look to the midface. Identification of the muscle is straightforward and accomplished by having the patient "scrunch" their nose. Some 3–5 units of BoNTA can be placed superficially into the muscle at the medial aspect of the proximal nasal sidewall on each side of the nose. Placement of BoNTA too far laterally can lead to unwanted paralysis of the adjacent levator labii superioris aleque nasi (LLSAN), resulting in elongation or drooping of the upper lip. The final cosmetic result can often be enhanced with concomitant treatment of the procerus in some patients with more significant bunny lines that seem to be most bulky on the proximal nasal dorsum.

Softening of the nasolabial fold or "gummy smile"

An overactive LLSAN can be a component of an accentuated or prominent superior nasolabial fold. Treatment of the LLSAN can be an option for young patients looking to soften the superior aspect of the nasolabial fold without using fillers or at a lower cost than fillers. A total of 1–2 units of BoNTA can often achieve a softening of the top of the nasolabial fold, and a 1992 anatomic study by Pessa illustrated that the LLSAN is actually the more important muscle contributing to the prominence of the nasolabial fold. Higher doses (typically 3–5 units) of BoNTA are usually used at the same location for patients with significant gummy smiles. Injection of 3–5 units per side of BoNTA into the belly of LLSAN at the pyriform aperture can elongate the upper cutaneous lip and partially correct the excessive gingival display [16]. Doses of 5–7.5 units of BoNTA in patients with very severe gummy smiles have been reported [16].

In cases of a prominent nasolabial fold or a gummy smile, injection of the LLSAN is primarily a treatment for younger patients who can compensate for the resulting pronounced elongation of the cutaneous lip with other musculature. In addition to the LLSAN, the muscles responsible for the elevation of the upper lip particulary in younger individuals are the levator labii superioris, levator anguli oris, zygomaticus major and minor, and the depressor septi nasi. Older patients seem to be more reliant on primarily the levator labii muscles alone.

Treatment of the lower face

Perioral lines

The lips are the cosmetic focal point of the lower face and careful, conservative corrections can often dramatically improve aspects of an aging face. Vertical "etched in" lines of the perioral skin are common and are caused by years of contraction of the orbicularis oris muscle, a sphincter-like muscle that encircles the mouth. Etched in lines are preceded by years of vertical muscle columns in women, leading eventually to imprinting of the perioral skin. The skin in this area is highly innervated and vascular, and therefore injections into this region are generally associated with more discomfort and can be associated with bruising or swelling. Topical anesthetics and the application of ice-packets can be very beneficial.

Tenants of injecting BoNTA into the lips include: use of low doses with frequent follow-up for retreatment, preservation of symmetry utilizing photography and carefully placed injections, treatment of both upper and lower lips at the same time, and avoidance of midline injections to preserve the desirable Cupid's bow. Injection technique varies depending on individual anatomy, but typical treatments include four superficial injection sites in the upper lip (two points on each side of the upper lip) just above the vermillion border. In patients with more significant vertical muscle columns (taller, bulkier, deeper) sometimes an additional site on each side of the upper lip (often 1 cm above the vermillion border) can be helpful. For the lower lip, usually four superficial injection sites are performed as well (two sites on each side of midline approximately 1.5 cm apart). It is important to inject superficially and use lower dosages, especially for a patient's first treatment. Follow-up 2 weeks later will typically allow the injector to see if additional units may be helpful. Some have advocated doses for perioral injection to be in a range of 4–5 units [13], but the authors sometimes use a total of 10–12 units for patients with more significant perioral vertical muscle columns.

Dimpled chin

The mentalis muscle originates in the incisive fossa and inserts into the skin of the chin. Contraction of this muscle can create a dimpled appearance of the chin that has been termed "pebbled chin," "golfball chin," "peau d' orange chin," and "apple dumpling chin." A total of 4–8 U of BoNTA, placed as a single midline injection or in two points 0.5 cm lateral to midline at the bony part of the chin can be very effective. Product placed too far laterally risks paralysis of the depressor labii inferioris and can cause speech problems.

Downturned smile

Descent of the lateral commisures of the mouth can result from gravity and volume loss and sometimes from hypertrophy of the depressor anguli oris (DAO) muscle. Injection of BoNTA (3–4 units per side) into the posterior aspect of the DAO in a single injection site can sometimes partially correct this appearance of a downturned smile (Figure 42.6). Complications associated with medial diffusion or injection of BoNTA into the depressor labii inferioris are discussed below. DAO prominence is often associated with volume loss of the lower face, and in our experience combination treatment with fillers and BoNTA is more consistently effective than BoNTA alone.

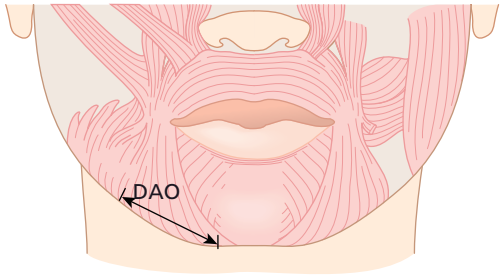


Figure 42.6 Treatment of a downturned smile is accomplished by injection into the posterior fibers of the depressor anguli oris (DAO) muscles. (Adapted from Sommer B, Sattler G, eds. (2001) *Botulinum Toxin in Aesthetic Medicine*. Blackwell Science, Boston, MA.)

Platysmal bands

The platysma is a thin, superficial muscle that can create vertical bands in the neck which are displeasing to many patients. Patient selection is key to successful treatment of this condition, and the most appropriate candidates are those with prominent vertical bands at rest. A typical treatment session includes injection of 2–3 bands with 20–35 U of BoNTA total (2–12 injection points per band). Dysphagia is a rare complication that has been reported with cosmetic use of BoNTA for treatment of platysmal bands [17]. Conservative treatment, with low dosages and superficial injections, is recommended in order to avoid this very rare and disturbing complication that can persist for weeks. Marking injection points and pinching the band between the thumb and forefinger can aid in the precise superficial placement of BoNTA.

In addition to the treatment of platysmal bands, placement of toxin along the inferior margin of the mandible and in the superior aspect of the posterior platysmal band may redefine the mandibular border. This procedure has been termed the "Nefertiti lift" and was described by Levy in a study of 130 patients [18]. Patients were treated with 2–3 units of BoNTA per injection site, with five sites being along the margin of the mandible and two sites being in the superior aspect of the posterior platysmal band. It was hypothesized that the resultant sharpening of the mandibular border was secondary to partial reversal of the chronic downward pull on the cheeks by the platysma.

Masseter hypertrophy

Prominent masseter bulk over the posterior mandible can create a squared-off shape to the face which is not desirable to some people. A study of 45 patients with masseter hypertrophy were treated with BoNTA and followed for 10 months [19]. Twenty-five to 30 units of BoNTA were injected into each masseter in 5–6 injection points. The maximum reduction in masseter thickness as measured by ultrasound was seen at 1 month and CT scan found continued reduction of masseter muscle thickness up to 3 months after treatment. Eighty-two percent of patients were satisfied with the treatment. Local adverse effects included masticatory difficulties (44% of patients) and speech disturbance (16% of patients). All side effects were transient.

A study specifically measuring bite force in patients treated with 25 units of BoNTA per masseter (50 units total) reported significant bite-force reduction at 2, 4, and 8 weeks post-injection ($p < 0.05$) [20]. Difference in bite-force reduction was not statistically significant at the 12-week measurement, and while bite-force measurements trended upward, they still did not achieve preinjection values at the end of 12 weeks. So while injection can beneficially alter the shape of the masseter, it may alter mastication. Further study is needed to better define the duration and significance of the observed bite-force reduction.

Combination of BoNTA with fillers

While BoNTA treatment works well for dynamic rhytides, resting lines and volume loss are not corrected by neurotoxin placement alone. Combination treatment consisting of hyaluronic acid and BoNTA often yield impressive results and may double the duration of response compared with filler treatment alone in some areas [21]. Combination therapy can be useful in the glabella, periorbital area, perioral, mentalis, and sometimes the nasolabial creases. Placement of filler prior to BoNTA treatment may decrease untoward migration of toxin caused by massage of the filler and the common practice of confirming placement of the filler product after injection. Areas lending themselves to combination treatment as well as injection tips are presented in Table 42.4.

Complications and management

Bruising, swelling, and mild asymmetry are commonly encountered issues. Less common is migration of toxin to adjacent but unintended musculature, which can result in significant asymmetry. Eyebrow ptosis can occur from toxin placement too close to the brow in the frontalis muscle, poor patient selection and use of higher dosages in the forehead. In fact, a recent consensus publication recommended using about half the frontalis dose of BoNTA previously suggested in an earlier statement by the same group [13].

Eyelid ptosis is also uncommon (less than 1% of patients in the hands of experienced injectors) and presumably occurs when injecting the lateral corrugator area, with migration of toxin through the orbital septum leading to the paralysis of the levator palpebrae superioris. This is a transient event (generally resolving by 2–3 weeks) and can be treated to some extent, but often not fully, by using ophthalmic drops such as Naphcon (Alcon, Fort Worth, TX, USA) (can be purchased over-the-counter) which exert mild

Table 42.4 Combination therapy with BoNTA and fillers.

Treatment area	Filler tip
Glabella	Prefer non-cross-linked collagen products* placed superficially and hyaluronic acid products with small particle size. Polymethylmethacrylate (Artefill), calcium hydroxylapatite (Radiesse), poly L lactic acid (Sculptra) and silicone should only be used by very experienced injectors in this area
Crow's feet	Thin skin requires thin product such as non-cross-linked collagen agent* or a hyaluronic acid designed for superficial placement in small aliquots with 32-gauge needle
Perioral lines	Prefer collagen products (type depending on depth of wrinkle) or hyaluronic acid of small particle size. Polymethylmethacrylate (Artefill), calcium hydroxylapatite (Radiesse), poly L lactic acid (Sculptra) and silicone should only be used by very experienced injectors in this area and still should not be placed shallowly
Downturned smile/marionette lines	Correction of downturned smile with BoNTA can be enhanced with filler placement in the marionette lines. Useful agents in this area include collagens, hyaluronic acids, silicone, poly L lactic acid and calcium hydroxylapatite. Choice of filler depends on skill and experience of the injector
Mentalis	Choice of filler depends on skill and experience of the injector

*Zyderm I or II and Cosmoderm I or II.

adrenergic effects, or Iopidine (Alcon, Fort Worth, TX, USA) prescription drops [22]. The mechanism of both treatments is adrenergic stimulation and contraction of the adjacent Mueller's muscle which can partially raise the eyelid. Iopidine may mask underlying glaucoma so this treatment should be reserved for short periods of treatment such as 3–5 weeks, as the eyelid ptosis is transient in nature [22].

In a double-blind, placebo-controlled, glabellar study, headache occurred in 20% of patients in the placebo group vs. 11.4% in the BoNTA treated group, leading authors to conclude that headache was likely related to trauma from the injection itself [23]. A non-blinded case series of 320 patients treated for cosmetic reasons with BoNTA reported the occurrence of severe, debilitating headaches in 1% of patients treated [24]. In this study, these headaches occurred within 2 days of injection with BoNTA and persisted at a high level for 2 weeks to 1 month after injection.

As far as bruising and swelling, it is best to wipe off the patient's make-up prior to injection (particularly in the lateral canthal area), to best identify little veins in the area to better avoid them and to avoid the risk of introducing foreign make-up material into the skin. Ice prior to injection to facilitate vasoconstriction is also very helpful in helping to reduce the mild pain of the injections themselves. If patients are on medications or vitamins for preventive purposes that may have an anticoagulant type of effect, it is certainly helpful if they discontinue these agents a few days prior to injection. An example of such an agent would be the use of aspirin as a preventive measure in patients lacking a history of atherosclerotic disease, stroke, or clot.

Immunogenicity to BoNTA has been reported in the literature but is very rare in patients treated with the newer (post-1997) formulation of BoNTA. The newer formulation of Botox has only 20% of the protein content that the older batch had (pre-1997) and presumably has made the product significantly less immunogenic. One case report, however, describes neutralizing antibody formation to the post-1997 formulation of Botox in a patient treated cosmetically for masseter hypertrophy [25]. Presence of neutralizing antibody was supported by two positive mouse protection assays and by ELISA testing [25]. Risks associated with immunogenicity are very large doses of toxin (more frequent in therapeutic uses of BoNTA) and short intervals (less than 3 months) between high-dose injections [1].

Generalized reactions have been reported related to toxicity and include headache, nausea, malaise, fatigue, flu-like symptoms, and rashes distant to injection sites from improper dosages and the use of "experimental strains of botulinum toxin" [26]. In studies measuring complications in patients treated with legitimate BoNTA, adverse events occurred in similar frequencies in both treatment and placebo groups. Most post-injection issues are transient in nature and resolve spontaneously, requiring no intervention other than reassurance.

Upper face

Injection into the frontalis muscle can lead to brow ptosis, and patients can develop a quizzical look (raising of the lateral brow because of residual non-treated frontalis fibers pulling upward) if only medial fibers of the frontalis are treated. This "Mr. Spock" look can usually be easily treated with placement of 1–2 units in each side of the lateral functional frontalis. In addition, patients can rarely experience painful electric shock-like sensations if the supraorbital or supratrochlear sensory nerves are inadvertently hit with the injection needle.

Lower face

Treatment of the orbicularis oris muscle for correction of vertical lip lines can very rarely lead to drooling or difficulty with phonation. Thus, when treating vertical muscle columns caused by a hyperfunctional orbicularis oris muscle, care should be taken to use lower dosages and avoid overtreatment. In addition, medial placement of these injections

can help avoid unintended musculature being affected, especially near the oral commissure.

Correction of downturned smile is best accomplished with careful BoNTA placement in the posterior aspect of the depressor anguli oris muscle. This posterior placement helps avoid unintended medial migration and effect on the depressor labii inferioris, a complication that can cause slurred speech and drooling and lasts weeks to months [27]. As far as the neck, injection of BoNTA into the neck for softening of platysmal bands has in one report led to prolonged dysphagia secondary to paralysis of the deeper strap muscles requiring placement of nasogastric tube [17]. This event can be best avoided by following the recently revised recommendations presented in this chapter.

Even the most experienced of injectors may observe asymmetric treatment effect, despite consistent technique. This unbalanced appearance is usually easily corrected with additional enhancement injections. Finally, temporary strabismus or diplopia are extremely rare and infrequently reported, and likely occur by either large diffusion or direct injection of toxin into the extraocular muscles.

References

1 Huang W, Foster JA, Rogachefsky AS. (2000) Pharmacology of botulinum toxin. *J Am Acad Dermatol* **43**, 249–59.

2 Carruthers JDA, Carruthers JA. (1992) Treatment of glabellar frown lines with *C. botulinum* exotoxin. *J Dermatol Surg Oncol* **18**, 17–21.

3 Sadick NS, Matarasso SL. (2004) Comparison of botulinum toxins A and B in the treatment of facial rhytides. *Dermatol Clin* **22**, 221–6.

4 Ting PT, Freiman A. (2004) The story of *Clostridium botulinum*: from food poisoning to Botox®. *Clin Med* **4**, 258–61.

5 Matarasso SL. (2003) Comparison of botulinum toxin types A and B: a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides. *Dermatol Surg* **29**, 7–13.

6 Lizarralde M, Gutierrez SH, Venegas A. (2007) Clinical efficacy of botulinum toxin type a reconstituted and refrigerated 1 week before its application in external canthus dynamic lines. *Dermatol Surg* **33**, 1328–33.

7 Hexsel DM, Trindade de Almeida A, Rutowitsch M, *et al*. (2003) Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to 6 consecutive weeks before application. *Dermatol Surg* **29**, 523–9.

8 Scott AB, Suzuki D. (1988) Systemic toxicity of botulinum toxin by intramuscular injection in the monkey. *Mov Disord* **3**, 333–5.

9 Cote TR, Mohan AK, Polder JA, Walton MK, Braun MM. (2005) Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol* **53**, 407–15.

10 Cox SE, Finn JC, Stetler L, Mackowiak J, Kowalski JW. (2003) Development of the Facial Lines Treatment Satisfaction Questionnaire and initial results for botulinum toxin type A-treated patients. *Dermatol Surg* **29**, 444–9; discussion 449.

11 Finn JC, Cox SE, Earl ML. (2003) Social implications of hyperfunctional facial lines. *Dermatol Surg* **29**, 450–5. Review.

12 Flynn TC. (2006) Update on botulinum toxin. *Semin Cutan Med Surg* **25**, 115–121.

13 Carruthers J, Fagien S, Matarasso SL, and the Botox Consensus Group. (2008) Advances in facial rejuvenation: botulinum toxin type a, hyaluronic acid dermal fillers, and combination therapies: consensus recommendations. *Plast Reconstr Surg* **121** (Suppl), 5–30S.

14 Kane MA. (2003) Classification of crow's feet patterns among Caucasian women: the key to individualizing treatment. *Plast Reconstr Surg* **112**(Suppl), 33–9S.

15 Cohen JL, Dayan SH. (2006) Botulinum toxin type A in the treatment of dermatochalasis: an open-label, randomized, dose-comparison study. *J Drugs Dermatol* **5**, 596–601.

16 Kane MA. (2003) The effect of botulinum toxin injections on the nasolabial fold. *Plast Reconstr Surg* **112** (Suppl), 66–72S; discussion 73–4S.

17 Carruthers J, Carruthers A. (1999) Practical cosmetic Botox techniques. *J Cutan Med Surg* **3** (Suppl 4), S49–52.

18 Levy PM. (2007) The "Nefertiti lift": a new technique for specific re-contouring of the jawline. *J Cosmet Laser Ther* **9**, 249–52.

19 Park MY, Ahn KY, Jung DS. (2003) Botulinum toxin type A treatment for contouring of the lower face. *Dermatol Surg* **29**, 477–83.

20 Ahn KY, Kim ST. (2007) The change of maximum bite force after botulinum toxin type a injection for treating masseteric hypertrophy. *Plast Reconstr Surg* **120**, 1662–6.

21 Carruthers J, Carruthers A. (2003) A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytides in adult female subjects: treatment of severe glabellar rhytides with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg* **29**, 802–9.

22 Klein AW. (2003) Complications, adverse reactions, and insights with the use of botulinum toxin. *Dermatol Surg* **29**, 549–56.

23 Carruthers JD, Lowe NJ, Menter MA, Gibson J, Eadie N, Botox Glabellar Lines II Study Group. (2003) Double-blind, placebo-controlled study of the safety and efficacy of botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg* **112**, 1089–98.

24 Alam M, Arndt KA, Dover JS. (2002) Severe, intractable headache after injection with botulinum a exotoxin: report of 5 cases. *J Am Acad Dermatol* **46**, 62–5.

25 Lee S. (2007) Antibody-induced failure of botulinum toxin type A therapy in a patient with masseteric hypertrophy. *Dermatol Surg* **33** (1 Spec No.), S105–10.

26 Bootleg Botox sentences. *New York Times* January 27, 2006. Available at: http://query.nytimes.com/gst/fullpage.html?res59B02EFDB113FF934A15752C0A9609C8B63. Accessed November 26, 2007.

27 Cohen JL. (2007) Botulinum neurotoxin clinical update. *Cosmet Dermatol* **20**, S3.

Chapter 43: Hyaluronic acid fillers

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BASIC CONCEPTS

- Hyaluronic acid fillers are used for 86% of the volume enhancing procedures performed in the USA.
- Hyaluronic acid filler are popular because they are non-permanent but long-lasting, have few allergic aspects, minimal side effects, are relatively painless to inject, and can be reversible.
- Hyaluronic acid is a polysaccharide, specifically a glycosaminoglycan, that is formed from repeating D-glucuronic acid and D-N-acetylglucosamine disaccharide units. The disaccharide units are linked together in a linear chain forming a large polymer with a total molecular weight of greater than 10 MDa.
- The different hyaluronic acid fillers possess various hyaluronic acid concentrations, sizes of particles, gel consistencies, type of cross-linking, degree of cross-linking, and the degree of gel hardness.
- Hyaluronic acids are injected in the deep dermis for optimal volume replacement.

Introduction

The appearance of the aging face is a compilation of intrinsic aging; influenced by genetics causing the preprogrammed loss of fat, muscle, and bone as well skin elasticity changes, and extrinsic aging; primarily photodamage that affects collagen, elastin, and accelerates the intrinsic aging process [1]. One of the hallmarks of the aging face is the loss of tissue volume and as well as the accentuation of lines and folds [2]. While many procedures can be used to improve the appearance of the aging face, the use of soft tissue, dermal fillers has become one of the most popular ways of filling lines and wrinkles as well as replacing volume in the aging face [3].

According to recent statistics of the American Society of Aesthetic Plastic Surgeons, the use of dermal fillers is only second to Botox® (Allergan, Inc., Irvine, CA, USA) as one of the most popular non-surgical cosmetic procedures performed in 2007. Of all the dermal fillers used in the USA, hyaluronic acid fillers accounted for nearly 86% of fillers used [4]. While hyaluronic acid fillers might not be the "perfect" filler in all aspects, they come very close to what most patients and physicians look for in the ideal filler, namely non-permanent but long-lasting, having few if any allergic aspects, minimal side effects, relatively painless to inject, and safe because of the reversible nature of hyaluronic acid fillers. This chapter outlines the science and use of hyaluronic acid fillers including:

1 The chemical composition and physical properties of hyaluronic acid fillers.
2 The indications for the variety of Food and Drug Administration (FDA) approved fillers.
3 Injection techniques, both beginner and advanced.
4 Complications of filler injections and their solutions.
5 Future uses and indications for hyaluronic acid fillers.

Chemical composition and properties of hyaluronic acid fillers

At this time, there are nine FDA approved hyaluronic acid fillers used in the USA. These are listed in Table 43.1. All hyaluronic acid fillers are formed from either bacterial-based or animal-based hyaluronic acid. Hyaluronic acid is a polysaccharide, specifically a glycosaminoglycan, that is formed from repeating D-glucuronic acid and D-N-acetylglucosamine disaccharide units. The disaccharide units are linked together in a linear chain forming a large polymer with a total molecular weight of greater than 10 MDa. While both animal-based and bacterial-based hyaluronic acid fillers are on the market, the vast majority of utilized fillers are based on bacterial production. Native hyaluronic acid would break down very quickly if injected into the skin and needs to be altered and stabilized primarily by cross-linking to have a long resident life in the skin. Because the basis of all bacterial-based dermal fillers is the same, the difference of the fillers and their properties depend upon the type and

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Table 43.1 Food and Drug Administration (FDA) approved fillers.

Allergan
Juvéderm™ Ultra/Juvéderm™ Ultra Plus
Captique/Hylaform/Hylaform Plus (phasing out)
Anika Therapeutics
Hydrelle™
Medicis
Restylane®
Perlane®
Mentor
Prevelle™ Silk

degree of cross-linking as well as the manufacturing process that forms the ultimate filler [5].

The important chemical and physical properties of the different filler substances include as noted, the type and degree of cross-linking, the total hyaluronic acid concentration, the size of the particle and/or the consistency of the gel, and the degree of gel hardness or G prime.

Cross-linking

The most commonly used hyaluronic acid products in the USA use 1, 4-butanediol diglycidyl ether (BDDE) as cross-linking agents. This includes Juvéderm® (Allergan, Inc., Irvine, CA, USA), Perlane®, and Restylane® (Medicis Aesthetics, Inc., Scottsdale AZ, USA), which are the most commonly used hyaluronic acid products in the USA. Hydrelle™ (Anika Therapeutics, Bedford, MA, USA) uses a different cross-linking agent called biscarbodiimide (BCDI). The degree of cross-linking indicates the percentage of hyaluronic acid disaccharide monomer units that are bound to a cross-linking molecule. For hyaluronic acid fillers, some feel that when all factors are equal, a higher degree of a cross-linking agent may translate into a longer persistence of the filler. However, there are questions about the effect that the cross-linking has on biocompatibility, setting the filler as a foreign substance. Therefore there may be an optimal degree of cross-linking that may give the longest term residence in the skin without causing biocompatibility issues.

Hyaluronic acid concentration

Total hyaluronic acid concentration refers to the amount of hyaluronic acid per milliliter in a product. It generally measures both cross-linked hyaluronic acid and free hyaluronic acid in a product. Free hyaluronic acid or uncross-linked hyaluronic acid is generally added in varying amounts to some products to improve lubrication or product flow. The most widely used hyaluronic acid products are of similar concentration but may vary as to the degree of free or uncross-linked hyaluronic acid, gel hardness, and hyaluronic acid gel consistency. The two most popular hyaluronic acid products, Restylane and Juvéderm, are produced by different mechanical means. The Restylane product line is pressed through screens to split the molecules into different size particles. Juvéderm is manufactured in a way that homogenizes the particles in a blender-type apparatus. The different formulations and production strategies yield different gel hardness or G prime to the variety of different products. Clinically, G prime can be thought of both as the amount of force that is necessary to inject a product through a specific-sized needle, as well as the lifting capacity of the filler. In general, fillers that are thicker are more difficult to inject through smaller needles, but based on their properties can act to bring in more water and thus cause more tissue lifting in a given area.

Indications

Virtually all fillers are FDA approved to fill "moderate to severe lines and folds" such as the nasolabial fold. Historically, fillers such as collagen were used to fill fine lines and wrinkles including those in the perioral and periorbital regions. Collagen fillers were injected in the mid-dermis and usually had a clinical life in the skin of approximately 3–6 months. Hyaluronic acid fillers are generally injected deeper in the skin, most often below the dermis in the superficial subcutaneous layer and traditionally have primarily been indicated for deeper lines and folds [6,7]. Hyaluronic acid fillers cannot be injected very superficially because of a complication known as the Tyndall effect; whereby the filler appears as a blue hue directly under the skin [8]. The majority of hyaluronic acid fillers used to date were initially used in the nasolabial fold, mesiolabial fold, as well as other similar lines and folds in the face. Over the last 3–4 years, the use of hyaluronic acid fillers has also eclipsed into volume replacement. Thicker hyaluronic acid fillers such as Perlane and Juvéderm Ultra Plus are indicated to replace volume in areas such as the midface and lower face to replace volume lost in both the intrinsic and photoaging process.

Hyaluronic acid fillers may be used to augment areas such as the lips by both replacing lost volume with aging and enhancing lip volume. Additionally, fillers are used to replace volume in areas such as the hands and resculpt and act as reshaping agents in areas such as the nose and the chin [9,10]. Hyaluronic acid fillers have significant advantage for these indications because of their longevity and overall low incidence of inflammation and significant swelling.

Injection techniques

Fillers in general are injected using three basic techniques:
1 Droplet injection;
2 Linear threading, either antegrade or retrograde;
3 Fanning.

As noted, the majority of hyaluronic acid are injected either in the deep dermis or superficial subcutaneous layer and studies have shown that the vast majority of injections are in the subcutaneous layer [7]. Most injectors use a combination of injection techniques depending upon the specific area that is being injected. Studies have shown that slower injection techniques tend to decrease side effects and swelling as well as decrease patient discomfort [11].

Patients are usually prepared by cleansing the area either with alcohol or another anti-infective topical cleansing substance. A topical anesthethic is often used either in the form of topical lidocaine, or compounded topicals that may include lidocaine and benzocaine. Many injectors also use cooling methods to both decrease pain of injection, as well as decrease swelling and bruising. As the injector gets more comfortable, advanced injection techniques, specifically with regard to volume, may utilize the use of large volumes of hyaluronic acid filler to replace and sculpt volume in areas of loss and these injections may take place in the deeper subcutaneous tissue or under the muscle layer. Injection sites that may be under the muscle include the tear troughs and malar regions.

Complications

Possible complications of hyaluronic acid fillers include unevenness of the filler substance, inflammation, swelling, and bruising, injection of the hyaluronic acid filler too superficially in the dermis, and, rarely, abscesses, both bacterial and sterile [12]. Swelling and bruising can be thought of by some as complications, but are usually normally associated with any filler injection. Depending upon the injection technique, swelling and bruising may be common but can often be mitigated by the use of ice as well as the use of a slow injection technique. Patients should be warned that they certainly can experience some swelling and bruising for at least the first 48 hours after injection.

The most common type of complication is the unevenness of hyaluronic acid fillers. The clinician needs to evaluate a patient and understand very clearly the needs of that patient and proper injection technique to minimize unevenness. Patients are not symmetrical and they often may need differing amounts of hyaluronic acid on one aspect of the face versus the other. It is also very important that the filler is massaged and the clinician can feel whether the various areas of the face are even upon completion of the injection of the filler. If a patient comes back in or is referred for unevenness, there are two methods of correcting this complication. The first is to simply inject more filler to correct the imbalance, and the second is the use of hyaluronidase to dissolve the uneven filler. Most unevenness can be adjusted by injecting small amounts of filler in the contralateral side to even; however, when bumps and areas are too apparent or uneven, hyaluronidase, usually in 25–50 units can be injected and within 48 hours the area of unevenness or of bulging can be dissolved.

When a filler is injected too superficially and a Tyndall effect occurs, often it can be extruded by making a small puncture with a 25 gauge needle and massaging the filler through the opening. If this fails, hyaluronidase can be used to dissolve the filler. Finally, in those rare cases of sterile abscess or long-term inflammation, topical anti-inflammatories can be used; if they fail, the use of clarithromycin may also be effective.

Treatment optimization: persistance of dermal fillers and *in vivo* collagen stimulation

Hyaluronic acid fillers injected as a single treatment in the nasolabial fold, with or without one touch-up 1–2 weeks later usually just for the initial treatment, persists in a subset of patients for up to 12 months or longer [13]. It has generally been hypothesized that the prolonged efficacy of stabilized hyaluronic acid fillers versus injectable substances such as collagen is attributed to the sustained persistence of the product in the skin because of the effect that cross-linking has on limiting breakdown from *in vivo* hyaluronidase. However, new data indicate that, in addition to residual product left at each reinjection which provides a base, hyaluronic acid fillers can stimulate collagen synthesis and inhibit collagen breakdown, which can contribute to their persistence and correlates with physician observations that patients require less overall filler over time to retain optimal correction.

A landmark study by Narins *et al.* [14], which is the basis for a new FDA approval for Restylane for up to 18 months, may provide a key piece of evidence to show that full correction followed by a single optimizing treatment can not only optimize longevity and in turn patient satisfaction, but also may enhance the patient's *in vivo* collagen stimulation. This paper is an 18-month interim analysis of a 30-month study to evaluate efficacy and persistence of non-animalized, stabilized hyaluronic acid 100 000 gel particles/mL filler based on different retreatment schedules. The results in this study seem to indicate initial full correction of the nasolabial folds, followed by an optimizing treatment at an interval between 4 and 9 months, causes improved

long-term persistence of the filler and may indicate that full correction followed by retreatment at optimum treatment intervals may enhance the patient's own *in vivo* collagen stimulation.

This hypothesis is supported by *in vivo* studies by Wang *et al*. [15] who demonstrated that NAHSA (non-animal stabilized hyaluronic acid) 100 000 gel particles/mL hyaluronic acid filler can induce synthesis of type I collagen probably by stretching fibroblasts. The effect of optimizing treatments intervals to enhance *in vivo* collagen stimulation is consistent with Wang *et al*.'s data and is further supported by data with other types of treatments that cause collagen stimulation *in vivo*, namely laser, light, and radiofrequency devices. The data by Narins *et al*., as well as Wang *et al*., leads to a new paradigm in the use of dermal hyaluronic acid fillers. Up until now, the standard for esthetic correction using hyaluronic acid dermal fillers has been to inject fillers to replace lost volume and to replace the fillers as they slowly degraded. These data may indeed indicate a new treatment approach. Optimizing initial treatment by achieving full correction and thereby stretching fibroblasts and maximally stimulating collagen synthesis, followed by a second optimizing treatment, perhaps at an interval of 4–9 months, may lead to long-term benefit and a continued enhancement effect by the hyaluronic acid filler. It is possible that with each touch-up injection set the product builds up on a base already there, the metabolism of filler degradation decreases, and collagen production is continually stimulated.

Conclusions

The use of dermal fillers, and hyaluronic acid fillers specifically, has become a mainstay in the treatment of the aging face. Hyaluronic acid fillers can be used safely and effectively in treating a variety of aspects of the aging face including folds and wrinkles as well as replacing lost volume. Hyaluronic acid fillers can also be used to sculpt areas such as the chin, the nose, tear troughs, and the eyebrows to enhance features in a non-invasive, completely reversible procedure. Over the next 2 years, there will probably be another four or five hyaluronic acid fillers approved in the USA. The near future will bring the addition of lidocaine to fillers that are already approved in the USA to decrease discomfort both upon injection and tenderness in the injection sites post-injection. New hyaluronic acid products will also look to have characteristics that will increase their use and utilization and may also increase their effective time in the skin. Finally, new treatment paradigms such as initial treatment followed by an optimization treatment within 6 months may cause long-term improvements and optimize *in vivo* collagen synthesis. Hyaluronic acid fillers will continue to be the mainstay of treatment for static folds, lines, wrinkles, and volume replacement in the near future.

References

1 Chung J, Soyun C, Sewon K. (2004) Why does the skin age? Instrinsic aging, photoaging, and their pathophisiology. In: Rigel DS, Weis RA, Lim HW, Dover JS, eds. *Photoaging*. New York: Marcel Dekker, pp. 1–13.

2 Rohrich RJ, Pessa JE. (2008) The fat compartments of the face: anatomy and clinical implications for cosmetic surgery. *Plast Reconstr Surg* **121**, 1061.

3 Brandt FS, Cazzaniga A. (2008) Hyaluronic acid gel fillers in the management of facial aging. *Clin Interv Aging* **3**, 153–9.

4 American Society for Aesthetic Plastic Surgery. (2007) Statistics on Cosmetic Surgery.

5 Tezel A, Fredrickson GH. (2008) The science of hyaluronic acid dermal fillers. *J Cosmet Laser Ther* **10**, 35–42.

6 Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. (2003) A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane® versus Zyplast® for the correction of nasolabial folds. *Dermatol Surg* **29**, 588–95.

7 Arlette JP, Trotter MJ. (2008) Anatomic location of hyaluronic acid filler material injected into nasolabial fold: a histologic study. *Dermatol Surg* **34**, S56–63.

8 Narins RS, Jewell M, Rubin M, Cohen J, Strobos J. (2006) Clinical conference. Management of rare events following dermal fillers: focal necrosis and angry red bumps. *Dermatol Surg* **32**, 426–34.

9 Gold MH. (2007) Use of hyaluronic acid fillers for the treatment of the aging face. Clin *Interv Aging* **2**, 369–76.

10 Beer KR. (2006) Nasal reconstruction using 20 mg/ml cross-linked hyaluronic acid. *J Drugs Dermatol* **5**, 465–6.

11 Glogau RG, Kane MA. (2008) Effect of injection techniques on the rate of local adverse events in patients implanted with non-animal hyaluronic acid gel dermal fillers. *Dermatol Surg* **34**, S105–9.

12 Cohen JL. (2008) Understanding, avoiding, and managing dermal filler complications. *Dermatol Surg* **34**, S92–9.

13 Lupo MP, Smith S, Thomas J, Murphy DK, Beddingfield FC 3rd. (2008) Effectiveness of Juvéderm Ultra Plus dermal filler in the treatment of severe nasolabial folds. *Plast Recontr Surg* **121**, 289–97.

14 Narins RS, Dayan SH, Brandt FS, Baldwin EK. (2008) Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Dermatol Surg* **34**, S2–8.

15 Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ. (2007) *In vivo* stimulation of *de novo* collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. *Arch Dermatol* **134**, 155–63.

Chapter 44: Calcium hydroxylapatite for soft tissue augmentation

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BASIC CONCEPTS

- Calcium hydroxylapatite is a fibroplastic filler in which volume correction is achieved in part through the biologic response of the host.
- Calcium hydroxylapatite is approved for correction of moderate to severe wrinkles and folds, treatment of HIV-associated lipoatrophy, and vocal fold insufficiency.
- The injectable filler is composed of microspheres of calcium hydroxylapatite suspended in an aqueous carrier gel.
- Ideal areas for correction with calcium hydroxylapatite are the malar eminences, center of the cheek, nasolabial and nasojugal (tear trough) folds, prejowl sulcus/marionette, and chin and jawline regions.
- Filler duration is documented for as long as 12 months, although some loss of correction may occur.

Introduction

Facial volume loss leads to dramatic changes in appearance resulting from aging, disease, or hereditary conditions. The deflation from lipoatrophy causes skin redundancy, which is compounded by loss of elasticity and collagen degeneration from solar radiation and oxidative damage. Skeletal bone resorption further leads to deflation, enlargement of the ocular orbit, and shrinkage of the jaw. These visual signs of aging cannot be corrected by surgical tightening without volumization as this procedure alone leads to a skeletal, windswept appearance.

Replacement of volume through soft tissue augmentation can often offer facial rejuvenation with or without surgery. A variety of suitable materials for soft tissue augmentation exists. Natural fillers, such as collagen, hyaluronic acid, and calcium hydroxylapatite (CaHA), are synthesized to mimic, or are derived from biologic materials. Synthetic fillers may be permanent, such as acrylates and silicone, or biodegradable, such as poly-L-lactic acid [1].

Physiology and pharmacology

CaHA is a new type of fibroplastic filler in which volume correction is achieved in part through the biologic response of the host. Radiesse® (Bioform Medical, San Mateo, CA, USA) is an injectable filler composed of microspheres of 30% CaHA suspended in an aqueous gel consisting of water, glycerin, and sodium carboxymethylcellulose. Once injected, the gel carrier is soon absorbed. The remaining microspheres are 25–45 μm in diameter, which facilitates injection but resists immediate phagocytosis. These bioceramic spheres have no antigenicity, foreign body or giant cell response, and cause a minimal inflammatory reaction. They do not stimulate ossification. Although visible on X-ray images and magnetic resonance imaging scans, they are radiolucent, appearing somewhat like frosted glass, and pose no impediment to radiologic analysis. The CaHA microspheres form a scaffold for the fibroplastic proliferation, which provides the natural tissue feel of the implant. The local fibroplastic response results in the fibrous encapsulation of the particles and their gradual dissolution into calcium and phosphate ions (Figures 44.1–44.3) [2].

Indications and techniques

CaHA is a thick, white, clay-like, cohesive material intended for subdermal injection. The density of the material would make intradermal injection difficult because of poor tissue intrusion into the dermal stroma. It is not intended or suitable for fine lines, superficial injection, or injection into highly mobile areas such as the lip or above the orbital rim, where accumulation of material from movement might result in nodule formation. Because of its density the filler is most easily injected through a 27-g standard needle or a 28-g wide bore (Exel®) needle. It is most commonly injected in a linear retrograde fashion following penetration of the

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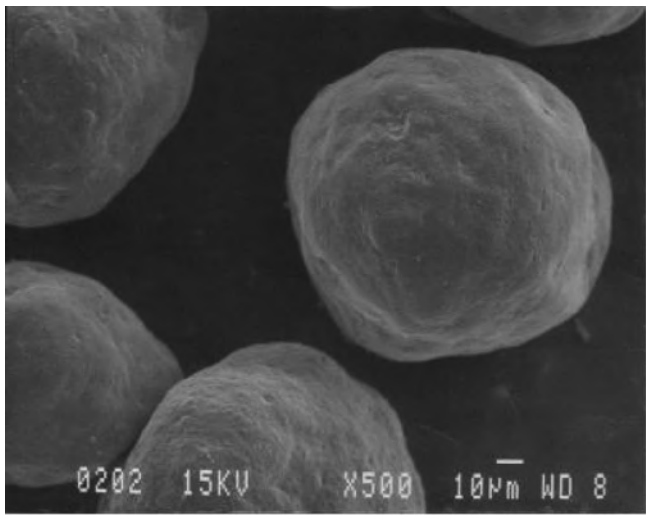


Figure 44.1 Calcium hydroxylapatite microspheres, 25–45 µm in diameter. (Illustration courtesy of BioForm Medical.)

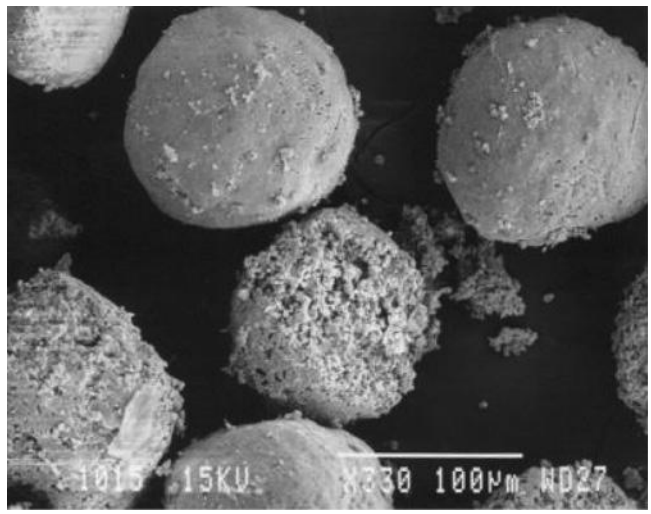
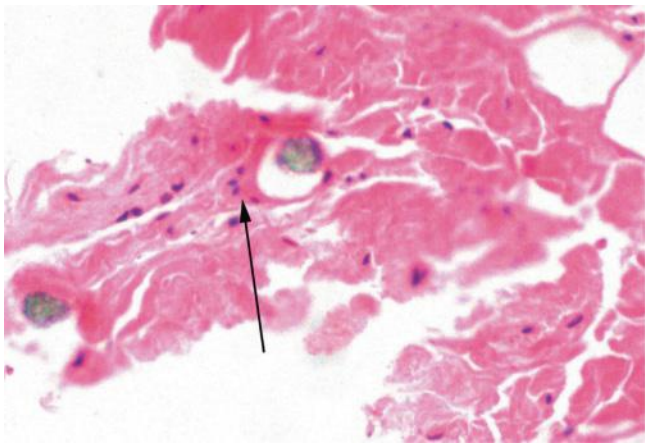
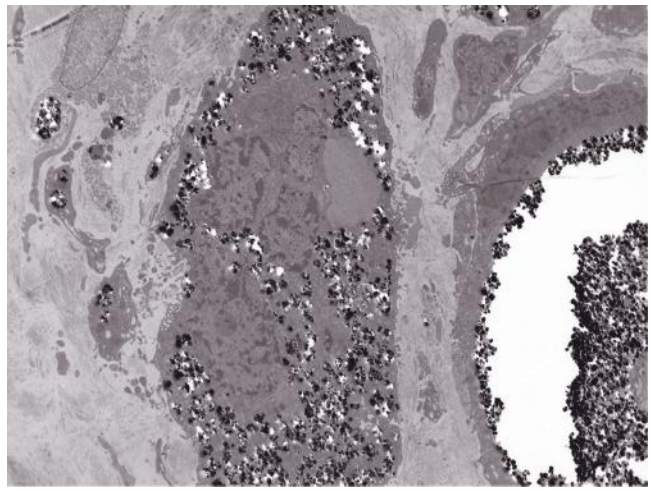


Figure 44.2 Gradual dissolution of microspheres. (Illustration courtesy of BioForm Medical.)



(a)



(b)

Figure 44.3 (a) Light microscopic section at 1 month post-injection showing microspherules at the dermal subcuticular junction and a slight increase in histiocytes (arrows). (Illustration courtesy of Drs. David J. Goldberg and Ellen Marmur.) (b) Electron microscopic section at 6 months showing both an intact microspherule and one undergoing a histiocytic derived catabolic process into smaller particles of calcium (black particles). The phosphate ions are not seen because they are dissolved in the processing of tissue for electron microscopy analysis. (Illustration courtesy of Drs. David J. Goldberg and Ellen Marmur.)

dermis at a 45° angle and then fully inserting the needle in the subcutaneous plane parallel to the surface. The material is then extruded upon withdrawal of the needle in a threadlike manner. Multiple parallel or layered repeat injections may be utilized to achieve correction of a soft tissue contour.

Fanning and cross-hatching are utilized to achieve greater volume by smooth even injections of 0.1–0.2 mL per pass, followed by massage to avoid lumps and irregularities. One of the advantages of CaHA is its immediate "moldability" by massaging the injected area firmly against underlying structures or bimanually between the injector's fingers. Supraperiosteal placement is used to correct bony deformity.

Several comparative studies have demonstrated that lesser volumes of CaHA are required for full correction than with collagen or hyaluronic acid [3]. Ideal areas for correction are the malar eminences, center of the cheek, nasolabial and nasojugal (tear trough) folds, prejowl sulcus/marionette, and chin and jawline regions. Reinflation of the midface, including the malar, cheek, nasolabial, tear trough areas, yields a facelift-like effect and a far more dramatic rejuvenation than simple "line filling" (Figures 44.4 and 44.5) [4]. CaHA is a structural, volumetric filler analogous to the

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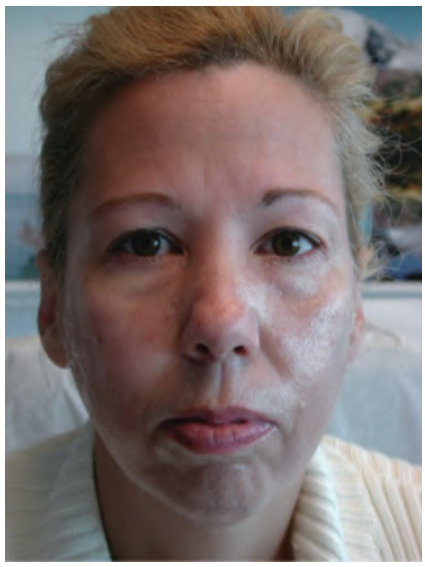

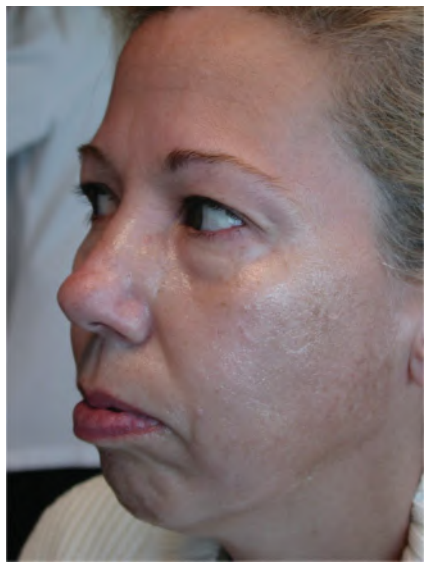

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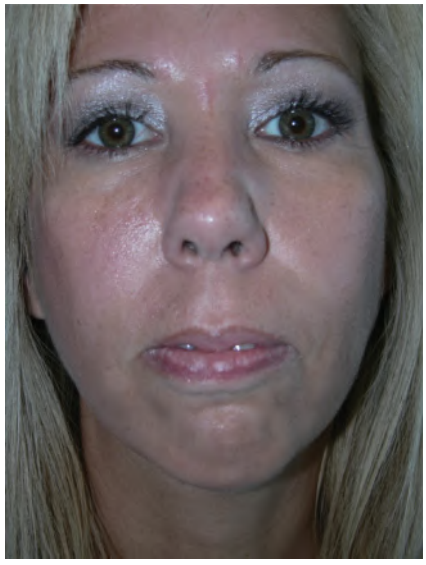

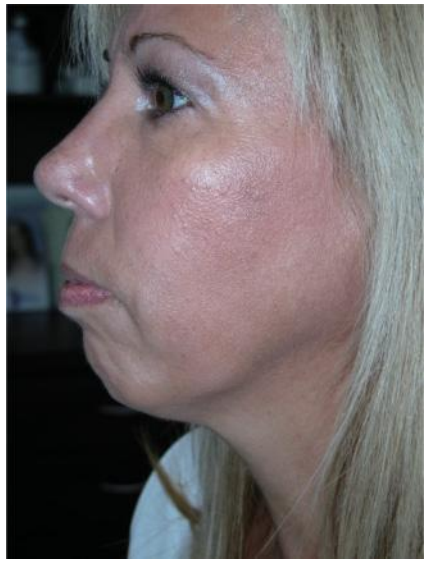

Figure 44.4 Preinjection (a) and post-injection (b) of 2.6 mL CaHA.

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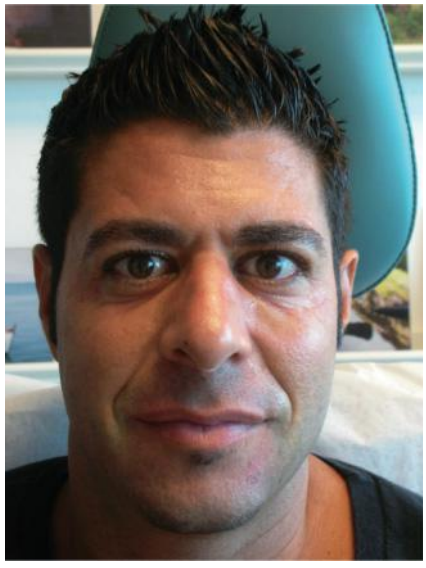
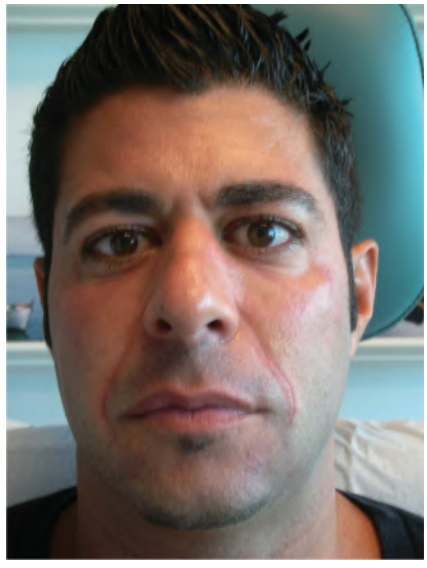




(b)

Figure 44.5 Preinjection (a) and immediately post-injection (b) of 2.6 mL CaHA.

concrete foundation of facial restructuring. It is compatible with other more superficial fillers that can be overlaid for fine line smoothing, and with use in conjunction with radiofrequency and laser devices.

Preinjection topical anesthesia, 20–30 minutes pretreatment, is very important to insure patient comfort. For large volume injections, injectable regional nerve blocks might be employed. A popular, non FDA-approved (off-label) means of achieving anesthesia is to mix CaHA with lidocaine via sterile syringe transfer [5]. CaHA is transferred via a female–female connector into a syringe containing 0.05–1.0 mL lidocaine and then the two are mixed by repeatedly passing the emulsion back and forth (Figure 44.6). Avoidance of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and other medications or supplements that promote bruising are advisable. Pre- and post-treatment viral prophylaxis is recommended in patients with a history of herpes simplex.

The first indication for Radiesse was for vocal fold correction. In 2006, it was approved for correction of moderate to severe facial wrinkles and folds, and restoration or correction of signs of lipoatrophy in patients with HIV [4]. In comparative studies of nasolabial fold treatment with CaHa versus collagen or hyaluronic acid, implants with CaHA gave significantly greater and more persistent correction with lower volumes at all time points [3,6].

Duration is documented for as long as 12 months, although some loss of correction may occur prior to that. Off label, non-FDA approved applications include correction of nasal defects, chin augmentation, and filling of the hands. Injection of a full syringe (1.3 mL) into each dorsal hand is accomplished through several bolus deposits in the subcutaneous space and between veins and tendons, followed by massage evenly over the entire hand to provide a full, more youthful appearance (Figure 44.7) [5].

All injections are performed percutaneously. Although some authors suggest intraoral approach to the tear trough area, this approach needlessly creates the opportunity to introduce bacteria into the implant with potentially serious consequences [7]. Glabellar injections are probably ill-advised because of the risk of vascular occlusion by embolization or compression, which has been reported with nearly all previous fillers.

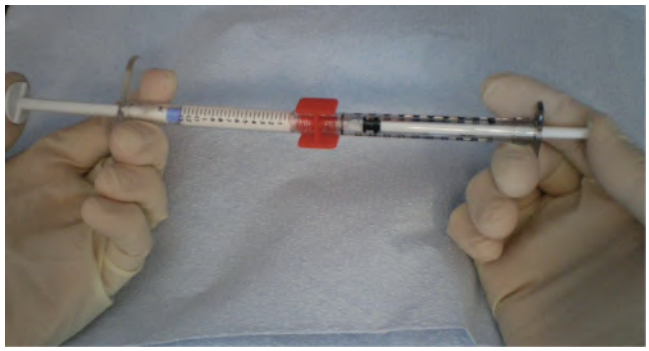
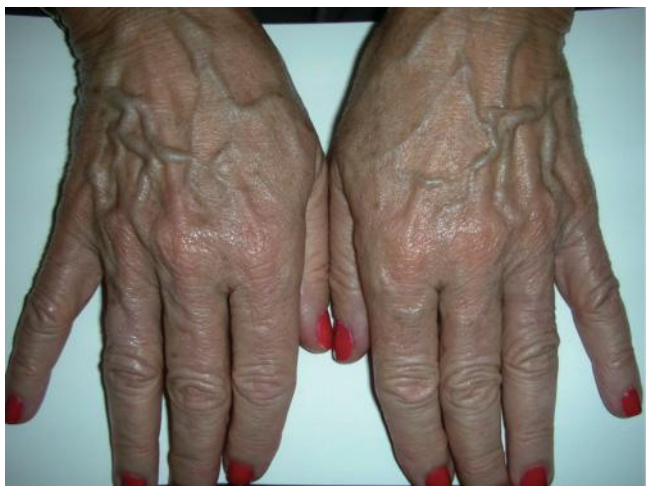


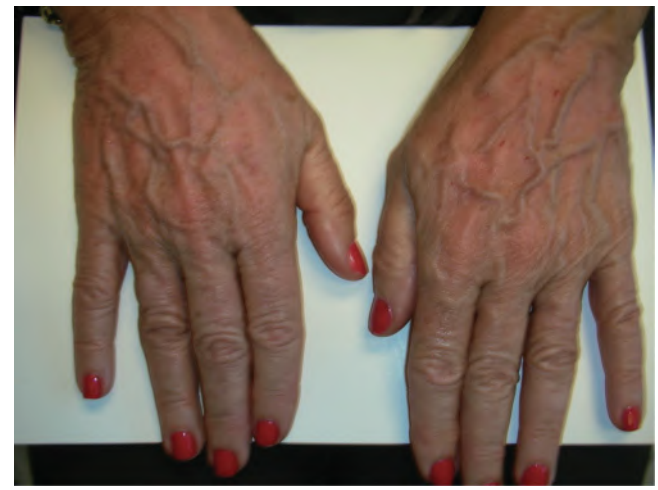
Figure 44.6 Radiesse mixed with lidocaine, using a female–female connector.

Complications

Edema, erythema, pain, and ecchymosis are the most common complications, comparable to collagen and hyaluronic acid injections. Too superficial an injection can yield a visible white papule or plaque, which is slow to resolve. Too much material in one placement, or failure to massage, can result in palpable or visible nodules. Many of the complications, in the experience of this author, seem to be reduced when lidocaine is mixed with the CaHA prior to injection in the method described earlier.

(a)





(b)

Figure 44.7 Preinjection (a) and post-injection (b) of CaHA into the hand.

Conclusions

Substantial facial volume restoration with facelift-like effect can be achieved with the injection of CaHA. Large volume correction can be accomplished in a practical fashion because of the greater volumizing effect of CaHA in contrast to other filling agents. Success is technique-dependent; complications are infrequent and comparable to other agents. Durability of this fibroplastic filler may be up to 1 year.

References

1 Mandy SH. (2008) Fillers that work by fibroplasia: poly-L-lactic acid. In: Carruthers A, Caruthers J, eds. *Soft Tissue Augmentation*, 2nd edn. Saunders Elsevier, pp. 101–4.

2 Marmur ES, Phelps R, Goldberg D. (2004) Clinical histologic and electron microscopic findings after injection of calcium hydroxylapatite filler. *J Cosmet Laser Ther* **6**, 223–6.

3 Moers-Carpi MM, Tufet JO. (2007) Calcium hydroxylapatite versus nonanimal stabilized hyaluronic acid for correction of nasolabial folds. *Dermatol Surg* **34**, 210–5.

4 Graivier M, Bass L, Busso M, Jasin ME, Narins RS, Tzikas TL. (2007) Calcium hydroxylapatite for correction of mid and lower face. *Plast Reconstr Surg* **120**:**6**, 55–66S.

5 Busso M, Applebaum D. (2007) Hand augmentation with Radiesse® (calcium hydroxylapatite). *Dermatol Ther* **20**, 385–7.

6 Smith S, Busso M, McClaren M, Bass LS. (2007) A randomized, bilateral, prospective comparison of calcium hydroxylapatite microspheres versus human-based collagen for the correction of nasolabial folds. *Dermatol Surg* **33**, S112–21.

7 Wolcott R, Ehrlich G. (2008) Biofilms and chronic infection. *JAMA* **299**, 2682–4.

Chapter 45: Skin fillers

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BASIC CONCEPTS

- Collagen fillers were the first introduced into the marketplace to replace volume loss in the aging face.
- Collagen fillers can be conveniently divided into: bioengineered human-derived, animal-derived, and bioengineered animal-derived.
- Bovine, humanized, and porcine-based collagen fillers are presently in the marketplace.
- Collagen may be combined with other fillers to produce the desired volumizing effect in the face and hands.

Introduction

Facial beauty and attractiveness continue to appeal. The quest for and maintenance of a youthful visage are well established. Youth equates with vitality, fecundity, and attractiveness; disguising the passage of time etched in the face is not a new phenomenon, although the proportion of people living to old age is. Facial appearance is rapidly perceived and processed by the brain biasing subsequent cognitive processes [1]. Four characteristics emerge as the most important determinants of attractiveness: averageness, sexual dimorphism, youthfulness, and symmetry.

As the population continues to age and cosmetic procedures gain more acceptance, adults from all age groups and socioeconomic backgrounds are seeking cosmetic enhancement. This demand is increasing in younger and older adults, in men as well as women. The demand for cosmetic procedures among people aged 50–65 years has doubled in the last 5 years, with 83% of the 11.5 million procedures performed in 2006 being non-surgical and with botulinum toxin and fillers leading the list [2].

The current understanding that volume loss contributes to the aging face appearance has driven the development of new filling products to replace lost subcutaneous fat. The search for the perfect filling material to eradicate rhytides, smooth scars, and fill traumatic defects continues. This chapter discusses those fillers based on collagen, the structural building block of the skin.

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Historical perspectives

Soft tissue fillers have been used for more than a century to improve and enhance facial esthetic units. At present, a popular substance for soft tissue augmentation is injectable bovine collagen. Collagen was first extracted from fresh calf skin in 1958 by Gross and Kirk at Harvard Medical School [3]. They showed that, under physiologic conditions, a solid gel could be produced by gently warming a solution of collagen to body temperature. It was found in the 1960s that selective removal of the non-helical amino and carboxy terminal telopeptides significantly reduced the antigenicity of bovine collagen molecules.

A team of investigators at Stanford University in the early 1970s, Perkins, Daniels, Luck, and Knapp, began work on the development of a clinically useful collagen implant material. In 1977, Knapp, Luck, and Daniels reported the successful injection of pepsin-solubilized, telopeptide-poor, purified human rabbit and rat collagen into the subcutaneous tissue of rats. They reported that the collagen implants remained stable and were progressively infiltrated by a matrix of viable host connective tissue.

These same investigators later conducted a human trial of bovine collagen in 28 human subjects. Collagen was injected into the dermal and subcutaneous planes to correct depressed acne scars, subcutaneous atrophy, wrinkling, viral pock marks, and other contour defects, with 50–85% improvement that was maintained for 3–18 months. Subsequently, Zyderm collagen was developed by Collagen Corporation. In 1981, Zyderm I® (McGhan Medical, Santa Barbara, CA, USA) became the first Food and Drug Administratiom (FDA) approved xenogenic agent for soft tissue augmentation.

Following this approval, two other formulations of bovine collagen, Zyderm II® and Zyplast®, were granted FDA approval.

The "potential face" for collagen implants

Evaluation of aging face

Although an aged face has several contributing factors, collagen implants are mainly used for tissue augmentation brought about by loss of dermal elasticity, volume, and subcutaneous fat [4].

A major component of esthetic disharmony in the aging face is the loss and/or redistribution of subcutaneous fat. The youthful face has an ample amount of volume evenly distributed, which displays a smooth transition from one area to another and confers a well-rounded, three-dimensional topography delineated by a series of arcs and convexities. Viewed frontally, the primary arc of the jaw line, convexities of the temples, and the smaller secondary arcs of the lips are evident [5]. In profile, the lateral cheek projection (the ogee curve) extending as an unbroken convex line from the lower eyelid to the cheek, the arc of the jaw line, and the arc of the forehead are the most definitive features of youth (Figure 45.1).

Facial aging is associated with the loss of soft tissue fullness in the periorbital, forehead, glabellar, temporal, malar, and buccal cheek perioral areas, resulting in accumulation of fat in the infraorbital fat pouches, nasolabial and labiomental folds, jowls, and submental areas. The fat pockets become more discernable as separate entities, as do many of the underlying facial structures (i.e. submaxillary glands and bony protuberances). Malar fat slides forward and down to bulge against the nasolabial crease, and preauricular and buccal fat slides down and forward to create the jowl, disrupting the defining arcs and convexities of a youthful face. This fat accumulates around the peripheral insertion of the orbicularis oris muscle into the overlying skin.

Different compartments of facial architecture can age independently and malpositioning of one compartment may lead to a cascade of changes in others. For example, loss of volume in deep midface fat would decrease the support for the medial cheek compartment, resulting in a diminished midface projection and an unmasking of the nasolabial fold and malar mound. The resulting negative vector would then allow excess traction to be placed on the lower eyelid leading to scleral show. Consequently, medial cheek tissue enhancement will improve the lower lid laxity. Just as volume loss may lead to undesirable changes elsewhere, the replacement of volume in one area may possibly lead to desirable changes in another area.

Analysis of "potential face" correctable with collagen fillers

Balance and proportions of the face have been measured over time in almost every conceivable way; however, some simple measurements are well-accepted standards (Figure 45.2). Compare changes in these areas between young and aged faces [6]. As the face ages, predictable changes occur in facial proportions. Looking at the face in vertical fifths and horizontal thirds, changes are visible from the so-called "triangle of youth" to the "pyramid of age." The forehead narrows because of temporal atrophy and elongates because of loss of underlying support, causing the brows to droop as the hairline recedes. The lower face widens as jowls form and shortens as bone is remodeled in the maxilla and mandible. Focusing on the perioral area, the young face shows

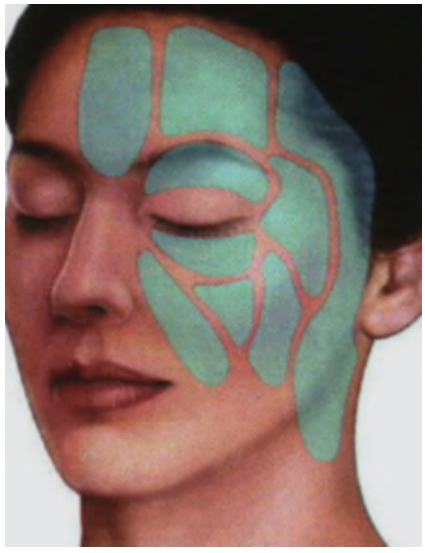

Figure 45.1 Facial fat partitioned in discrete compartments in facial architecture.

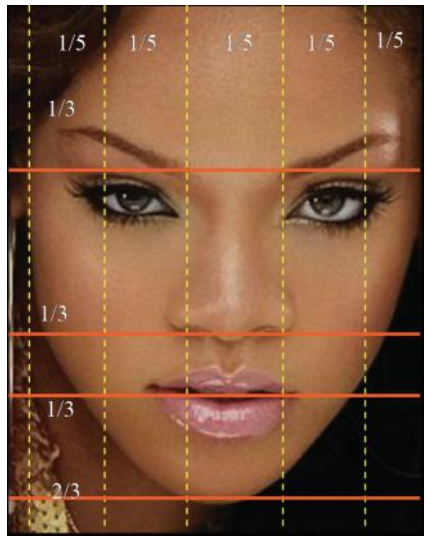

Figure 45.2 Horizontal and vertical facial proportions in a youthful face.

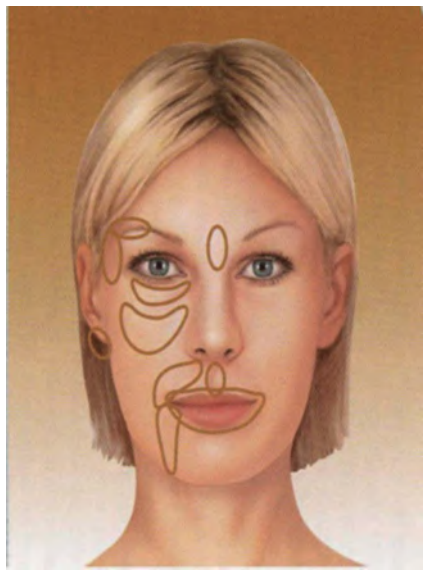

Figure 45.3 Potential sites for collagen fillers.

a one-third : two-thirds ratio of upper lip to chin, the so-called "golden mean." With age this ratio approaches 1 : 1. Finally, most faces exhibit some bilateral asymmetry, which may reflect a developmental instability, accounting for its importance in the assessment of attractiveness.

The changes in proportions in the aging face caused by bone loss and soft tissue repositioning cause speculation as to whether these changes could be improved with non-surgical bony augmentation. Mild asymmetry caused by unequal volume loss can be addressed with collagen fillers. Specific areas of facial volume loss that are amenable to correction with collagen implants are distributed in a rather mask-shaped area (Figure 45.3).

Collagen-based filler materials, alone and in combination

Collagen

Collagen is the major structural component of the dermis and is responsible for providing strength and support to human skin. Dermal matrix in adult skin is composed of type I (80–85%) and type III collagen (10–15%), in addition to glycosaminoglycans and elastin fibers. Collagen types I and III are synthesized by dermal fibroblasts as alfa-procollagens. Hydroxylation of proline and lysyl residues is performed by prolyl and lysyl hydroxylase in the presence of copper and ascorbic acid (vitamin C). The alfa chains form the triple helix and are then secreted into the extracellular space, where the protocollagen N-proteinase and protocollagen C-proteinase cleave the amino and carboxy terminal domains of the propeptides. Collagen type I triple helices comprise two alfa-1 and one alfa-2 chains and collagen III triple helices contain three identical alfa-1 chains. Collagen molecules then assemble to form fibrils with other non-collageneous molecules.

During the embryonic period, type III collagen, "fetal collagen," outweighs type I collagen in human skin. However, after birth, the ratio changes favoring collagen type I, which remains the predominant type during childhood and early adulthood in non-sun-exposed skin. However, with aging, the proportion of collagen III will increase in human skin. The matrix metalloproteinases, including collagenase, are responsible for degrading collagen. UV radiation has been shown to increase the level of matrix metalloproteinases *in vivo*, therefore increasing collagen degradation and accounting for aging of the skin. In addition, decreased collagen formation and low levels of types I and III procollagen precursors have been demonstrated in photodamaged skin, correlating with the clinical severity of photoaged skin [7].

Filler materials

A recent survey among plastic surgeons and dermatologists (Professional Education Panel Meeting, Berlin, Germany, 2005) revealed that the ideal filler material should be biodegradable but demonstrate longevity of at least 12 months and no more than 2 years.

Although most collagen fillers do not satisfy the longevity criteria, these have been very popular as a dermal replacement filler since their inception. Collagen fillers can be conveniently divided into: bioengineered human-derived, animal-derived, and bioengineered animal-derived (Table 45.1).

Bioengineered human-derived collagen fillers

Human-based collagen implants include Cosmo-Derm I, CosmoDerm II, and CosmoPlast (Inamed Corporation, Santa Barbara, CA, USA). These products, which were approved by the FDA in March 2003, contain types I and III human collagen. Dermal fibroblasts harvested from bioengineered human skin cells are placed into a three-dimensional mesh and cultured in a bioreactor simulating the human body. Dermal fibroblasts, supported nutritionally by the medium, produce collagen and extracellular matrix proteins. CosmoDerm I contains 35 mg/mL human-based collagen dispersed in a phosphate-based saline solution and 0.3% lidocaine. The collagen concentration in CosmoDerm II is about twice as much as that found in Cosmoderm I. CosmoPlast has the same ingredients as CosmoDerm I, but is cross-linked by glutaraldehyde, making it more resistant to degradation, allowing for deeper placement of the injectable implant. No skin testing is required for any of the human-derived collagen products, and adverse reactions are limited to bruising, erythema, and swelling. CosmoDerm is used in more superficial furrows, whereas CosmoPlast is ideal for deeper lines and the vermillion border of the lip. These products require refrigeration.

Table 45.1 Collagen filler products, their advantages and disadvantages.

Product	Components	Type and duration	Advantages/disadvantages
Zyderm I and Zyderm II	Bovine collagen 0.3% lidocaine	Xenograft 3 months	Long history of use Commonly used Allergic reactions 1% Requires pretesting Requires refrigeration
Zyplast	Bovine collagen 0.3% lidocaine	Xenograft 3 months	Long history of use Commonly used Allergic reactions 1% Requires pretesting Requires refrigeration Possible vascular necrosis
Cosmoderm I and II	Human-derived collagen 0.3% lidocaine	Homograft 4 months	Commonly used Does not require pretesting No allergic reactions reported Requires refrigeration Shorter duration of action
Cosmoplast	Human-derived collagen 0.3% lidocaine	Homograft 4–7 months	Commonly used Does not require pretesting Lasts longer than cosmoderm No allergic reactions reported Requires refrigeration Possible vascular necrosis
Cymetra	Cadaveric human Dermal matrix	Homograft 4–18 months	Lasts longer Requires pretesting Allergic reactions reported Edema High cost
Artecoll and Artefill	Bovine collagen encapsulated in PMMA	Xenograft Semi-permanent	Semi-permanent Might cause allergic reaction Permanent granulomatous reactions Cannot be used for fine lines Requires refrigeration
Resoplast	Bovine collagen encapsulated in PMMA	Xenograft Semi-permanent	Semi-permanent Might cause allergic reaction Permanent granulomatous reactions Cannot be used for fine lines Requires refrigeration
Isologen	Cultured autologous fibroblasts	3 mm punch of patient's skin Cryo-preserved	Semi-permanent No allergic reactions Costly, effort to harvest skin
Autologen	Autologous collagen, large piece of patient's skin		No allergic reactions Cost of shipping and handling Not currently available
Dermalogen	Human-based collagen and elastin	Cadaveric skin	Stored at room temperature No longer available Allergic reactions

Table 45.1 *Continued*

Product	Components	Type and duration	Advantages/disadvantages
Evolence	Porcine-collagen cross-linked in ribose sugar	Porcine 8–12 months	Skin pretesting not required Lasts up to 12 months Less edema Can be used for lip augmentation Requires refrigeration Can cause allergic reactions in porcine-sensitive patients Nodules Possible granulomatous reactions

PMMA, polymethyl methacrylate microspheres.

The cosmetic effects of CosmoDerm and CosmoPlast are immediate and last about 4–7 months, depending on the area of treatment, injection technique, and amount of collagen filler. It is believed that the collagen in the product contains platelet-aggregating effects that may decrease the risk of bruising [8]. Additionally, they contain lidocaine. CosmoPlast has a slightly stiffer consistency than hyaluronic acid-containing fillers, which make it ideal for use in the vermillion border of the lip, the bridge of the nose, and to elevate the corners of the mouth. It is often injected in medium to deep wrinkles alone or, in combination with hyaluronic acid. Contraindications to CosmoDerm and CosmoPlast include hypersensitivity to these products and allergy to lidocaine.

Alloderm (LifeCell Corp., Branchburg, NJ, USA) is an acellular allograft human dermal matrix derived from cadaveric skin. The freeze–drying process eliminates the cellular component of human skin leaving behind collagen, laminin, elastin, and proteoglycans. Immunohistochemical staining has failed to show class I or II histocompatibility antigens.

Alloderm has the capacity to incorporate into the surrounding tissue and support rapid revascularization, decreasing the risk of infection and rejection [9]. This product is manufactured as sheets and may be used for treating full-thickness burns, surgical defects, and acne scars.

Cymetra (Lifecell Corp., Branchburg, NJ, USA), available since 2000, is the injectable form of Alloderm, containing micronized cadaveric-derived collagen. The product is prepared in powdered form and needs to be rehydrated and mixed with lidocaine. The mixing process needs to be carried out properly and takes about 10 minutes. Cymetra has been used for soft tissue augmentation and has been shown to have more durability than Zyderm in lip augmentation [10]. Alloderm and Cymetra are both provided by the American Association of Tissue Banks after appropriate screenings for infectious agents and teratogenicity have been performed. These products are contraindicated in patients with infection of the treated site, allergy to gentamicin, and collagen vascular disease.

Autologen (Collagenesis Corporation, Beverly, MA, USA) is an autologous collagen suspension, made of a patient's own tissue, containing 3.5% collagen. The process, which takes 6–8 weeks, includes harvesting skin from the patient, usually from mammoplasty or abdominoplasty, which is then sent to the laboratory for culture and processing. About 2 inches of donor skin is needed to produce about 1 mL of Autologen. The advantages of this type of autologous injectable is that there is no risk of hypersensitivity to this product, and the correction may last up to 18 months – considerably longer than with other types of collagen. The disadvantages include the delays in harvesting and processing the skin as well as the need for a relatively large skin specimen and the cost of culture and processing. Autologen can be used for lip augmentation in addition to scars and furrows. However, it is no longer available in the USA.

Isologen (Isologen Technologies Inc., Paramus, NJ, USA) is composed of cultured autologous fibroblasts. A 3-mm punch biopsy is obtained from the patient and sent to the laboratory as a frozen specimen. In about 6 weeks the living cultured fibroblasts with extracellular matrix are sent back to the physician for treatment. Injections should be placed within 24 hours of receiving the product. There is a minimal risk of hypersensitivity to this product and therefore a 2-week pretreatment skin allergy test is required prior to injection. It is of note that the fibroblast culture may be cryo-stored and used for additional injections. Disadvantages to this product are cost, processing time, and pain with injections. Also, because the fibroblasts require time to produce collagen, immediate correction is usually not observed with this product, making it dissatisfying to certain patients.

Animal-derived collagen fillers

There are three types of bovine-derived collagen products: Zyderm I (Inamed Aesthetics, Santa Barbara, CA, USA),

Zyderm II, and Zyplast. Zyderm I, FDA-approved in 1981, is composed of 3.5% bovine dermal collagen, suspended in physiologic phosphate-buffered sodium chloride solution and 0.3% lidocaine. Zyderm II differs from Zyderm I by containing 6.5% bovine dermal collagen and was approved by the FDA in 1983. Zyplast, approved by the FDA in 1985, contains 3.5% bovine dermal collagen cross-linked with 0.0075% glutaraldehyde, which strengthens the collagen fibers and extends the duration of action. Each of these products contains 95% type I collagen and 5% type III collagen. All three products are manufactured in 0.5–1.5 mL preloaded syringes and must be kept refrigerated.

Zyderm I and II are used for correction of the superficial lines of the skin including glabellar lines, horizontal forehead lines, crow's feet, fine perioral lines, and scars [11]. Zyderm II has more collagen and therefore is more effective in moderate to deep wrinkles. Zyplast is more valuable in treating deeper lines such as nasolabial folds, deep acne scars, and the vermilion border of the lip. The cosmetic correction with bovine collagen products usually lasts about 3 months, as the product becomes degraded by collagenase. However, there are reports of bovine collagen lasting for up to 18 months. Zyplast tends to lasts longer than Zyderm. In addition, the amount of the filler, area of treatment, and injection techniques are important factors in the longevity of the correction. It is of note that because Zyderm and Zyplast contain lidocaine, the treatment area will be partially anesthetized; therefore additional numbing agents are usually not required. However, if a patient experiences pain, topical lidocaine, and, rarely, nerve blocks may be used to reduce the pain of injection.

Patients treated with bovine collagen implants are at risk of developing allergic reaction to the foreign material. Therefore, two consecutive skin tests are recommended (6 and 2 weeks) prior to treatment. The skin test contains 0.3 mL of Zyplast I in a prefilled tuberculin syringe and is injected subcutaneously on the volar aspect of the forearm. About 3% of the general population is sensitive to bovine collagen [12]. It is generally safe to treat a patient with injectable bovine collagen if there is no reaction with the two skin tests. The risk of allergy remains 1.3–6.2% after one negative test, 0.5% after two negative tests, and rarely may occur after multiple treatments. The patient should then be instructed to check the site between 48 and 72 hours after placement and then again at 4 weeks by the treating physician.

Patients with hypersensitivity reactions to bovine collagen may be reassured that it usually resolves within 4–24 months. However, if needed, topical, intralesional, or a brief course of systemic corticosteroids may be used to treat these reactions.

It has been proposed that there may be a triggering effect of an autoimmune process, particularly dermatomyositis, in patients with the use of bovine collagen [13]. However, in a study performed by Hanke *et al*. [14] the incidence rate of polymyositis and/or dermatomyositis in patients who received bovine collagen was not higher than the control-matched population. Studies have indicated that the possibility of patients developing autoimmune disease is unlikely.

Bioengineered animal-derived collagen fillers

Artecoll (Canderm Pharma Inc., St-Laurent, QC, Canada) is a solution that contains polymethyl methacrylate microspheres (PMMA) suspended in bovine collagen and lidocaine. PMMA is non-biodegradable; therefore it results in durable augmentation after the collagen is absorbed. This product is bovine-derived, a pretreatment skin test is required prior to injection. Artecoll has been used for facial furrows, lip, chin, and malar augmentation. Patients treated with Artecoll may have treatment effects lasting for up to 12 months [15].

Artefill is another form of bioengineered bovine collagen, encapsulated in PMMA microspheres, recently approved for use in the USA for nasolabial folds. Limited data are available in the USA regarding the safety and efficacy of this filler. However, it shares very similar chemical properties to Artecoll, with 80% by volume of bovine collagen in 0.3% lidocaine.

Evolence® (ColBar LifeScience Ltd., Herzliya, Israel) is a new dermal filler manufactured specifically to closely resemble the composition of the collagen matrix found in human skin. Evolence is produced by means of a novel cross-linking process that uses a natural sugar ribose to cross-link porcine collagen, which mimics the natural cross-linking pathway of collagen in the body known as glycation. The safety and longevity of Evolence (30 mg/mL formulation) have initially been assessed in an appropriate animal model (rabbit ear assay), and the filler has been compared with two currently available bovine collagen treatments. Evolence has been shown to be safe with no significant degradation at 1, 6, 12, and up to 18 months after injection. It has demonstrated shape preservation and longevity superior to those of the bovine collagen filler, Zyplast [16]. In this study, both histologic and clinical findings supported the conclusion that there were no abnormal or hypersensitivity reactions in any of the study subjects.

The immune response in humans to xenogeneic porcine dermal collagen is very reserved and of low frequency compared with bovine collagen because collagen has been well conserved during evolution with little change in basic amino acid composition among mammalian species.

Techniques for collagen filler injections

Collagens are still used as the sole dermal-filling agent, but now even more often in a layering fashion with other

dermal and subcutaneous fillers. As with most dermal fillers, injection techniques will vary between injectors.

When using any injectable, it is important to make the patient as comfortable as possible for the procedure. This will allow the injection process to be easier for both patient and physician. In most cases it is best to have the patient sitting upright in order to delineate the areas of wrinkling and/or dermal defects. In the reclined position, most of these defects will be minimized, resulting in undercorrection and patient dissatisfaction.

Pain control is also important. As a result of the addition of lidocaine in the most commonly used, collagen-containing dermal fillers, most patients are able to tolerate injection of these agents without regional anesthesia. In the author's practice, a topical anesthetic alone is typically used. When using collagen in combination with one of the other fillers, such as the hyaluronic acids, the collagen product is injected first, as this provides additional anesthesia, making the hyaluronic acid injection relatively painless.

After visually delineating the areas to be corrected, the depth of the defect is determined in order to decide which agent to use. Very superficial epidermal and dermal defects are best corrected with either Cosmoderm or Zyderm. These agents are injected into the papillary dermis using a serial puncture or serial threading techniques (Figure 45.4). A slight, temporary blanching of the skin is noted at the time of injection, which represents accurate placement of the needle in papillary dermis. When using Zyderm, slight overcorrection is necessary as the product causes slight swelling which abates after 24 hours. Cosmoderm causes less swelling.

Artecoll/Artefill, Evolence30, and, sometimes, Cosmoplast and Zyplast are used for deeper dermal defects when placed in mid–deep dermis. Injections should be placed at 45° angle with a 30-gauge needle using a linear threading technique (Figure 45.5).

Other techniques such as fanning and cross-hatching can be used when combining collagen fillers with more fillers for deeper defects such as hyaluronic acid, fat, calcium hydroxylappatite, and poly-L-lactic acid. Collagen-based filler can be used after the placement of a deeper filler to fill in the more superficial defects such as for fine, perioral lines after lip augmentation with hyaluronic acid (Figure 45.6).

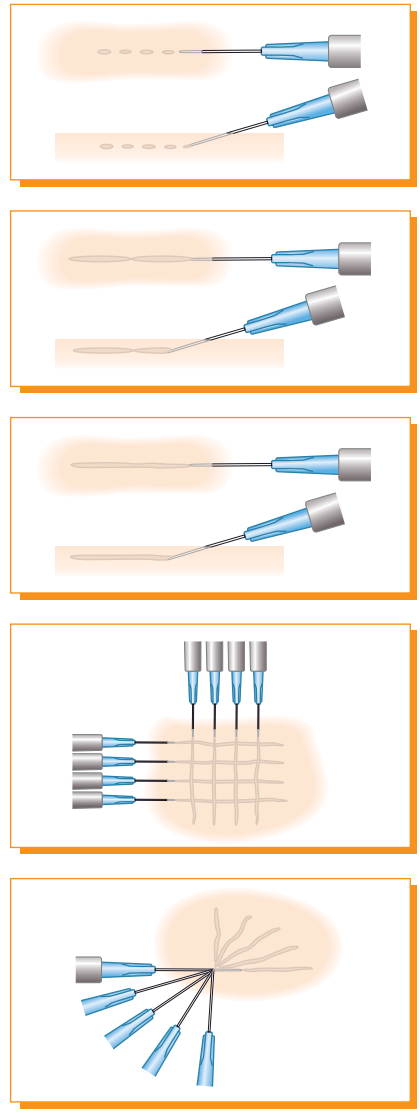

Figure 45.4 Various injection techniques.

Facial augmentation

Approach to the upper third of the face

The primary objective in the management of aging in the upper third of the face is to attenuate wrinkles while maintaining patient facial animation. Collagen fillers are used for correction of fine lines, alone and in combination with botulinum toxin type A (Figure 45.6) [17]. Collagen fillers such as Cosmoderm or Zyderm can be used to correct rather superficial rhytids of the glabella and forehead. Linear threading technique is used for this purpose. Deeper injections of collagen fillers such as Cosmoplast and Zyplast, Artecoll/Artefill, and Evolence are generally avoided for the correction of deeper glabellar complex because of the seriousness of adverse effects (see below). Fine lines in the periorbital area can be corrected with more superficially placed fillers such as Cosmoderm I/II or Zyderm I/II. Serial threading or serial puncture techniques are best used. Pretreatment of the rhytids with botulinum toxin A significantly increases the longevity of soft tissue fillers.

Approach to the middle third of the face

The middle third of the aging face is primarily treated with dermal fillers. Dermal fillers are useful for correction of the

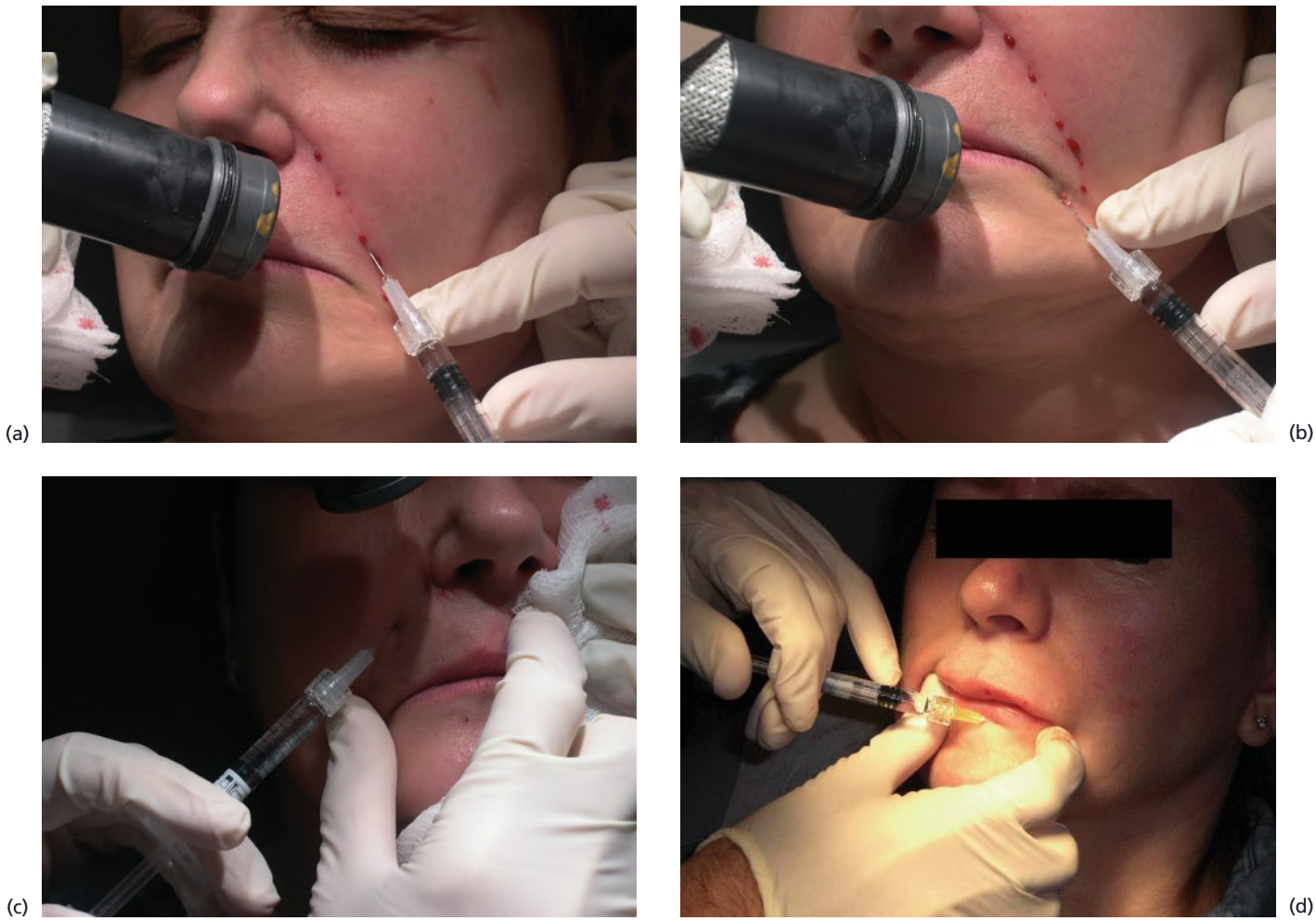

Figure 45.5 Techniques for injecting into the nasolabial folds and lower lip vermilion border (a–d).

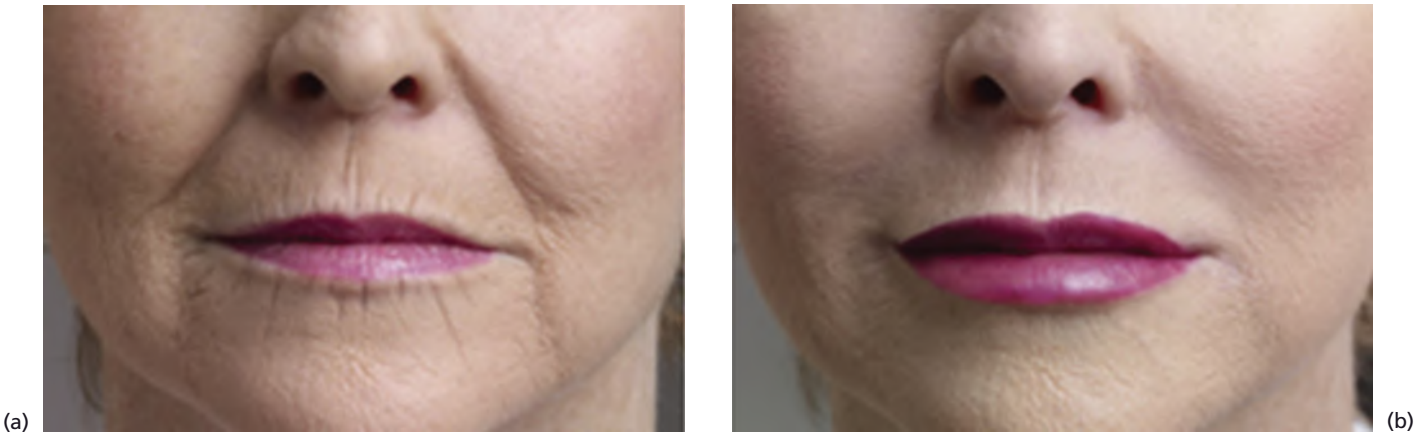

Figure 45.6 Correction of perioral rhytids and lip augmentation using a combination of dermal fillers and botulinum toxin type A. (a) Before. (b) After.

midface ptosis and volume loss, especially in patients who are considering non-surgical treatment modalities. The nasolabial folds are best treated with Zyplast or Cosmoplast, alone or in combination with hyaluronic acid fillers. The collagen fillers are placed using a 30-gauge needle at a 45° angle in a cross-hatching or fanning technique (Figure 45.5).

As in the correction of the upper one-third of the face, synergism between filler and chemodenervation with botulinum toxin type A is still applicable.

Bioengineered animal-derived collagens such as Artecoll/Artefill and Evolence can also be used for correction of nasolabial folds. These fillers are ideal for patients who seek lasting results. The fillers are placed using cross-hatched or fanning techniques.

Approach to the lower third of the face

Dermal fillers are widely used for lower face augmentation, most notably lips. Three aspects of lip augmentation are:

1 Definition of vermilion border;
2 Fullness; and
3 Poutiness.

Non-cross-linked human collagen is usually used to highlight the vermilion border, injected by serial puncture technique. Fullness is achieved by creating tubercles (three sites for upper lip and two sites for lower lip). To achieve poutiness, collagen is injected above the gingivolabial sulcus to create eversion of the upper and lower lips.

Perioral lines are optimally treated with specifically human-derived collagen for fine lines and bovine collagen for deeper rhytids (Figure 45.5d).

Marionette lines are also amenable to collagen fillers. Zyplast or Cosmoplast can be used in a cross-hatched or linear threading technique. The irregular contours of the chin (i.e. "peau d'orange" or "cobblestoning") may benefit from fillers, as these irregularities are a result of dermal and subcutaneous atrophy. Cross-linked bovine or human collagens are the fillers of choice. Additionally, the contraction of mentalis can exacerbate the "peau d'orange" appearance. This can be minimized by augmenting the lower third of the face with botulinum toxin type A.

Hand rejuvenation with collagen fillers

Resurgence in the examination of the aging hand is occurring, both in delineating the esthetics of the hand and in volumetric options for the intrinsic aging. The use of dermal fillers for hand rejuvenation is a new concept. Collagen fillers can be used to correct for volume loss and dermal atrophy of the dorsal hands and to "give it altitude." Patients seem to tolerate collagen fillers better than the more popular hyaluronic acid derivatives [18] as far as pain is concerned. Collagen fillers can be injected using the linear threading technique followed by a gentle massage (Figure 45.7).

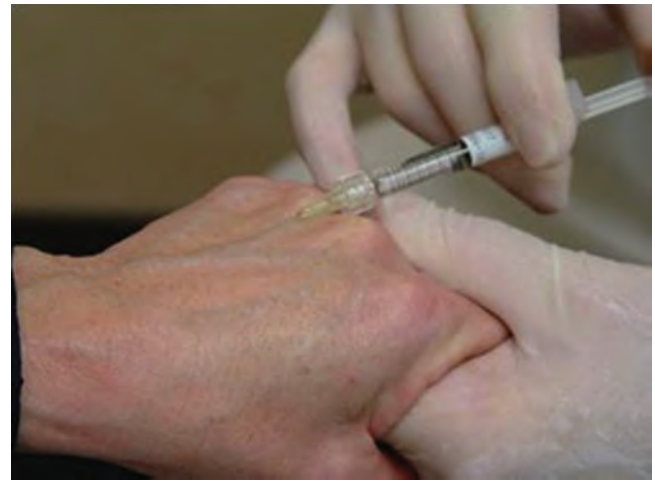

Figure 45.7 Linear threading technique for injecting into the dorsal hand for hand rejuvenation using collagen dermal filler.

Although collagen fillers are better tolerated than hyaluronic acid fillers, their longevity has been of concern. Work carried out by Man *et al.* [18] clearly shows significantly higher patient satisfaction regarding long-term results for the hyaluronic acid treated sites versus collagen. Nonetheless, collagen fillers can be used for patients seeking temporary correction for volume loss and dermal atrophy.

Adverse reactions to collagen dermal fillers

The occurrence of adverse reactions relates to both the inherent properties of the product and to inappropriate delivery or dilution of the filler, which may lead to harmful sequelae. Although injectable substances are subject to approval by the FDA, most are classified as class III devices. Thorough training of specialist physicians (dermsurgeons), including appropriate product selection, preparation, and injection techniques, is required to minimize avoidable adverse tissue responses.

Evaluating adverse reactions

Most adverse reactions are mild and transient; however, responses of greater significance can occur, demanding anything from a short course of medication to surgery. By definition, patients undergo intervention to improve some aspect of their appearance; therefore, any risk of disfigurement from a filler is unacceptable. Some products may induce adverse events because of their inherent properties, such as their ability to elicit hypersensitivity reactions. Some reactions occur immediately after treatment, whereas some have a delayed onset [19], as summarized in Table 45.2.

Table 45.2 Adverse effects associated with collagen implants.

Early adverse reactions (occurring up to several days post-treatment)

Injections site reactions
Erythema
Edema
Pain/tenderness
Bruising
Itching

Infection
Erythema
Edema
Pain/tenderness
Acne papule formation
Nodule

Hypersensitivity
Erythema
Edema
Pain/tenderness
Non-fluctuant nodules

Lumps
Poor technique

Discoloration
Redness
Whiteness
Hyperpigmentation

Local tissue necrosis
Vascular occlusion

Delayed adverse reactions occurring from weeks to years post-treatment

Infection (atypical mycobacterial)
Erythema
Edema
Pain/tenderness
Nodule
Systemic manifestations

Granuloma formation
Subclinical
Large disfiguring nodules

Hypersensitivity
Sterile abcesses
Persistent discoloration
Scarring

Early injection-related events

Temporary swelling and bruising

With all injectable fillers, the injection itself can initiate tissue response. The intensity is proportional to the degree of tissue injury. With some injectable collagen fillers such as Zyderm/Zyplast, CosmoDerm/CosmoPlast, Artecoll, and Evolence this reaction manifests itself as a temporary swelling and/or erythema which resolves within a day. Bruising can occur in patients on anticoagulants. Temporary make-up can be used to camouflage the erythema (Figure 45.8).

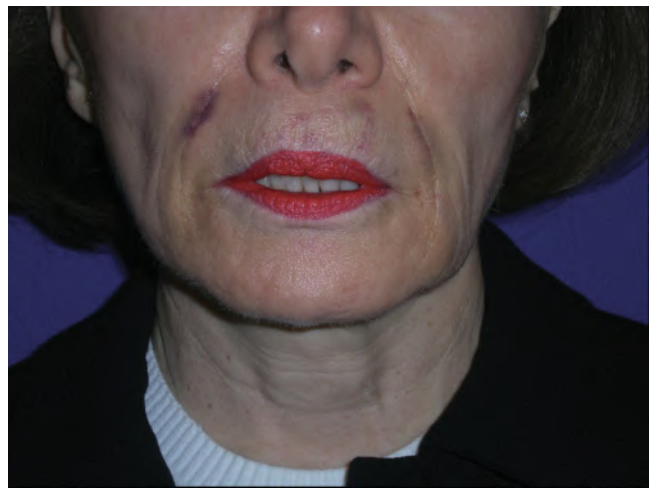

Figure 45.8 Bovine collagen adverse effect. Ecchymosis after injecting Zyplast into the nasolabial folds in a patient on anticoagulants.

Newer, bioengineered collagen fillers have also been reported to cause temporary reactions. Acute post-injection swelling and bruising have been reported with the use of Artecoll. Evolence has been associated with lesser tissue swelling and post-procedure erythema.

Skin discoloration

Skin discoloration of esthetic significance can occur at the site of treatment; such reactions typically occur immediately after injection and generally resolve within a few weeks. Redness occurs as a result of the inflammatory response, whereas whiteness at the injection site can be attributed to overcorrection and the color of the injected substance.

Product-specific training and rigorous adherence to the manufacturer's instructions should minimize the risk of discoloration occurring (e.g. correct depth of injection).

Hypersensitivity reactions

Hypersensitivity reactions to fillers can be severe and cases of severe anaphylaxis have also been reported. Autologous collagen fillers such CosmoDerm and CosmoPlast do not cause a reaction. However, bovine-derived collagen fillers have been shown to cause reactions.

Fortunately, potential allergenicity to injectable collagen is reliably determined by skin testing. A positive skin test (seen in 3.0–3.5% of patients), characterized by a change in the contour of the injected implant, erythema, edema, itching, and, occasionally, an indurated papule or inflamed dermal nodule, is a definite contraindication to treatment. Because 1–3% of patients with one negative skin test sub-

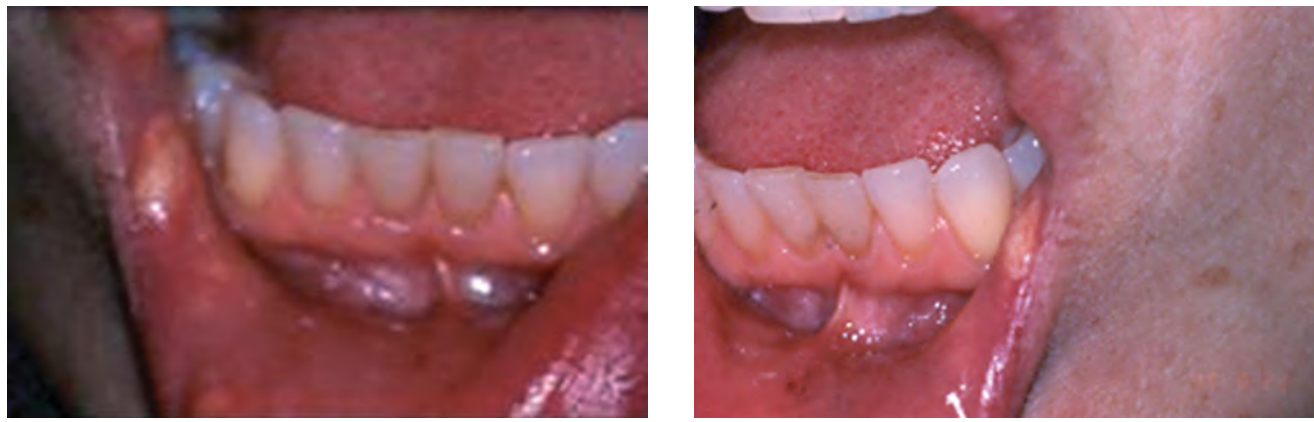
(a) (b)

Figure 45.9 Bovine collagen adverse effect. (a,b) Formulation of nodules in the mucosal lip after lip augmentation.

sequently develop a reaction at the treatment site, double skin testing is advocated. Of note is the fact that allergy to bovine collagen does not contraindicate the use of human-derived collagen (CosmoDerm or CosmoPlast).

Although Artecoll/Artefill has denatured bovine collagen encapsulated in microspheres of PMMA it also possesses an allergic risk. Skin testing prior to injection is therefore advised. Evolence however has not been shown to cause hypersensitivity reactions. This is partly because it is derived from porcine collagen which resembles very closely to human collagen and does not elicit an allergic reaction.

Vascular compromise with collagen dermal fillers

There has been at least one case report of blindness from retinal artery thrombosis following an injection of Zyplast into the glabellar complex [20]. This is believed to be exceedingly rare and an idiosyncratic event. It is therefore recommended to inject glabellar complex rather superficially and with fillers such as Cosmoderm and Zyderm.

Late adverse reactions

Nodule formation

Nodules can arise from a number of causes and are not uncommon in soft tissue augmentation. Non-erythematous nodules can form immediately after injection as a result of the uneven distribution of product. Such nodules are distinct from the inflammatory responses that are to be expected early following injection, whether as a reaction to injury (which should disappear within days) or infection. Clinical presentation of infection can include single or multiple nodules with inflammatory signs. Nodules may present subcutaneously or in the dermis and may or may not be painful. Nodules may be transient inflammatory granulomatous reactions, although some have suggested that they are the result of the development of a fibrous reaction as a response to the presence of the implant.

Lip nodules are common with thicker collagen fillers such as Zyplast or Cosmoplast, especially when used for lip augmentation (Figure 45.9). If these fillers are injected into the superficial dermis a visible white, yellow, or blue discoloration may persist at the injection site [20].

Granuloma formation

Foreign body reactions can occasionally precipitate the appearance of lumps and bumps by leading to granulomatous inflammation. However, without histologic examination, a definite diagnosis of granuloma is impossible. Patients with granulomas usually present with non-fluctuant lumps felt under the skin. Granulomas occur less frequently after injection of resorbable implants compared with more permanent products. The risk of granuloma is reduced following the implantation of products containing microspheres with smooth surfaces, such as PMMA containing filler (Artecoll/Artefill) and Evolence, compared with particles with irregular surfaces. Clinically significant granuloma can be treated successfully by the administration of local or systemic corticosteroids, although the therapeutic role of these agents in the treatment of cosmetic orofacial granulomas has yet to be extensively studied.

For well-circumscribed nodular lesions, surgical excision is a very effective approach to eradication. However, where lesions are widespread, surgery may lead to scarring and fistulae [19].

Infections

Recovered bacterial microorganisms associated with cosmetic procedures usually include common skin and soft tissue pathogens, such as *Streptococcus aureus*. Patients usually present with single or multiple erythematous and/or fluctuant nodules, which can be treated with a short course of appropriate antibiotics. However, presentation of a new lesion more than 2 weeks post-procedure strongly suggests atypical infection, with mycobacteria being a possible culprit [19]. As a response to infection, patients may also

experience systemic reactions, such as fever, leukocytosis, weight loss, and fatigue. In such cases, lesions should be aspirated or a biopsy should be performed, and the specimens should be sent for bacterial, fungal, and acid–fast stains and culture.

Atypical or non-tuberculous mycobacterial organisms are commonly found in the soil and water. In normal healthy individuals, the organisms tend to be associated with low pathogenicity, the exceptions being *Mycobacterium chelonae* and *Mycobacterium fortuitum*, which represent more serious strains. Such infections are related to poor surgical technique and inadequate sterilization of the instruments and syringes used for injections. Such infections, if suspected, should be treated promptly with appropriate antibiotics.

Conclusions

There are many causes for cutaneous defects, with a correspondingly wide range of techniques for addressing them. Dermal fillers are only one means to improve tissue and volume loss associated with aging. There is no single filler appropriate for all defects. That is partly because aging is a multifactorial process with a slowly progressive change in the three-dimensional facial anatomy, affecting essentially all components of the human face. Dermal fillers can provide temporary but adequate replacement for tissue volume, dermal elasticity, and support by enhancing subcutaneous fat. However, just like any other procedure, these have limitations. Additionally, serious side effects can occur if the practioner is not familiar with their use and potential adverse effects. Finally, regardless of the choice of dermal filler, it is the combination of clinical judgment, realistic expectations, meticulous preparation, and surgical skills that provide optimal results.

References

1 Olson IR, Marshuetz C. (2005) Facial attractiveness is appraised in a glance. *Emotion* **5**, 498–502.

2 American Society for Aesthetic Plastic Surgery. (2007) *2005 Cosmetic Surgery National Data Bank Statistics*. pp. 1–20. http://www.cosmeticplasticsurgerystatistics.com/index.html

3 Klein AW, Elson ML. (2000) The history of substances for soft tissue augmentation. *Dermatol Surg* **26**, 1096–105.

4 Glogau RG. (1994) Chemical peeling and aging skin. *J Geriatr Dermatol* **2**, 30–5.

5 Donofrio LM. (2000) Fat distribution: a morphologic study of the aging face. *Dermatol Surg* **26**, 1107–12.

6 Azizzedeh B, Murphy MR, Johnson CM. (2006) The aging face consultation. In: *Master Techniques in Facial Rejuvenation*. Elsevier, pp. 1–16.

7 Baumann L, Kaufman J, Saghari S. (2006) Collagen fillers. *Dermatol Ther* **19**, 134–40.

8 Perret S, Eble JA, Siljander PR, Merle C, Farndale RW, Theisen M, *et al*. (2003) Prolyl hydroxylation of collagen type I is required for efficient binding to integrin alpha-1 and beta-1 and platelet glycoprotein VI but not to alpha-2 and beta-1. *J Biol Chem* **278**, 29873–8.

9 Menon NG, Rodriguez ED, Byrnes CK, Girotto JA, Goldberg NH, Silverman RP. (2003) Revascularization of human acellular dermis in full-thickness abdominal wall reconstruction in the rabbit model. *Ann Plast Surg* **50**, 523–7.

10 Sclafani AP, Romo T, Jacono AA III. (2002) Rejuvenation of the aging lip with an injectable acellular dermal graft (Cymetra). *Arch Facial Plast Surg* **4**, 252–7.

11 Baumann L. (2002) Soft tissue augmentation. In: Baumann L, ed. *Cosmetic Dermatology, Principals and Practice*. New York: McGraw-Hill, pp. 155–72.

12 Stegman SJ, Chu S, Armstrong RC. (1988) Adverse reactions to bovine collagen implants: clinical and histological features. *J Dermatol Surg Oncol* **14**, 39–48.

13 Cukier J, Beauchamp RA, Spindler JS, Spindler S, Lorenzo C, Trentham DE. (1993) Association between bovine collagen dermal implants and a dermatomyositis or a polymyositis-like syndrome. *Ann Intern Med* **118**, 920–8.

14 Hanke CW, Thomas JA, Lee WT, Jolivette DM, Rosenberg MJ. (1996) Risk assessment of polymyositis and dermatomyositis after treatment with injectable collagen. *J Am Acad Dermatol* **34**, 450–4.

15 Cohen SR, Holmes RE. (2004) Artecoll: a long-lasting injectable wrinkle filler material: report of a controlled, randomized, multicenter clinical trial of 251 subjects. *Plast Reconstr Surg* **114**, 964–76.

16 Monstrey S, Pitaru S, Hamdi M, Van Landuyt K, Blondeel P, Shiri J, *et al*. (2007) A two-stage phase I trial of Evolence collagen for soft-tissue contour correction. *Plast Reconstr Surg* **120**, 303–11.

17 Wise JB, Greco T. (2006) Injectable treatments for aging face. *Facial Plast Surg* **22**, 140–6.

18 Man J, Rao J, Goldman M. (2008) A double-blind, comparative study of nonanimal-stabilized hyaluronic acid versus human collagen for tissue augmentation of dorsal hands. *Dermatol Surg* **34**, 1026–31.

19 Lowe NJ, Maxwell A, Patnaik R. (2005) Adverse reactions to dermal fillers. *Dermatol Surg* **31**, 1616–25.

20 Alam M, Gladstone H, Kramer EM, Murphy JP Jr, Nouri K, Neuhaus IM, *et al*. (2008) ASDS guidelines of care: injectable fillers. *Dermatol Surg* **34**, S115–48.

Chapter 46: Polylactic acid fillers

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BASIC CONCEPTS

- Polylactic acid fillers (PLLA) is a volume stimulator rather than a direct volume replacement.
- PLLA is best suited for areas that are concave.
- PLLA results are dependent on techniques such as dilution and injection.
- Complications from PLLA are different from those from fillers and include subcutaneous papule formation.
- PLLA results (both good and bad) may last for years.

Introduction

Poly-L-lactic acid is the active ingredient found in Sculptra® (also known as New-Fill; Sanofi-Aventis, Paris, France). Each bottle of material also contains sodium carboxymethylcellulose (USP) and non-pyrogenic mannitol [1]. The sodium carboxymethylcellulose and mannitol act to stabilize the PLLA and have no biologic effect on the volume stimulation. The material comes as a freeze-dried powder that must be reconstituted with sterile water [2]. At the present time, Sculptra is the only product of its kind and as such is unique.

Although the amount of PLLA in a bottle of Sculptra is fixed at 367.5 mg, the methods of reconstitution are variable. The ability to add different amounts of water and/or lidocaine is one opportunity for physicians to vary the use of this material and may contribute to varying reports of success and complications. Initial reports of product use in Europe utilized dilutions of 3 mL per bottle [3]. The duration of reconstitution for these early studies was 4 hours. The package insert for the product recommends a reconstitution time of 4 hours; however, many PLLA injectors advocate longer periods, with some recommending that water imbibe for at least 24 hours with longer periods of up to 3 weeks also touted. At the present time, there is no uniform consensus nor clinical trial to suggest what is the optimal dilution or reconstitution time. This author recommends using at least 4 mL water for at least 24 hours, with longer periods of time being preferable.

In addition to the 4 mL water, various anesthetic agents are added to the mixture. The anesthetic added to the product varies depending on injector preferences and experiences. Among the alternatives used, 1% lidocaine with 1:100 k epinephrine added is perhaps the most frequently used. Lidocaine without epinephrine (1%) and 2% lidocaine are also used.

Volumes of anesthetic added to the reconstituted material also vary based on the location of each injection and the experience of the injector. At the present time, many skilled injectors utilize 4 mL water for at least 24 hours and immediately before injection add 3–4 mL of 1% lidocaine with epinephrine. When injecting areas such as the back of the hands or the tear trough under the eye, this dilution may require additional water and the total reconstitution volume for these areas is 9 mL for many injectors. For the 9-mL dilution, the author uses 4 mL water and 5 mL 1% lidocaine with 1:100 000 epinephrine.

Once reconstituted, the bottle should be signed and dated and the material should be stored in a refrigerator. Before injection, it should be left out so that it can warm to room temperature. Whether or not gently heating it to body temperature before injecting to improve outcomes is another area of controversy. At the present time, it seems reasonable to inject material that is at room or body temperature but not to heat the product beyond these temperatures.

Advantages and disadvantages

PLLA has many unique properties and strengths and weaknesses. Among the strengths of the product are its long-lasting nature, ability to correct large volume losses, and ease of injection. Weaknesses of the product include the formation of subcutaneous papules, multiple injection visits, expense, and, most importantly, there is no way to predict the degree of improvement that will result from any given injection. This latter point means that unlike the hyalurons,

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collagens, or calcium hydroxylapatite, there is no way for a physician to correct a given area with a 1 1 defect to product replacement ratio. Instead, the injector must wait to see the extent to which new collagen will form.

One of the advantages of this product is its ability to produce collagen, providing a correction that lasts for more than 1 year [4]. Unlike any of the fillers, except for the permanent ones such as silicone or Artefill, once PLLA has attained a volume correction it will last for a prolonged amount of time. In addition, when the correction is diminishing, it can be enhanced with a touch up injection. Despite the initial high cost of injection, the degree and duration of the PLLA correction makes it cost effective. Volume replacement for moderate lipoatrophy costs $3000–4000. When compared with the cost of other fillers for the same time interval, PLLA correction is reasonably priced.

PLLA is technically easy to inject. In fact, the difficulty associated with this product lies more with poor patient selection, inappropriate and inadequate volume reconstitution. The very nature of the product as it is injected (it is a suspension rather than a solution or gel) means that even with the best technique, particles of PLLA will migrate following injection. In addition, density differences both in the syringe and in the patient as the PLLA particles settle provide non-homogeneous product dispersion even with the best technique.

Standard injection techniques

Beginners should not have technical problems injecting this product as long as they select the right patients and locations to treat. The most common problem encountered by novice injectors is clogging of material in the needle, resulting in sporadic injections of product under high pressure and placement of the product at the wrong plane.

Rapid injection is the best technique for injecting PLLA. This avoids needle clogs producing high pressure injections and areas of high and low concentration product placement. Injection needles should be either 25 or 26 gauge and 0.5 inch in length. Smaller bore and longer needles may result in difficulty extruding the product into the tissue.

Injections of PLLA require deep product placement. Thus, the needle should be at the level of the deep dermis or dermal–subcutaneous junction. Superficial placement will increase the probability of visible papule formation. Various methods of injecting including serial puncture, linear threading, and fanning have been described and espoused. Standard injection techniques should try to include aspects of each because the goal of the injection is to obtain a homogeneous distribution of product at the plane where it will do the most good. Which technique predominates for a given individual depends on the area being injected and the amount of product being placed. Following any technique, it is essential to massage the product vigorously to distribute it. When massaging, deep pressure adequate to move product from discrete pearls into a contiguous plane is required.

The most frequently injected areas are the cheeks, jawline, and temples. For the cheeks, it is helpful to inject half a bottle (3.5 mL) per session into each cheek. Each injection should be accomplished such that approximately 0.05 mL is inserted and the space between injections is about 0.5 cm. Serial puncture and fanning may be combined to produce a spoke-like network of injections (Figure 46.1). Typical injection schedules for the cheeks include three injections spaced at least 1 month apart. Patients with severe lipoatrophy may require more injections and it is acceptable to continue injections until full volume restoration is accomplished. However, it is not advisable to decrease the time interval between sessions.

Correction of jawline volume loss may be required following loss of subcutaneous tissue and bone resorption. PLLA

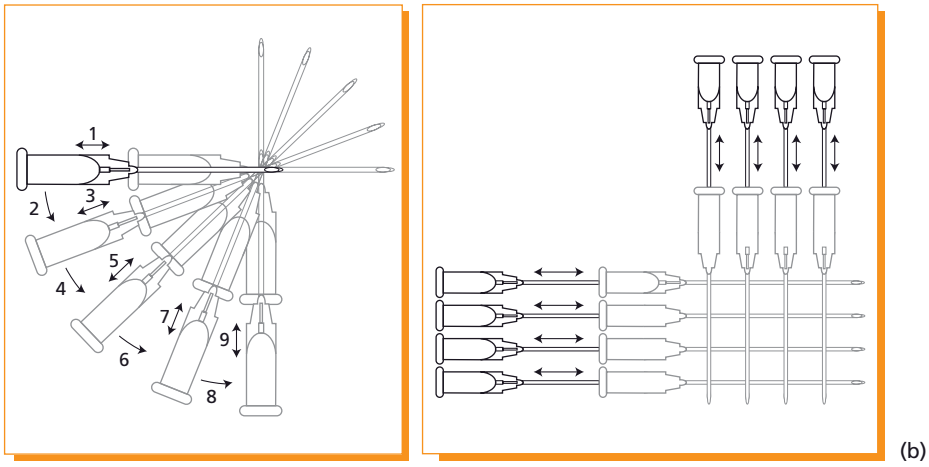

Figure 46.1 Serial puncture and fanning techiques. (a) Fan technique. (b) Cross-hatching technique.

injections may be performed to stimulate collagen in this area with outstanding results. Standard injection techniques for this area are serial puncture and fanning. Needle insertion for this location should be at the level of the deep tissue (subcutaneous or just above the periosteum). As with other locations, deep massage is necessary to move the product into a homogeneous plane.

Needle orientation for the jawline is typically at 45° to the skin. Moderate volume loss may be treated with 2–3 mL of the 7-mL dilution of PLLA and can be completed in three visits for many patients. Severe volume loss may be treated with four or more injection sessions.

Temporal wasting is one of the hallmarks of facial aging. Although other products may be used to treat this, PLLA is exceptionally well suited for this application. Injections in this location have several potential pitfalls that need to be avoided.

The plethora of blood vessels in this area provides one potential pitfall for injection of any product and the particulate nature of PLLA is no exception. When injecting the temples with PLLA, it is important to aspirate prior to inserting product. Needle placement should be deep and at the level just superficial to the periosteum. Placement at this level will help avoid formation of visible subcutaneous papules.

Average injection volume per side is 2–3.5 mL using the 7-mL volume dilution. The technique for injecting PLLA in this area is predominantly the fanning method but serial puncture is also used.

Advanced techniques

Perhaps the most important consideration when performing advanced techniques is to change the dilution and volume to accommodate the different areas being treated. Advanced techniques for injecting PLLA may be utilized to treat areas such as the tear troughs and the dorsum of the hands. When treating these areas, it is worthwhile to dilute each bottle with 9 mL of total volume rather than with 7 mL.

Tear troughs are one of the most difficult areas to treat with any injection and PLLA is no exception. There are some additional considerations for this material that warrant special consideration. Unlike standard techniques, this area is one that should be treated only by injectors with advanced skills and experience. Whereas half of the bottle is used for each side of each location treated with simple techniques, it is recommended that about 1–2 mL of the 9-mL diluted product be used for each side of the tear trough. When treating the tear trough, using the non-dominant hand to palpate the margin of the infraorbital rim will help to protect the eye and make certain that the injections remain outside of the globe. As with injections into the temple, aspiration of the syringe is essential prior to the injection. The multitude of vessels in this area require caution when injecting and although blindness has not yet been reported with PLLA injections, it is a theoretical possibility that needs to be remembered when injecting.

Placement of the needle for treatments of the tear trough are at the level immediately superficial to the periosteal plane. Orientation of the needle is either perpendicular to the skin or at 45° to the skin and directed medially. When injecting the tear troughs, never point the needle towards the globe as this may result in inadvertent punctures.

Each injection should place a small amount of material (about 0.05 mL). Injections should be about 3–5 mm apart. Following placement, each should be massaged to avoid discrete nodule formation. Despite perfect technique, injections of PLLA may result in the delayed formation of nodules and patients should be aware of this possibility prior to treatment [5].

Dorsal hand lipoatrophy and photoaging are hallmarks of aging that are frequently left untreated because of the lack of effective modalities. The use of PLLA for this location is a technique utilized by advanced injectors with very good results. As with injections of the tear trough, the dorsal hands are covered with skin that is typically thin and translucent. Thus, dilution of each bottle of Sculptra with 9 mL liquid is appropriate.

Longer needles such as 1 inch may be used to treat the dorsal hands. The needle may be inserted proximally and advanced parallel to the tendons and material inserted as the needle is withdrawn. Photoaged hands typically have prominent veins and care must be taken to avoid injections into these structures. Each hand will require about half a bottle per treatment session and approximately 9–10 injection sites to cover the entire hand.

Complications

The most common complications related to injections of PLLA are injection site related [2]. These include bruising, erythema, and site-related discomfort. More serious complications include nodule formation known as subcutaneous papules. These nodules are typically foreign body type granulomas mixed in with collagen matrix [6]. The subcutaneous nodules may be treated with injections of intralesional cortisone and it is reasonable to begin treatments with 2.5–5 mg/mL triamcinolone acetonide. Injections may be performed on a monthly basis until the nodule resolves. In the event that the nodule does not resolve after multiple injections it is possible to remove it surgically using a small incision.

More serious complications are possible with injections of PLLA (or any material) and these include necrosis of the skin. This could result from intravascular injection of PLLA and it is wise to aspirate prior to injections near major

vascular structures. Inadvertent excursions of the needle into the globe may also occur with PLLA injections (or those of any product) when the periorbital area or tear troughs are injected. The injector should take care to use the non-dominant hand to palpate the infraorbital ridge and to orient the needle away from the eye so that if the patient makes a sudden movement, the needle will not jab them.

PLLA compared with other fillers

With the advent of porcine collagen, calcium hydroxylapatite, and new forms of hyaluronic acid, one question asked by some physicians is when PLLA should be used and what patients should be treated with it. PLLA is not a direct volume replacement material and instead causes the body to replace collagen. Thus, it is not a substitute product for the various fillers. Many patients that need discrete line filling will have volume loss associated that can be treated with PLLA. Patients that only require volume replacement of the malar, temporal, or jaw areas may also obtain optimal results with PLLA.

Deciding where PLLA fits into one's practice is as much a patient selection issue as a technical one. Patients who have the temperament and budget to accept a gradual volume replacement should be treated with this product. Patients demanding a single visit correction should not. In addition, because there is no way to anticipate fully how any given individual will manufacture collagen, patients who will not tolerate a treatment program should be avoided.

Conclusions

PLLA is a unique molecule capable of restoring significant amounts of subcutaneous volume for long periods of time. It causes the body to make collagen and other extracellular matrix proteins. Unlike other products used in cosmetic dermatology, PLLA cannot produce exactly predictable results and it requires multiple treatment sessions to achieve its planned correction. Used judiciously, it can correct deficits that would otherwise be difficult to correct. PLLA has some unique complications that should be understood before it is used and patient selection is perhaps more important with this product than any other. However, its unique properties offer cosmetic dermatologists unique opportunities and this product should be embraced by injectors who understand its strengths and weaknesses.

References

1 Beer K. (2007) Optimizing patient outcomes with collagenic stimulators. *J Drugs Dermatol Suppl* **6**.
2 Sculptra Package Insert. Bridgewater, NJ: Sanofi-Aventis.
3 Vleggar D, Bauer U. (2004) Facial enhancement and the European experience with Sculptra. *J Drugs Dermatol* **3**, 542–7.
4 Burgess C, Quiroga R. (2005) Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV associated facial lipoatrophy. *J Am Acad Dermatol* **52**, 233–9.
5 Beer K. (2009) Delayed formation of nodules from PLLA injected in the periorbital area. *Dermatol Surg* **35** Suppl 1, 399–402.
6 Lombardi T, Samson J, Plantier F, Husson C, Küffer R. (2004) Orofacial granulomas after injection of cosmetic fillers: histopathologic and clinical study of 11 cases. *J Oral Pathol Med* **33**, 115–20.

Part 3: Resurfacing Techniques

Chapter 47: Superficial chemical peels

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BASIC CONCEPTS

- Chemical exfoliating agent causes destruction of the epidermis (to varying degrees) with subsequent repair and rejuvenation.
- Factors that influence the depth of a peel.
- Specific peeling agents, chemical action, and results.
- Standard and advanced techniques for superficial chemical peels.
- Complications.

Definition

Superficial chemical peels involve the application of a chemical peeling agent to the skin, resulting in destruction of the epidermis. The peel may have effects anywhere from the stratum corneum to the basal cell layer. There are many factors that affect the depth of the peel including the peeling agent and the technique of application. Chemical peels create a controlled wound which the body then heals. Permanent histologic changes can be seen after a series of superficial peels.

Physiology

Indications

Superficial chemical peels are generally safe and can be used on all Fitzpatrick skin types. The peeling agent only affects the epidermis and so this procedure is only indicated for superficial processes such as mild photoaging, superficial dyschromias (melasma, lentigines, post-inflammatory hyperpigmentation [PIH]), acne, and actinic keratoses [1]. Typically, a series of peels is required for the best clinical response.

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Depth of peel

Multiple factors influence the depth of a given peel, including chemical agent selection and technique of application (Table 47.1). Each of these factors should be considered when selecting a superficial peel for a patient.

Histologic changes

Superficial chemical peels injure and rejuvenate the epidermis; however, histologic changes can also be seen in the dermis, including collagen formation in the papillary dermis. Repeated application of alfa-hydroxy acids to the skin surface resulted in a 25% increase in epidermal thickness as well as increased acid mucopolysaccharides and increased density of collagen in the papillary dermis [2].

Formulation

In a superficial peel, chemical agents are applied to the skin to create a wound by destroying the epidermis. There are multiple different chemicals that fall into this category (Table 47.2).

Alfa-hydroxy acids (glycolic, lactic, malic, oxalic, tartaric, and citric acid)

These acids have been used on the skin for centuries. Ancient Egyptian women would bathe in sour milk (containing lactic acid) to smooth the skin [3,4]. They are naturally occurring in sugarcane, sour milk, and various fruits. When applied to the skin, they decrease corneocyte adhesion above the granular layer, reduce the number of desmosomes, and result in

desquamation [2,4]. The application is typically painless, although some mild stinging may occur. These acids require neutralization with sodium bicarbonate or dilution with water. Prolonged contact with the skin may result in uneven penetration and deeper peel depths being achieved [1].

Pyruvic acid (alfa-keto acid)

This product has keratolytic, antimicrobial, and sebostatic properties. It is a small molecule with a low pKa which allows deep penetration in the skin. Typical formulations fall into the category of medium depth peels. This potent acid carries a high risk for scarring. Application is associated with an intense burning sensation and neutralization is required with a 10% sodium bicarbonate solution [1,3].

Berardesca *et al*. [3] describe the efficacy of a 50% pyruvic acid preparation with dimethyl sulfone. This buffered solution has a lower pH value. The overall result is a superficial peel with mild burning on application and mild erythema following the peel.

Table 47.1 Variables that affect the depth of a superficial peel.

Peeling agent and concentration
Technique of application (number of coats and pressure of application)
Duration of contact with the skin (prior to neutralization)
Anatomic location
Pretreatment regimen

Jessner's solution (resorcinol 14%, lactic acid 14%, and salicylic acid 14% in alcohol)

The penetration of this solution is limited to the epidermis. The peel results in separation of the stratum corneum and upper epidermal edema [1]. Application is best with a sable hair brush. Wrung-out gauze pads may also be used. Typically, two to three coats are applied. The skin will first become erythematous and then a white, powdery appearance will emerge. This is caused by precipitation of the

Table 47.2 Characteristics of various chemical peeling agents.

Peeling agent	Activity	Neutralization	Frosting	Unique properties	Side effects
Alfa-hydroxy acid	Diminishes corneocyte adhesion/desquamation	+	–		Deeper peel may be achieved with prolonged skin contact
Pyruvic acid	Keratolytic, sebostatic, antimicrobial	+	–	Intense burning with application	Newer formulation used for superficial peels
Jessner's solution	Stratum corneum separation, dermal edema	–	–*	Intense burning with application 2–3 coats applied	
TCA (10–25%)	Coagulation of epidermal proteins	–	+	True frost forms, intensity correlates with depth of injury	Burning with application Erythema for several days
Salicylic acid	Keratolytic, comedolytic, desquamation of upper SC Enhances other peeling agents	–	–*	Burning with initial application, then acid becomes an anesthetic	Transient salicylism may occur
Tretinoin	Not destructive Increases cell turnover	–	–	Painless Discolors skin (yellow) Must remain on skin for 6 hours Decomposed by UV light	Produces strong erythema Fine white flakes with peeling
Resorcinol	Weakens hydrogen bonds of keratin	–	–	Daily application for 3 days Time consuming	Irritant or contact allergy possible Continued use associated with thyroid dysfunction
Solid carbon dioxide	Freezes and destroys epidermis			Block of dry ice dipped in acetone/ethanol solution Used to treat acne	Cold sensitivity

* White precipitate can occur as vehicle evaporates, does not represent true frost.

chemical compounds onto the skin with vehicle evaporation. This is not equivalent to a "frost" which indicates depth of peeling in a trichloroacetic acid (TCA) peel. Complications are rare with this type of peel because of the limited penetration of the peeling solution.

Trichloroacetic acid

TCA is a much stronger acid than alfa-hydroxy acid (AHA), and higher concentrations produce medium and deep peels. Superficial peels can be achieved using concentrations of 10–25%.

TCA is an inorganic compound that occurs naturally in the crystalline form. It is dissolved in distilled water to form an aqueous solution of the desired concentration. It is stable for a long time (23 weeks) and is not heat or light sensitive. Use and storage may affect the concentration of the solution and care should be taken to handle appropriately [1]. Cotton tip applicators and debris can contaminate the solution.

The mechanism of action for TCA is coagulation of epidermal proteins and necrosis of the cells. The skin gradually turns whitish gray, creating a "frost" as the epidermal proteins coagulate and precipitate (Figure 47.1) [5]. This is a self-neutralizing acid. Histologically, the epidermis and upper papillary dermis are destroyed along with new collagen deposition [1,4,6].

TCA must be applied in a controlled setting. Analgesia and/or sedation are typically required. Cotton-tipped applicators are dipped in a container with TCA solution and rolled on the edge to prevent dripping of solution. The acid is then painted on the skin, typically along cosmetic units until the desired level of frosting is achieved [6]. Multiple coats may be needed and depth of the peel correlates to the intensity of the frost. Cool compresses can be used to ease burning sensation, but do not neutralize the solution. Patients should expect several days of erythema followed by desquamation over 7 days.

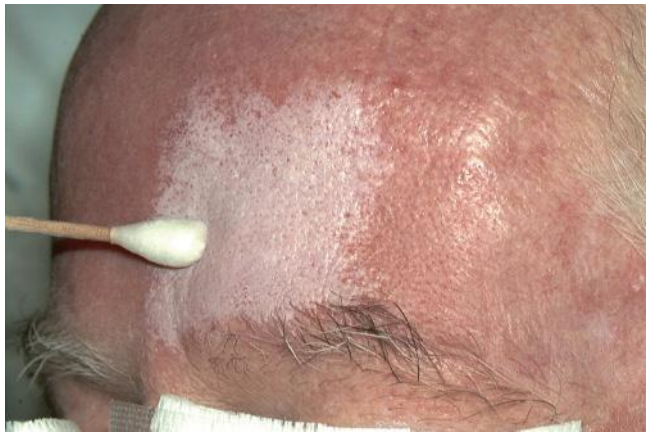


Figure 47.1 White frost seen with a trichloroacetic acid (TCA) peel indicating epidermal protein coagulation. The intensity of the frost corresponds with the peel depth.

This peel is operator dependent and potential for error and complications are high. The greatest risk exists for peeling more deeply than originally intended.

Salicylic acid (ortho-hydroxybenzoic acid)

This is a beta-hydroxyl acid. It is a lipophilic acid that allows desquamation of the upper layers of the stratum corneum without inflammation [1,6]. This peeling agent can be safely used on all skin types, even those prone to PIH. This agent also has keratolytic and comedolytic qualities making it ideal for acne patients. It also enhances the penetration of other acids and is often used in combination peels (such as Jessner's solution).

A mild–moderate burning sensation occurs on application. Typically, this is easily managed with a cool fan. The acid causes superficial anesthesia and so this quickly dissipates after a minute or more. The acid should be left on the skin for about 3–5 minutes. This is a self-neutralizing acid, but is typically washed off the skin after 5 minutes with plain water. A white precipitate will be seen on the skin after about 1 minute from evaporation of the vehicle (Figure 47.2). This is not a true frost and does not indicate depth of penetration. Desquamation will begin 2–3 days after the peel and continue for 7 days [1,4,6].

Salicylism is possible with this peel, although unlikely. Care should be taken to avoid peeling large areas at the same time. Patients may experience tinnitus, dizziness, and headache. The symptoms are transient and self-resolving [7]. Increased water intake may improve symptoms more quickly.

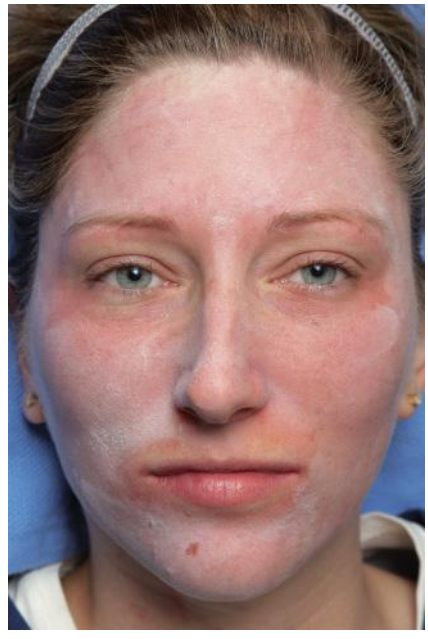


Figure 47.2 White discoloration of the skin seen during a salicylic acid peel caused by evaporation of the vehicle and precipitation of salicylate on the skin.

Tretinoin peel

Tretinoin applied in high concentration (1–5%) in propylene glycol is used for peeling. The solution is canary yellow and discolors skin on application. Tretinoin decomposes on UV exposure and should be applied late in the day. The application is painless and the peeling agent must be left on the skin at least 6 hours. This is a safe peel and the desquamation consists only of fine white flakes. It typically produces strong erythema and the risk for prolonged erythema is increased with this type of peel [6].

Tretinoin cream is typically used as part of a pre-peeling regimen to help improve penetration of peeling agent and improve healing time. Most practices advocate at least 2 weeks of pretreatment prior to the peel [7].

Resorcinol (m-hydroxybenzene)

Resorcinol is structurally and chemically related to phenol and acts as a potent reducing agent. It disrupts the weak hydrogen bonds of keratin and is therefore a keratolytic. It remains stable in water, ethanol, and ether.

Typically, the peeling agent is applied as a paste in concentrations of 10–50%. It is applied daily for 3 consecutive days and the skin contact time is slowly increased daily [1,7]. The paste is then wiped off the skin. Water and creams must be avoided for up to 1 week.

Rescorcinol is not typically used as a peeling agent. The process is time-consuming and the results can be achieved by other methods. It also can cause a non-specific irritant reaction or contact allergy. Additionally, there are reports of thyroid dysfunction with continued use (over months to years) [7]. More recent reviews indicate no danger when used in the standard fashion (as described above) [8].

Solid carbon dioxide (dry ice)

This modality has been used to treat acne for over 60 years. Brody describes a technique using a block of dry ice wrapped in a hand towel and dipped in a 3:1 solution of acetone and alcohol. Acetone dissolves sebum and lowers the temperature of the carbon dioxide. Individual lesions or segments of the face can be treated then using slow even strokes. The depth of injury is modified with pressure of application. Brody reports 5–8 seconds of moderate pressure as sufficient to freeze comedones. This is less destructive than liquid nitrogen which is more than twice as cold (–186 °C) compared to dry ice (–78 °C) [7].

Advantages and disadvantages

Superficial chemical peels are generally very safe procedures with a minimal risk profile. They can safely be performed on all Fitzpatrick skin types [4]. Patient discomfort is typically minimal and local anesthesia is not typically needed. Patients usually tolerate the erythema and desquamation following the peel quite well.

Appropriate management of patient expectations is critical with superficial peels. Patients must be aware that a series of peels is required for maximum benefit. In addition, patients should be selected appropriately, based on the degree of skin disease to ensure a successful peel candidate.

Standard technique

Initial consult

The initial consult is essential. This allows the treating physician to determine if the patient is an appropriate candidate for a chemical peel. They should have a dermatologic condition that is amenable to this therapy. A history of recent isotretinoin use, hypertrophic scarring, facial radiation, or significant psychologic disorder may make the patient a less desirable candidate. Also, a history of oral contraceptive use or hormonal agents should be noted as this may increase the chance of PIH [4]. Photographs should be obtained at this visit. Perhaps the most important aspect of this consult is managing the patient's expectations and preparing him or her for the procedure. The peel is superficial in nature and the need for serial treatments should be emphasized. Also, adherence to priming and post-treatment recommendations is essential to treatment success.

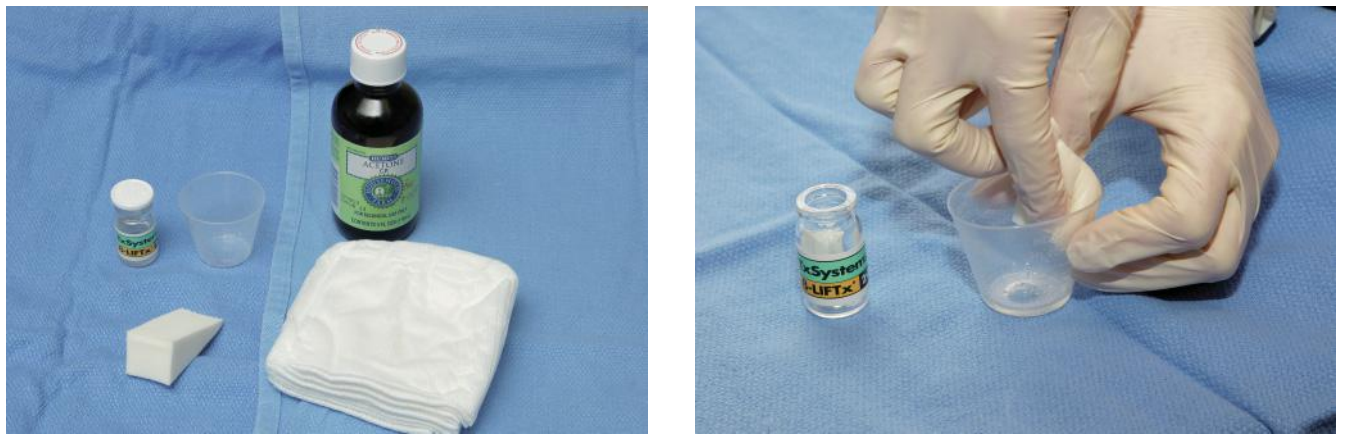
Priming

Pretreatment is important for peeling. It allows for melanocyte suppression, uniform penetration of the peeling agent, and increased healing time. Ideally, priming occurs for 2–3 weeks prior to the peel procedure. The regimen can be customized to the patient but often includes glycolic acid products (around 10%), tretinoin, hydroquinone, and sunscreen on a regular basis. The regimen (except sunscreen) should be discontinued 3 days prior to the procedure [4,5].

Peel procedure

The depth of the chemical peel is determined by multiple variables; however, the key factors are amount and concentration of peeling agent used, pressure used with application, and duration of contact with the skin.

Basic peel protocol is similar for all types of superficial peels (Table 47.3). The procedure begins with cleansing and defatting the skin. Defatting is achieved by applying acetone or isopropyl alcohol to remove excess oil and sebum and allow for even penetration of the peeling agent. Occlusive ointment can be used to protect the lips and eyes; hair should be tied back away from face. Ideally, the office should be equipped with an eyewash station or have access to water for flushing [9].



(a) (b)

Figure 47.3 (a) Typical tray set-up for a salicylic acid peel. (b) Excess peel solution is removed from sponge prior to application.

Table 47.3 Standard procedure for a superficial peel.

Initial consult
Includes pre-peel photographs
Priming
2–3 weeks prior to peel
Pre-treatment with glycolic acid, tretinoin, hydroquinone, sunscreen
Peel
Degreasing with acetone or alcohol
Application of peeling agent
Desired exposure to skin
Rinse skin or neutralize with appropriate material
Application of sunscreen and possibly anti-inflammatory agent
Post-peel
Cool compresses
Sunscreen/sun avoidance
Creams/lotions as recommended

All of the materials needed should be gathered prior to beginning. This includes a neutralization solution if needed. Patients may be more comfortable with a fan blowing cool air during the peel. Applications with either cotton-tip applicators or gauze are typically used (Figures 47.3 and 47.4).

There are inherent errors that can occur with peeling and care should be taken to avoid these situations. One error is incorrect formulation, either secondary to error in compounding or incorrect storage leading to evaporation of alcohol/water vehicle. The latter results in a stronger peeling solution than intended. Careful labeling and storage of peeling agents is essential. If greater than one strength is being used at a time, it is recommended that only one solution be on the tray at any given time and this should be clearly marked with concentration [8].

Post-care

Post-peel care includes gentle cleansing. Light moisturizing lotions can be used 24 hours after the peel procedure (Figure 47.5). Sun protection (avoidance or sunscreen) is essential for 1 month following the peel. It is critical in the first week after the peel.

Advanced techniques

Depth controlled TCA peel

Consistent results with TCA peels can be difficult to achieve and potential complications can occur more frequently depending on physician skill level and patient selection. A recent product, the TCA Blue Peel, offers a depth controlled TCA peel with more standardization in acid absorption [10]. The fixed concentration (15% or 20%) of TCA is mixed with the Blue Peel base (glycerin, saponins, and a non-ionic blue color). This base increases the surface tension of the solution and results in slower penetration of TCA into the skin. The blue color allows the physician to easily identify the areas that have been treated. Frosting occurs more slowly which allows the physician to control the depth of peel more consistently. Several coats may be applied depending on the desired depth of peeling.

Fluor-hydroxy pulse peel

This peel combines 5-flurorouracil with glycolic acid (70%) peels to treat actinically damaged skin. The two agents appear to have synergistic effects. One randomized study showed this combination cleared 91% of actinic keratoses, compared with 19% when treated with glycolic acid alone. The peel was repeated once weekly for 8 weeks [11].

Chemical reconstruction of skin scars

Chemical reconstruction of skin scars (CROSS) is a technique to address acne scars while minimizing the risks of

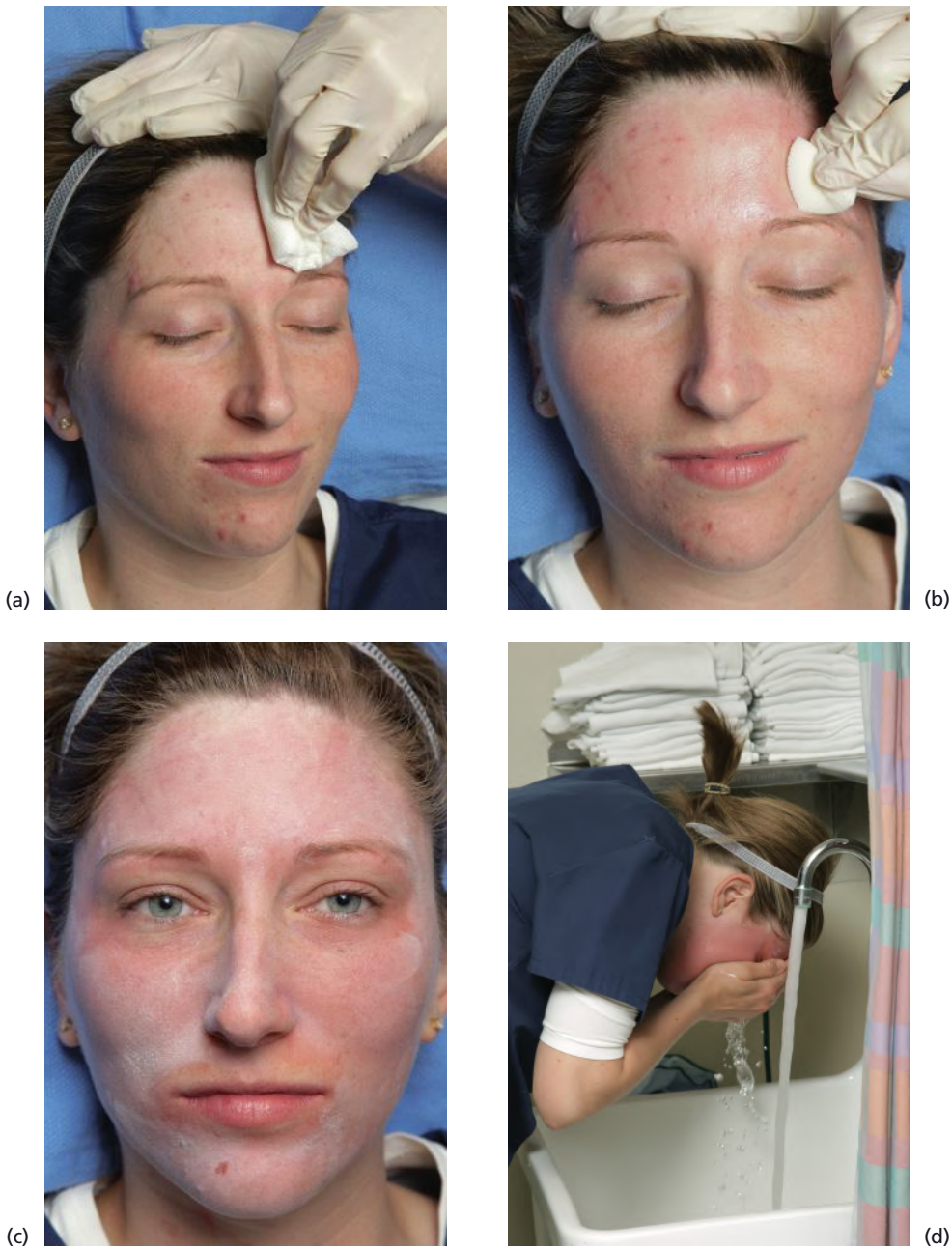


Figure 47.4 Standard peel procedure for a salicylic acid peel. (a) Face is degreased with acetone; (b) peel solution is applied; (c) erythema and white precipitate form on skin; (d) patient rinses face with water.

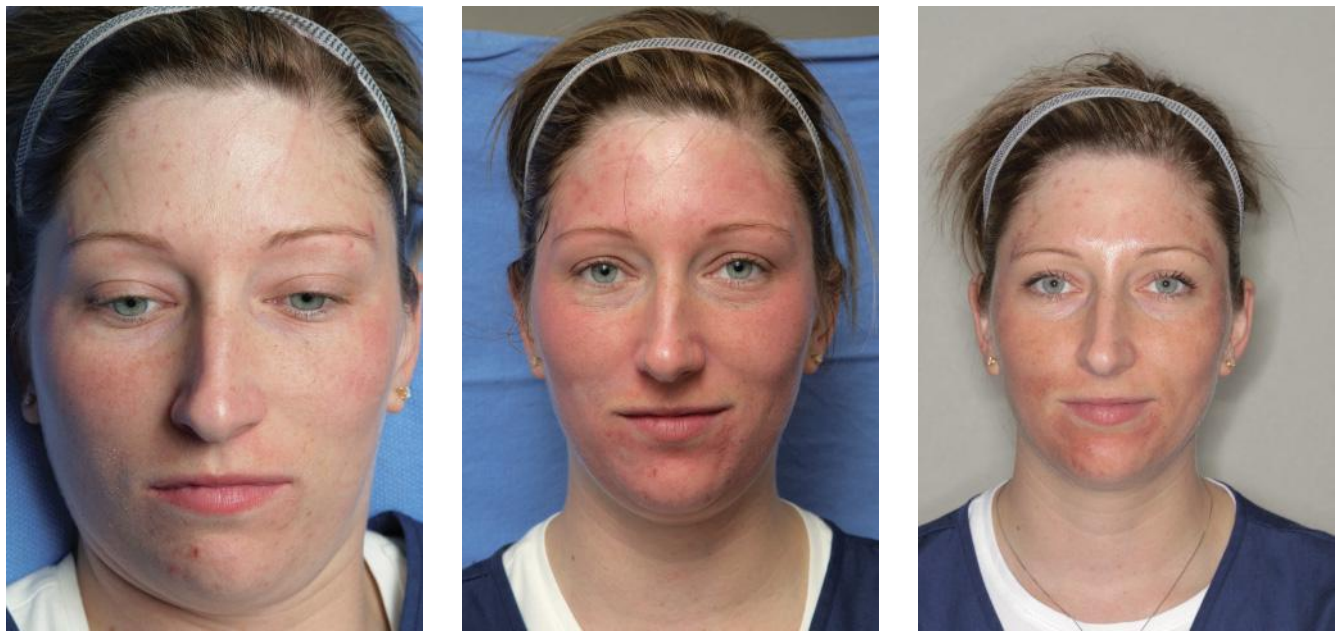
deeper peels (such as scarring and pigmentary changes). The CROSS technique involves focal application or high concentration TCA (65–100%) to atrophic acne scars. Each scar is pressed firmly with a sharpened wooden applicator. Variable improvement can be seen with this technique but typically it requires a series of treatments [12].

Complications

Complications arising from superficial chemical peels are relatively rare (Table 47.4) [9]. Post-inflammatory hyperpigmentation can occur, particularly in darker skin types. Technical errors (dripping of acid in the eyes) or incorrect formulation must also be avoided.

Conclusions

Superficial chemical peels wound the epidermis with destruction or desquamation. This leads to increased epidermal thickness and new collagen formation in the papillary dermis with repeated application. They are indicated for superficial processes such as superficial dyschromias, mild



(a) (b) (c)

Figure 47.5 (a) Pre-peel; (b) immediately post-peel; (c) 24 hours after a salicylic acid peel.

Table 47.4 Potential complications associated with superficial peels.

Pigmentary changes
Infection
Reactivation of herpes
Prolonged erythema/pruritus
Contact dermatitis
Lines of demarcation
Transient textural changes (enlarged pores)
Milia
Cold sensitivity (CO_2)

photoaging, acne, and actinic keratoses. They can safely be performed on all skin types and complications are rare. A series of peels is often required for the best clinical outcome.

References

1 Zakopoulou N, Kontochristopoulos G. (2006) Superficial chemical peels. *J Cosmet Dermatol* **5**, 246–53.

2 Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WC, *et al*. (1996) Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol* **34**, 187–95.

3 Berardesca E, Cameli N, Primavera G, Carrera M. (2006) Clinical and instrumental evaluation of skin improvement after treatment with a new 50% pyruvic acid peel. *Dermatol Surg* **32**, 526–31.

4 Roberts WE. (2004) Chemical peeling in ethnic/dark skin. *Dermatol Ther* **17**, 196–205.

5 Roenigk RK. (1998) Facial chemical peel. In: Baran R, Maibach HI, eds. *Textbook of Cosmetic Dermatology*, 2nd edn. Malden, MA: Blackwell Science, pp. 585–94.

6 Landau M. (2008) Chemical peels. *Clin Dermatol* **26**, 200–8.

7 Brody HJ. (1992) Superficial peeling. In: *Chemical Peeling*. St. Louis, MO: Mosby Year Book, pp. 53–73.

8 Brody HJ. (2001) Complications of chemical resurfacing. *Dermatol Clin* **19** (3).

9 Drake LA, Dinehart SM, Goltz RW, Graham GF, Hordinsky MK, Lewis CW, *et al*. (1995) Guidelines of care for chemical peeling. Guidelines/Outcomes Committee: American Academy of Dermatology. *J Am Acad Dermatol* **33**, 497–503.

10 Obagi ZE, Obagi S, Alaiti S, Stevens MB. (1999) TCA-based blue peel: a standard procedure with depth control. *Dermatol Surg* **25**, 773–80.

11 Marrero GM, Katz BE. (1998) The new fluor-hydroxy pulse peel: a combination of 5-fluorouracil and glycolic acid. *Dermatol Surg* **24**, 973–8.

12 Lee JB, Chung WG, Kwahck H, Lee KH. (2002) Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method. *Dermatologic Surgery* **28**, 1017–21.

Chapter 48: Medium depth chemical peels

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BASIC CONCEPTS

- Indicated both for therapeutic field treatments of precancerous skin lesions and for various cosmetic indications.
- Induce controlled chemical damage through the epidermis and variable portions of the dermis.
- Pretreatments including even cleansing, degreasing, and subsequent application of Jessner's solution will open the epidermal barrier for more even and deep penetration of trichloracetic acid.
- Affords the patient a single procedure with healing time within 1 week to 10 days.
- Are considered safe and effective when used by experienced dermatologists.

Introduction

A number of acidic and basic chemical agents have been used to produce the varying effects of light, medium, or deep chemical peels, mediated by differences in their ability to penetrate and damage epidermal and dermal skin components. The level of penetration, destruction, and inflammation determines the level of peeling. The stimulation of epidermal growth through the removal of the stratum corneum without necrosis characterizes light superficial peels. Through exfoliation, it thickens the epidermis with qualitative regenerative changes. Destruction of the epidermis defines a full superficial chemical peel inducing the regeneration of the epidermis. Further destruction of the epidermis and induction of inflammation within the papillary and upper portions of the reticular dermis constitutes a medium depth peel. Further inflammatory response in the medium reticular dermis induces new collagen production and ground substances constituting a deep chemical peel [1].

Formulations

Trichloracetic acid

Trichloracetic acid (TCA) has become the gold standard of chemical peeling agents, based on its long history of usage, its versatility in peeling, and its chemical stability. Its first documented use for skin rejuvenation dates back as far as 1882, when German dermatologist Paul Gerson Unna described the properties of salicylic acic, resorcinol, phenol, and TCA [1]. TCA has since been used in many concentrations because it has no systemic toxicity and can be used to create superficial, medium, or even deep wounds in the skin. TCA is naturally found in crystalline form and is mixed weight-by-volume with distilled water. It is not light sensitive, does not need refrigeration, and is stable on the shelf for over 6 months. The standard concentrations of TCA should be mixed weight-by-volume to assess the concentration accurately. TCA crystals weight 30 g are mixed with 100 mL distilled water to give an accurate 30% weight-by-volume concentration. Any other dilutional system – volume dilutions and weight-by-weight – are inaccurate in that they do not reflect the accepted weight-by-volume measurements cited in the literature.

Because TCA, at concentrations of 50% or above, has a high potential to be scarring, the use of higher concentrations has fallen out of favor [2]. Therefore, combined applications using an initial modifying treatment followed by a 35% TCA formula were developed to better control the level of damage and minimize the risk of side effects [3].

Brody [4] first developed the use of solid CO_2 applied with acetone to the skin as a freezing technique prior to the application of 35% TCA. The preliminary freezing appears to break the epidermal barrier for a more even and complete penetration of the 35% TCA. Monheit [5] then introduced the use of Jessner's solution prior to the application of 35% TCA (Table 48.1). The Jessner's solution was found to be very effective in destroying the epidermal barrier by breaking up individual epidermal cells. This allows a deeper penetration of the 35% TCA and a more even application of the peel solution. Similarly, Coleman and Futrell [6] have demonstrated the use of 70% glycolic acid prior to the applica-

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Table 48.1 Jessner's solution (Combes' formula).

Resorcinol	14 g
Salicylic acid	14 g
85% Lactic acid	14 g
95% Ethanol (q.s.ad.)	100 mL

q.s.ad, a sufficient quantity up to.

Table 48.2 Agents used for medium depth chemical peeling.

Agent	Comment
40–50% TCA	Not recommended
Combination 35% TCA + solid CO_2 (Brody)	The most potent combination
Combination 35% TCA + Jessner's solution (Monheit)	The most popular combination
Combination 35% TCA + 70% glycolic acid (Coleman)	An effective combination
88% phenol	Rarely used

tion of 35% TCA. Its effect has been very similar to that of Jessner's solution.

All three combinations have proven to be as effective as the use of 50% TCA; however, with a greater safety margin. The application of acid and resultant frosting are better controlled with the combination so that the "hot spots" with higher concentrations of TCA can be controlled, creating an even peel with less incidence of dyschromias and scarring (Table 48.2).

Advantages and disadvantages

The advantages of chemical peeling compared with other modalities used to treat photoaging or precancerous lesions include the low cost, the ease of a single application, the ability to be performed in a routine treatment setting without the need for specialized equipment, and reliable efficacy. Additionally, chemical peeling may be performed in any office setting with routine dermatologic supplies such as 2×2 or 4×4 inch gauze pads and cotton-tipped applicators, and does not require special equipment (Figure 48.1). When performed properly on the correctly chosen patient, a medium depth peel will reliably improve the appearance of photoaged skin and produce sustained clearing of most precancerous skin lesions for a period of several months to several years.

Table 48.3 Major indications for medium depth chemical peels.

Destruction of premalignant epidermal lesions – actinic keratoses
Resurfacing moderate to advanced photoaged skin (Glogau Levels II, III)
Improving pigmentary dyschromias
Improving mild acne scars
Blending laser, dermabrasion, or deep chemical peeling in photoaged skin (transition from treated to non-treated area)

Figure 48.1 Standard setup for Jessner's and trichloracetic acid (TCA) combination peel. The standard setup includes a facial cleanser such as Septisol, acetone, Jessner's solution, 35% TCA, cotton-tipped applicators, 2×2 inch and 4×4 inch gauze pads, and cool-water soaks for patient comfort.

Indications

While very light and light peels may improve conditions such as acne and skin texture, and deep peels may help improve moderate rhytids and acne scarring, current indications for medium depth chemical peeling include Glogau type II photoaging, epidermal lesions such as actinic keratoses, pigmentary dyschromias, acne scarring, and also to blend the effect of deeper resurfacing procedures (Table 48.3) [7].

Several contraindications exist when choosing a medium depth chemical peel (Table 48.4). Because patient compliance during the recovery period is essential to avoiding permanent negative sequelae, a medium depth peel should not occur in the setting of a poor physician–patient relationship. Likewise, a frank discussion of what the peel can and cannot accomplish is necessary, and unrealistic expectations on the part of the patient must be recognized. Furthermore, poor general health and nutritional status will compromise wound healing and should dissuade a procedural approach.

Table 48.4 Contraindications to medium-depth chemical peeling.

Absolute contraindications
Poor physician–patient relationship
Unrealistic expectations
Poor general health and nutritional status
Isotretinoin therapy within the last 6 months
Complete absence of intact pilosebaceous units on the face
Active infection or open wounds (e.g. herpes, excoriations, or open acne cysts)
Relative contraindications
Medium depth or deep resurfacing procedure within the last 3–12 months
Recent facial surgery involving extensive undermining, such as a rhytidectomy
History of abnormal scar formation or delayed wound healing
History of therapeutic radiation exposure
History of certain skin diseases (e.g. rosacea, seborrheic dermatitis, atopic dermatitis, psoriasis, or vitiligo) or active retinoid dermatitis

Moreover, isotretinoin therapy within the previous 6 months has been associated with increased risk of scarring, and a medium depth chemical peel should be delayed until the patient is beyond 6 months of finishing a course of isotretinoin. Additionally, active infections or open wounds such as herpes simplex vesicles, excoriations, or open acne cysts should postpone the treatment until such conditions resolve. All patients with a history of herpes simplex virus I of the facial area should be premedicated with an antiviral agent such as acyclovir or valacyclovir and remain on prophylactic therapy for 1 week.

While not absolute contraindications, patients with overly sensitive, hyperreactive, or koebnerizing skin disorders such as atopic dermatitis, seborrheic dermatitis, psoriasis, or contact dermatitis may find their underlying disease exacerbated by a chemical peel. In particular, patients with rosacea typically develop an exaggerated inflammatory response to the peeling agents, which serves as a trigger factor for symptoms. A history of keloid formation should be screened for prior to chemical peeling. Likewise, patients with a recent history of extensive or major facial surgery, or those who have recently had a medium depth peel in the preceding months should be evaluated closely with regard to risks and benefits. The collagen remodeling phase of wound healing due to prior treatments is still underway in such patients, and an altered wound healing response may occur. Another important relative contraindication is a history of radiation therapy to the proposed treatment area. An absence of pilosebaceous units should serve as a harbinger that the area does not have the reserve capacity of follicular epidermal cells with which to repopulate. While Fitzpatrick skin types I and II are at low risk for post-resurfacing hyperpigmentation or hypopigmentation, types III–VI are at greater risk for these complications [8].

Standard technique

Jessner's TCA peel procedure after Monheit:
1 The skin should be cleaned thoroughly with Septisol® (Vestal Laboratories, St. Louis, MO, USA) to remove oils.
2 Acetone or acetone alcohol is used to further débride oil and scale from the surface of the skin.
3 Jessner's solution is applied.
4 35% TCA is applied until a light frost appears.
5 Cool saline compresses are applied to dilute the solution.
6 The peel will heal with 0.25% acetic acid soaks and a mild emollient cream.

Informed consent

A thorough pretreatment discussion is imperative. It allows the opportunity to discuss the risks and benefits, as well as to educate the patient on the expected timeframe and course of recovery. It also allows the surgeon to assess the patient's goals and expectations so that the procedure is performed only on appropriate candidates. Those who are not willing to tolerate an acute event followed by 7–10 days of desquamation and 2–3 weeks of erythema are best served by other treatments. The patient must fully understand the potential benefits, limitations, and risks of the procedure, and an informed consent form must be signed. Pretreatment photographs are also highly recommended to allow for post-treatment comparison.

Setup

All necessary reagents for a Jessner's + 35% TCA medium depth peel may be obtained in bulk for multiapplication use from leading dermatologic suppliers. When ordering TCA, one must ensure that the strength of the acid is as intended by the physician. While both weight-to-weight and volume-to-volume methods of calculating acid concentration may be used, the authors prefer the more common method of weight-to-volume calculations. When changing vendors or ordering new products, the distributor's method of calculation should be confirmed so as to avoid application of a more highly concentrated or less highly concentrated than intended product. The standard setup includes a facial cleanser such as Septisol, acetone, Jessner's solution, TCA, cotton-tipped applicators, 2 × 2 inch and 4 × 4 inch gauze pads, and cool-water soaks for patient comfort (Figure 48.1).

Patient preparation

All patients with a history of oral or facial herpes simplex virus (HSV) infection should be pretreated with antiherpetic agents such as aciclovir or valcyclovir to prevent herpetic activation during the post-peel period. Because a negative history of HSV infection does not always correspond with actual prior exposure, and because antiviral medications are extremely safe, it is prudent to place all patients undergoing medium depth peels on a post-procedural course of medication. All antiherpetic agents act by inhibiting viral replication in the intact epidermal cell, such that the skin must be re-epithelialized before the agent has its full effect. Thus, the antiviral agent must be continued after a medium depth peel for at least 10 days. Routine antiviral agents are not necessary in light or superficial chemical peeling, as the injury pattern usually is not enough to activate the HSV.

Analgesia and sedation

Medium depth peels may be performed without anesthesia, with preceding topical anesthesia, with local nerve blocks, with mild preoperative sedation, or anxiolytic medications, or a combination of any of the above. For full-face peels in anxious patients, it is useful to give preoperative sedation (5–10 mg diazepam orally) along with mild analgesia in the form of 50 mg meperidine (Demerol, Winthrop, New York, USA) and a mild sedative such as 25 mg hydroxyzine hydrochloride intramuscularly (Vistaril, Lorec, New York, USA). The discomfort from this peel is not long-lasting, so short-acting anxiolytics and analgesics are all that are usually recommended [8].

Application technique

Vigorous cleansing and degreasing of the skin prior to application of the active peeling agent represents a crucial and often overlooked step in the protocol. The removal of skin surface lipids deriving from sebum and epidermal lipids, scale and thickened stratum corneum is particularly important for even penetration of the solution. The face is first washed with an antibacterial cleanser in glycerin (Septisol) applied with 4 × 4 inch gauze pads, then rinsed with water. Acetone is then applied with 4 × 4 inch gauze pads to remove residual oils and debris. The skin is thus débrided of stratum corneum and excessive scale. The necessity for thorough degreasing in order to achieve reliable and even penetration cannot be overemphasized. Prior to application of the active peeling agent, one should assess the thoroughness of degreasing. If oil or scale is felt, the degreasing step should be repeated. Particular attention should be focused on the hairline and nose. Thorough and uniform degreasing conditions the skin to ensure an even peel over the entire face.

Next, Jessner's solution is evenly applied, either with cotton-tip applicators or 2 × 2 inch gauze pads. Jessner's solution alone constitutes a very light peel, and thus will open the epidermal barrier for a more even and more deeply penetrating TCA application. Only one coat of Jessner's solution is usually necessary to achieve a light, even frosting with a background of erythema. The expected frosting is much lighter than that produced by the TCA. The face is treated in sequential segments progressing inferiorly from the hairline. Even strokes are used to apply the solution to the forehead first then each cheek, the nose, and the chin. The perioral area should follow, and the eyelids are treated last, creating the same erythema with blotchy frosting.

As with the application of Jessner's solution, cosmetic units of the face are then peeled sequentially with TCA from forehead to temple to cheeks, and finally to the cutaneous lips and eyelids. The 35% weight-to-volume TCA is applied evenly with 1–4 cotton-tipped applicators rolled over different areas with lighter or heavier doses of the acid. Four well-soaked cotton-tipped applicators are used with broad strokes over the forehead and the medial cheeks. Two mildly soaked cotton-tipped applicators can be used across the lips and chin, and one damp cotton-tipped applicator on the eyelids. The amount of acid delivered is thus dependent upon both the saturation of an individual cotton-tipped applicator and the number of cotton-tipped applicators used. In this manner the application is titrated according to the cutaneous thickness of the treated area.

The white frost from the TCA application, which represents the keratocoagulated endpoint, should appear on the treated area within 30 seconds to 2 minutes after application (Figure 48.2). An even application should eliminate the need for a second or a third pass, but if frosting is incomplete or uneven, the solution should be reapplied. TCA takes longer to frost than a deep phenol peel, but less time than the superficial peeling agents. After a single application to an area, the surgeon should wait at least 3–4 minutes to ensure that frosting has reached its peak. The thoroughness of application can then be analyzed, and a touch up, or less commonly another pass, can be applied as needed. Areas of poor frosting should be retreated carefully with a thin application of TCA.

The physician should seek to achieve a level II–III frosting. Level II frosting is defined as white-coated frosting with a background of erythema [9]. A level III frosting, which is associated with penetration to the reticular dermis, is solid white enamel frosting with no background of erythema. A deeper level III frosting should be restricted only to areas of heavy actinic damage and thicker skin. Although heavily damaged actinic skin may require a level III frosting, most medium depth chemical peels should strive to obtain no more than a level II frosting. This is especially true over

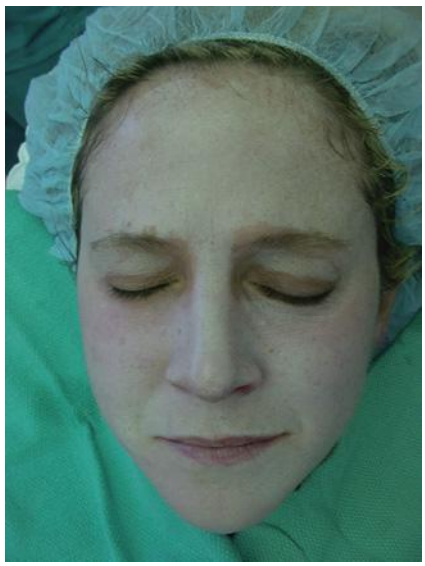


Figure 48.2 Frosting observed immediately after combined Jessner's and TCA peel. Typical opaque white frosting with mild erythema observed 2 minutes after TCA application.

eyelids and areas of sensitive skin. Those areas with a greater tendency to scar formation, such as the zygomatic arch, the bony prominences of the jawline, and chin, should only receive up to a level II frosting. Overcoating TCA with multiple passes or highly saturated cotton-tipped applicators will increase its penetration, so that a second or third application will create further damage. One must be extremely careful to retreat only areas where the amount of solution taken up was not adequate or the skin is much thicker. One should never overcoat a fully frosted area.

Certain facial features require special attention. Careful feathering of the solution into the hairline and around the rim of the jaw and brow conceals the line of demarcation between peeled and non-peeled areas. The perioral area has fine, radial rhytids that require a complete and even application of solution over the lip skin to the vermilion border. This is best accomplished with the help of an assistant who stretches and fixates the upper and lower lips as the peel solution is applied. Alternatively, the TCA may be applied along the rhytid to the vermilion border with the wooden end of a cotton-tipped applicator. It should be noted that deeper furrows such as expression lines will not be eradicated by a medium depth peel and thus should be treated like the remaining skin.

Thickened keratoses should stand in contrast to the frosted background because they do not pick up peel solution evenly and thus do not frost evenly. Additional applications rubbed vigorously into these lesions may be needed for penetration.

Eyelid skin must be treated delicately and carefully. A damp, rather than saturated, applicator should be used. This is accomplished by draining the excess TCA on the cotton tip against the rim of the bottle or onto a dry gauze pad before using it for application. The patient should be positioned with the head elevated at 30° and the eyelids closed. The applicator is then rolled gently on the lids and periorbital skin within 2–3 mm of the lid margin. Never leave excess peel solution on the lids, because the solution can roll into the eyes. Dry tears with a separate, dry cotton-tipped applicator during peeling because they may wick peel solution to the puncta and eyes by capillary attraction.

The patient will experience an immediate burning sensation as the TCA is applied, but this subsides as frosting is completed. A circulating fan may be placed beside the patient for comfort. Cool saline or water compresses also offer symptomatic relief for a peeled area. The compresses are placed over the face for 5–6 minutes after the peel until the patient is comfortable. The burning subsides fully by the time the patient is ready to be discharged. At that time, most of the frosting has faded and a brawny desquamation is evident.

Post-procedure

Postoperatively, edema, erythema, and desquamation are expected. With periorbital peels and even forehead peels, eyelid edema can be severe enough to close the lids. For the first 2–4 days, the patient is instructed to soak four times a day with a 0.25% acetic acid compresses made of 1 tablespoon white vinegar in 1 pint warm water. A bland emollient is applied to the desquamating areas after soaks. After 4 days, the patient can shower and clean gently with a mild facial cleanser. The erythema intensifies as desquamation becomes complete within 4–5 days. Thus, healing is completed within 7–10 days. At this time the bright red color has faded to pink and has the appearance of a sunburn (Figure 48.3). This erythema may be covered by cosmetics and will fade fully within 2–3 weeks.

Complications

Many of the complications seen in peeling can be recognized early on during healing stages. The cosmetic surgeon should be well acquainted with the normal appearance of a healing wound in its timeframe for medium depth peeling. Prolongation of the granulation tissue phase beyond 1 week may indicate delayed wound healing. This could be the result of viral, bacterial, or fungal infection, contact irritants interfering with wound healing, or other systemic factors. A red flag should alert the physician that careful investigation and prompt treatment should be instituted to forestall potential irreparable damage that may result in scarring. Thus, it is critically important to understand the stages of wound healing in reference to medium depth peeling. The

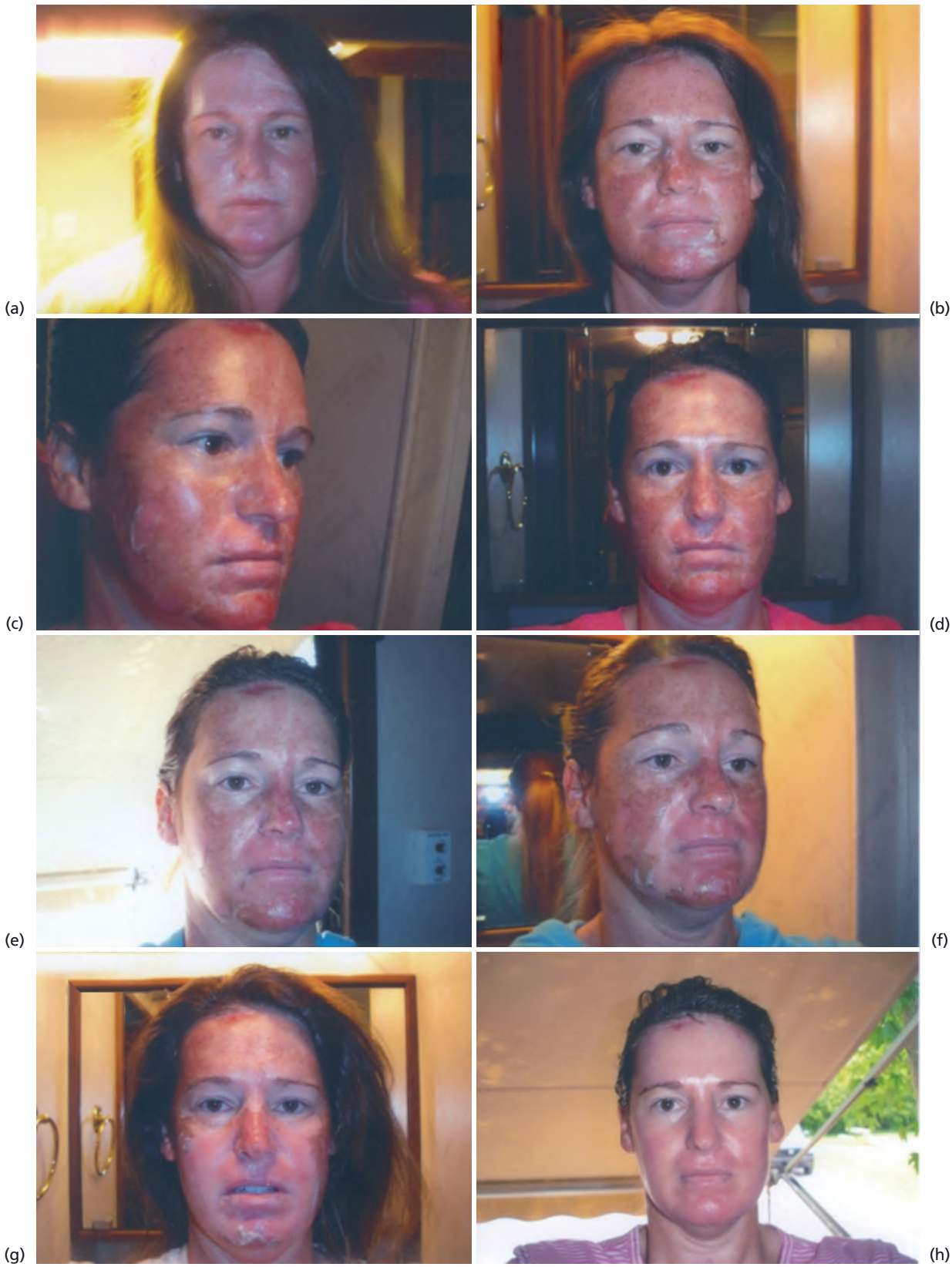
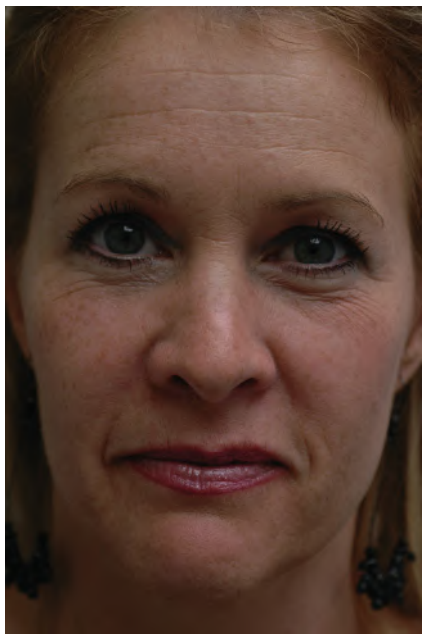
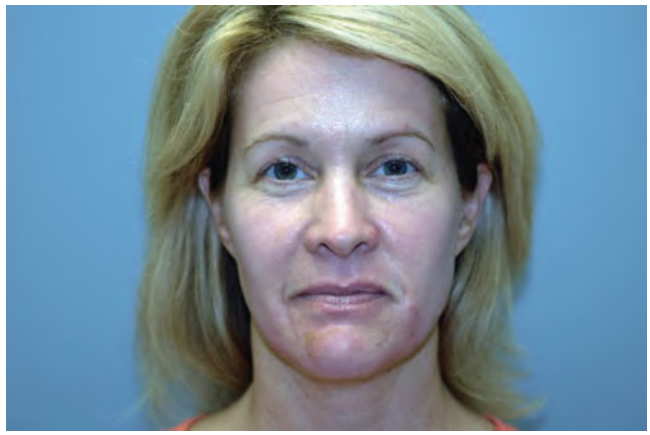


Figure 48.3 Sequential exfoliation, granulation, and re-epithelialization after Jessner's and TCA combination medium depth peel. (a) Postoperative day 1: inflammation with edema, erythema; (b) day 2: early epidermal separation with hyperpigmentation; (c, d) day 3 morning; and (e, f) day 3 afternoon: dermal inflammation with granulation tissue and early re-epithelialization; (g, h) days 5 and 6, respectively: full desquamation with regeneration of new epidermis and beginning dermal remodeling.



(a)



(b)

(c)

Figure 48.4 Jessner's TCA peel performed for photoaging skin and actinic keratoses. (a) Preoperative; (b) 5 weeks postoperative; (c) 10 weeks postoperative.

physician then can avoid, recognize, and treat any and all complications early (Figure 48.4).

Long-term care

Long-term care of peeled skin includes sunscreen protection for up to 6 months along with reinstitution of medical treatment such as low strength hydroxy acid lotions and topical tretinoin formulations. Repeeling areas should not be performed for 6 months from the previous peel. If any erythema or edema persists, the peel should not be performed as the reinjury may create complications. Medium depth peels should not be performed on undermined skin such as facelift or flap surgery performed up to 6 months prior to the peel [10].

Conclusions

The evolution of medium depth chemical peeling has changed the face of cosmetic surgery. It has introduced new techniques into the armamentarium of the cosmetic surgeon to treat problems that previously have been approached with tools inadequate to obtain the results for moderate photoaging skin or with overly aggressive treatment using deep chemical peeling agents. The combination peels have provided some of the more popular tools needed to approach a burgeoning population with photoaging and photocarcinogenesis.

The presented medium depth peel will produce excellent results for a variety of skin conditions, including actinic keratoses (Figure 48.5). A comparison study of the efficacy

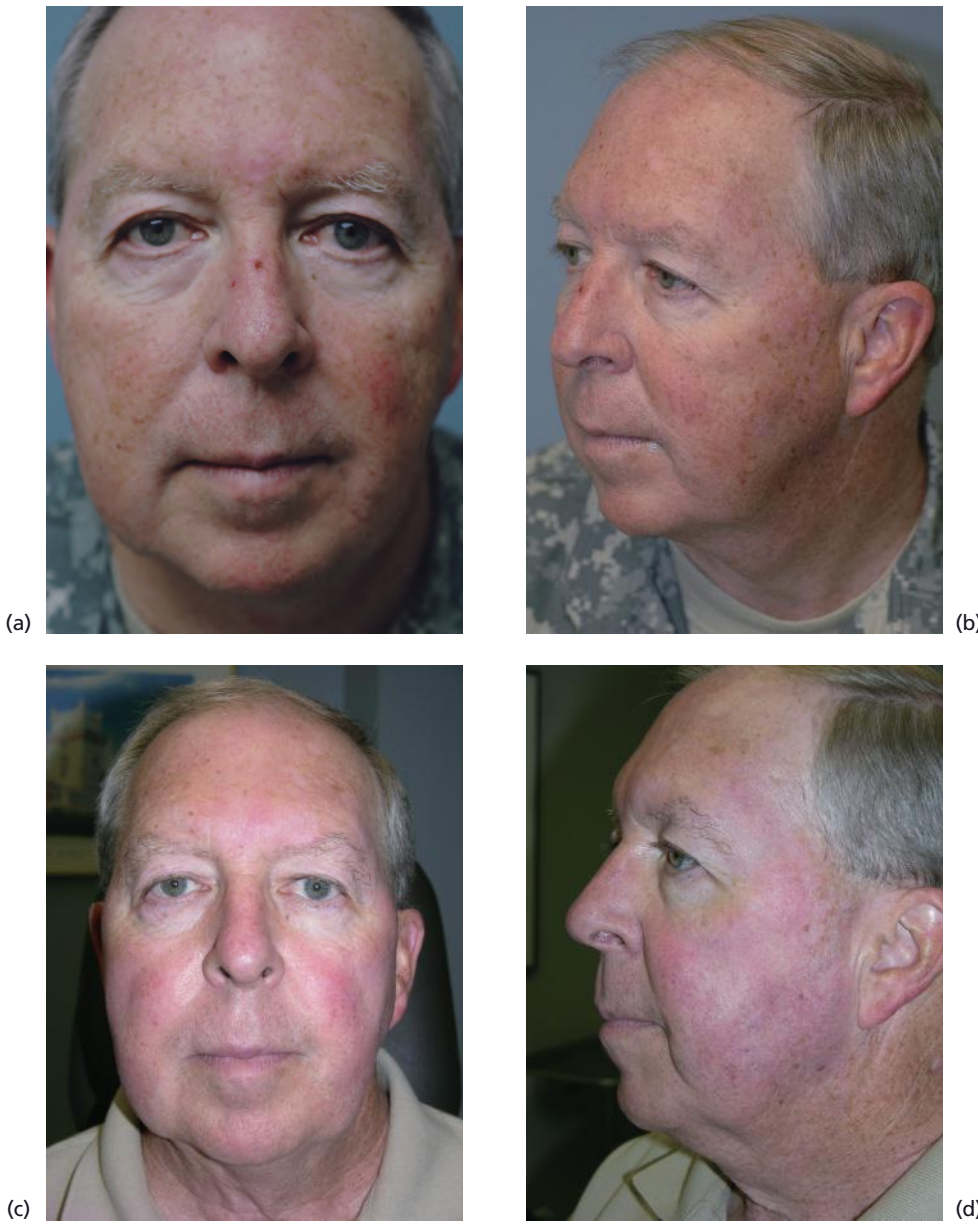


Figure 48.5 Jessner's 35% TCA peel for actinic keratoses. (a & b) Preoperative diffuse actinic keratoses and seborrheic keratoses; (c & d) 9 months postoperative.

of Jessner's solution plus 35% TCA with 5-fluorouracil documented superior effectiveness of this single procedure over 5-fluorouracil, with a significant reduction in morbidity [11]. Medium depth combination peels thus provide an effective, safe, and simple single procedure that can be used as both a therapeutic and cosmetic procedure to counteract cutaneous photodamage.

References

1 Brody HJ, Monheit GD, Resnik SS, Alt TH. (2000) A history of chemical peeling. *Dermatol Surg* **26**, 405–9.
2 Brody HJ. (1989) Variations and comparisons in medium depth chemical peeling. *J Dermatol Surg Oncol* **15**, 960–3.
3 Monheit GD. (2004) Chemical peels. *Skin Ther Lett* **9**, 6–11.
4 Brody HJ. (1997) *Chemical Peeling and Resurfacing*. Mosby, p. 110.
5 Monheit GD. (1989) The Jessner's + TCA peel: a medium depth chemical peel. *J Dermatol Surg Oncol* **15**, 945.
6 Coleman WP, Futrell JM. (1994) The glycolic acid + trichloroacetic acid peel. *J Dermatol Surg Oncol* **20**, 76–80.
7 Glogau RG. (1994) Chemical peeling and aging skin. *J Geriatr Dermatol* **2**, 30–5.
8 Monheit GD. (1995) The Jessner's trichloracetic acid peel. *Dermatol Clin* **13**, 277–83.

9 Rubin M. (1995) *Manual of Chemical Peels*. Philadelphia, PA: Lippincott, pp. 120–1.
10 Monheit GD. (1994) Advances in chemical peeling. *Facial Plast Surg Clin North Am* **2**, 7–8.
11 Lawrence N, Cox SE, Cockerell CJ, Freeman RG, Cruz PD Jr. (1995) A comparison of efficacy and safety of Jessner's solution and 35% trichloracetic acid vs. 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Arch Dermatol* **131**, 176–81.

Chapter 49: CO_2 laser resurfacing: Confluent and fractionated

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BASIC CONCEPTS

- Fractionated laser resurfacing with ablative lasers gives better results than with non-invasive lasers.
- Confluent ablative laser resurfacing gives better results than fractionated laser resurfacing.
- More "down-time" correlates with better results.
- Cold air cooling and advanced topical anesthesia provides optimal pain control.
- Fractionated ablative resurfacing has minimal adverse effects.

Introduction

Carbon dioxide (CO_2) lasers are currently available in two forms: confluent and fractionated. The differences between the results, adverse effects, and down-time are compared and contrasted in this chapter.

CO_2 laser resurfacing

The modern era of CO_2 laser resurfacing began in 1994 with the development of the UltraPulse CO_2 laser by Coherent Medical (now Lumenis, Inc., Santa Clara, CA, USA). This laser delivers peak fluences above the ablation threshold of cutaneous tissue (5 J/cm^2) with tissue dwell times shorter than the 1 ms thermal relaxation time of the epidermis. These new generation CO_2 lasers limited tissue dwell time by either shortening the pulse duration (i.e. UltraPulse) or using scanning technology to rapidly sweep a continuous wave CO_2 laser beam over the tissue such that the laser beam does not remain in contact with any particular spot on the tissue for longer than 1 ms (i.e. SilkTouch, Sharplan Laser Corporation, now Lumenis Inc., Santa Clara, CA, USA). These high peak-power, short-pulsed, and rapidly scanned CO_2 laser systems allow laser surgeons to precisely and effectively ablate 20–30 μm of skin per pass while leaving in its wake a considerably smaller residual zone of thermal damage (up to 150 μm) than left behind by the previous generation of continuous wave CO_2 lasers (up to 600 μm). Clinically, this technologic advancement translates into superior clinical results and a much more favorable safety profile than seen previously with the continuous wave CO_2 lasers.

The thermal effect of the CO_2 laser acts on dermal collagen stimulating neocollagenesis and tightening of facial skin. Successful ablation maximizes thermal stimulation of the dermis while limiting non-specific thermal damage. Another method used to decrease thermal damage is to follow a session of CO_2 laser ablation with the erbium:yttrium aluminum garnet (Er:YAG) laser. With this technique, the residual non-specific thermal damage left from the CO_2 laser is vaporized by subsequent passes with an Er:YAG laser which leaves little if any non-specific thermal damage.

Given the impressive clinical results achieved with the high peak power, short pulsed, and rapidly scanned CO_2 lasers, they quickly replaced chemical peels and dermabrasion as the treatment of choice for cutaneous resurfacing. However, the impressive results achieved with these new generation CO_2 lasers were not without drawbacks. Re-epithelialization can take 5–14 days and postoperative erythema and/or post-inflammatory hyperpigmentation can last 1–6 months depending on the depth of laser ablation, amount of residual non-specific thermal damage, and patient's skin type. Finally, there is a risk of fungal, viral, and bacterial infections on the denuded skin as well as permanent hypopigmentation from destruction of melanocytes and resultant scarring. Minimizing these potential adverse effects requires excellent postoperative care and is time-consuming for both the patient and physician.

These side effects, as well as the significant "down-time" typically associated with CO_2 laser resurfacing and extensive postoperative care, are unacceptable to many patients and

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

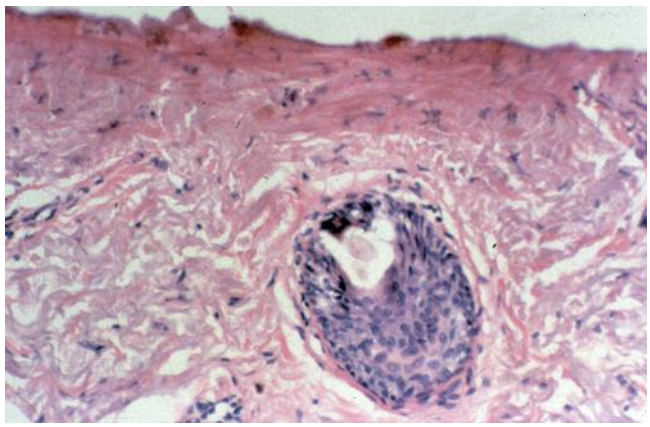
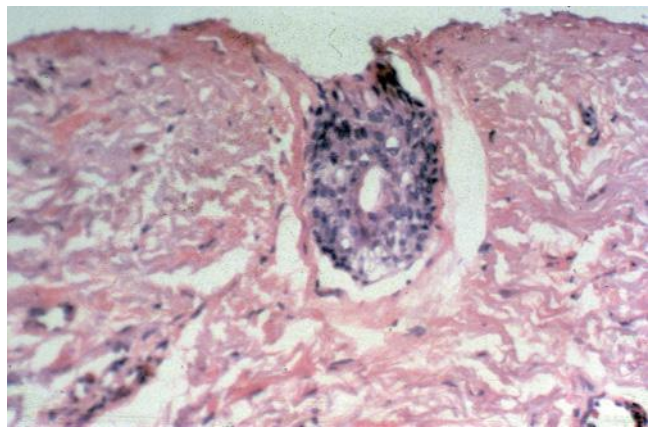
(a)   (b)

Figure 49.1 (a) Two passes of CO_2 laser at 7 J/cm^2 leaves approximately 70 μm of residual thermal necrosis. (b) Two passes of Er:YAG laser at 10 J/cm^2 results in removal of approximately 50 μm of this necrotic tissue. (From Carcamo AS, Goldman MP. (2006) Skin resurfacing with ablative lasers. In: Goldman MP, ed. *Cutaneous and Cosmetic Laser Surgery*. London: Mosby-Elsevier, figure 7.44, p. 234.)

significantly dampened the initial enthusiasm associated with their use.

Because the CO_2 laser typically operates near its tissue ablation threshold (5 J/cm^2) in most resurfacing applications, a large fraction of its energy is invested in heating rather than ablating tissue. Consequently, the CO_2 laser produces relatively large residual thermal damage zones and causes significant desiccation of the target tissue after only a few passes. With each subsequent pass, the amount of vaporized tissue decreases while thermal damage increases and a "plateau" of ablation is typically reached after the fourth pass. Non-specific thermal damage has a negative impact, not only on the CO_2 laser's ablative capacity, but also on its side effect profile. Our research suggests that the relatively large thermally induced residual zone of necrosis (up to 150 μm) left behind by the CO_2 laser is one of the main factors contributing to its adverse sequelae including prolonged erythema, postoperative pain, delayed healing, infection, hypopigmentation, and scarring.

To minimize the issues resulting from a large residual thermal zone the Er:YAG laser was introduced for resurfacing. While it was successful in reducing thermal damage it was unable to penetrate beyond papillary dermis as a result of poor hemostatic properties. A multimode Er:YAG system, the Tunable Resurfacing Laser (TRL), was developed (Sciton, Inc., Palo Alto, CA, USA) which allows the user to blend a variety of ablation and thermal coagulation depths by extending the pulse duration of the Er:YAG laser which is typically less than 0.5 ms. Extending the pulse duration to 4–10 ms allowed for less flash vaporization and more prolonged thermal heating to occur. The TRL can be tuned for pure ablation or CO_2-like thermal injury, or any point in between.

Modifications of technical protocols have continued to improve clinical outcomes. Combination therapy with CO_2 immediately followed by Er:YAG lasers allow cosmetic surgeons to capitalize on the unique benefits of each laser system and to minimize their disadvantages. Er:YAG laser treatment can be used to bypass the ablation "plateau" characteristic of CO_2 resurfacing to ablate deeper into the dermis. Improved postoperative healing can also be attained when the short-pulsed Er:YAG laser is used to remove the residual zone of thermal necrosis left behind after CO_2 resurfacing (Figures 49.1 and 49.2).

Additionally, the ablative lasers have turned out to be extremely versatile therapeutic tools. Cosmetic surgeons now regularly combine ablative laser resurfacing with other problem-specific non-ablative technologies to address multiple cosmetic concerns for the patient in a single treatment session. The efficacy of Q-switched lasers in the treatment of pigmented lesions is enhanced when these lasers are used after ablative resurfacing. Treatment of vascular lesions with the pulsed dye laser or other vascular lasers has been shown to be extremely successful when performed prior to skin resurfacing with an ablative laser. Despite early reports advising against it, full-face laser resurfacing is now safely being combined with rhytidectomy and autologous fat transfer to achieve a more comprehensive approach to facial rejuvenation.

Pretreatment and post-treatment protocols have also improved. Although some controversy remains surrounding the topic of antibiotic prophylaxis, a number of studies in the last decade have provided relevant information on common pathogens, effective antibiotic prophylaxis regimens, and clinical situations at increased risk for infection after cutaneous laser resurfacing. Improved laser wound care regimens have reduced recovery time and decreased morbidity after laser skin resurfacing. The benefits of occlusive dressings in accelerating laser wound healing have been well established in a number of studies. Timely institution of topical medications in the postoperative period is now allowing surgeons to effectively address a number of

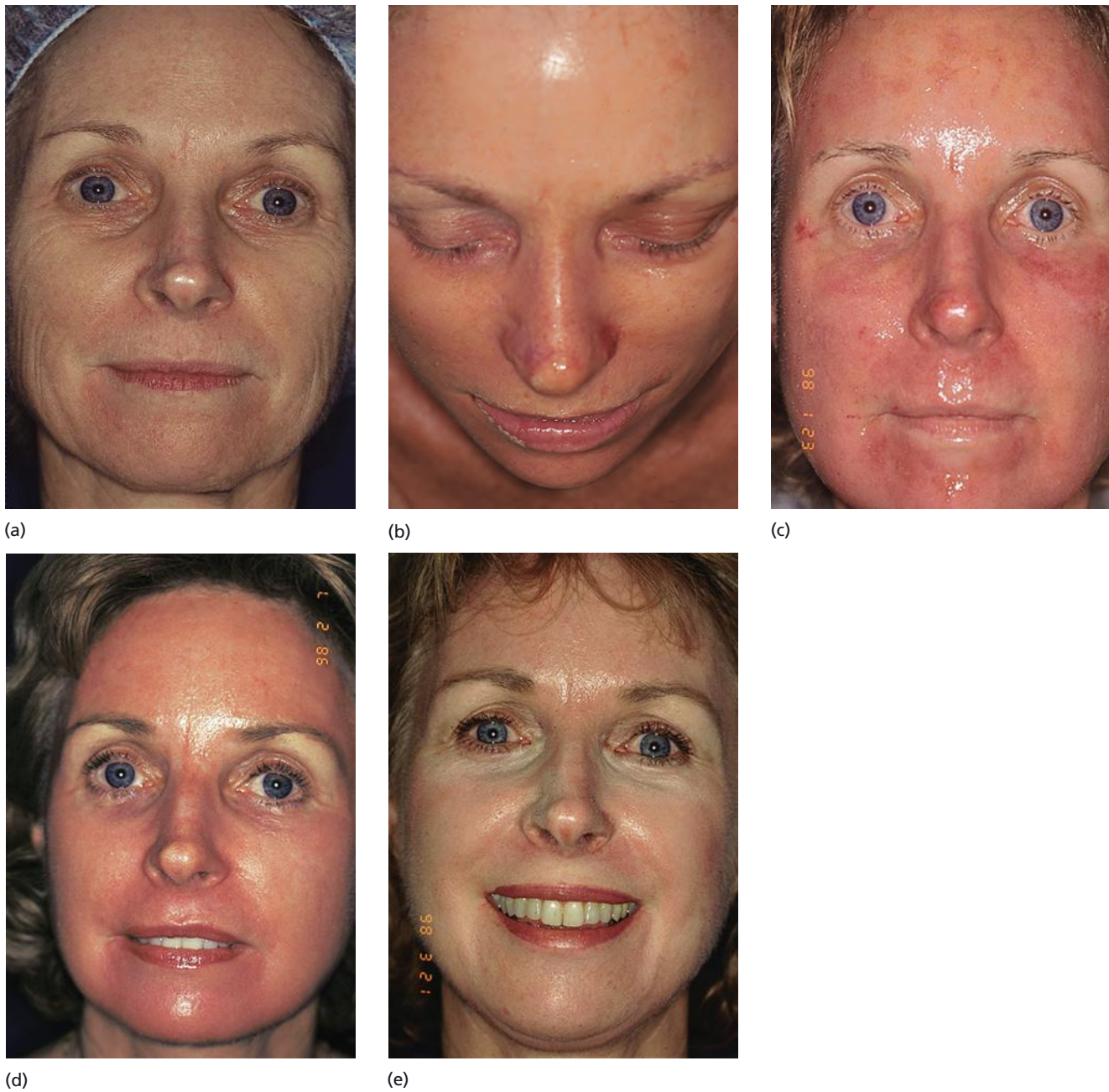


Figure 49.2 Combination UltraPulse CO_2 ($UPCO_2$) and Er:YAG laser (patient's right side) showing improvement equal to left side treated with $UPCO_2$ alone. (a) Before treatment; (b) immediately after treatment; (c) 7 days after laser resurfacing; (d) 3 weeks after laser resurfacing; (e) 2 months after resurfacing. (From Carcamo AS, Goldman MP. (2006) Skin resurfacing with ablative lasers. In: Goldman MP, ed. *Cutaneous and Cosmetic Laser Surgery*. London: Mosby-Elsevier, figure 7.37 p. 225.)

expected postoperative symptoms and complications including postoperative erythema and edema, pruritus, and post-inflammatory hyperpigmentation.

Fractionated CO_2 laser resurfacing

Because of the prolonged and meticulous postoperative care in addition to potential adverse effects, as well as the advancement in minimally invasive procedures with rapid healing times, confluent CO_2 and/or Er:YAG ablative resurfacing is rarely necessary. Physicians and patients find it easier to have minimally invasive procedures performed even at the expense of minimal results. The current consensus among patients is to embrace a treatment modality that delivers maximum results with minimal down-time. Unfortunately, the promises by most laser companies who have developed and are promoting these minimally

invasive, non-ablative lasers have not lived up to their stated efficacy in improving photodamage. The development of fractionated lasers that treat a percentage of the skin while leaving the intervening areas untreated, allows for the more dramatic results of a variety of laser wavelengths including the 10 640 nm CO_2 laser to be associated with quicker healing times and fewer postoperative sequelae.

Initially, fractional lasers were introduced in a non-ablative format. This technology was developed to overcome the homogeneous thermal damage typically created after treatment with standard CO_2 and/or Er:YAG lasers and instead create microscopic thermal wounds which spares the tissue surrounding each wound. A 2.1% linear shrinkage of periorbital rhytids was noted at 3 months with this non-ablative fractionated laser which is much less than that achieved with standard ablative CO_2 and/or Er:YAG laser resurfacing. It did not take long for fractional photothermolysis to be applied to ablative lasers, allowing for a more aggressive treatment option. My recommendation is that non-ablative fractionated lasers be reserved for patients who can not accept any "down-time" and are willing to wait at least 6 months and have 4–6 treatments to see definite improvement in wrinkles and/or scarring.

Interestingly, physicians have had the ability to perform fractionated CO_2 laser resurfacing since the development of the scanning UltraPulse hand-piece in 1995. This scanner was developed to deliver precisely overlapped laser pulses that occurred in a Gaussian distribution uniformly to ablate and/or vaporize the epidermis. Recognition that one could use this scanner with a negative 10% overlap along with the development of smaller laser spot sizes (0.1 and 1.2 mm) produced the first fractionated CO_2 laser.

There are an ever-increasing variety of both fractionated CO_2 and Er:YAG lasers to assist in facial rejuvenation. Table 49.1 summarizes the available lasers by company, wavelength, spot size, treatment area, density, speed, power, and maximal depth (if known). The remaining portion of this chapter discusses the available systems at the time of this writing (Fall 2008). Because I have not been able to test each system and very little if anything is currently available in the peer-reviewed medical literature, I am thankful to my friends and colleagues for sharing their experience.

Active and Deep FX Lumenis

The Active and Deep FX fractionated CO_2 laser delivers the equivalent of 240 W to the tissue compared to the other 30

Table 49.1 Summary of available lasers by company, wavelength, spot size, treatment area, density, speed, power, and maximal depth.

Company	Product	Wavelength (nm)	Spot size (μm)	Treatment area (mm)	Max Depth (μm)	Density	Frequency (Hz)	Power (W)
Lumenis	Deep FX	10 600	120	7 × 7	Any	5–45%	300	60
Lumenis	Active FX	10 600	1300	9 × 9	300	55–100%	600	60
Reliant	Fraxel re:pair	10 600	120	15 × 15	1600	10–70%	2100 MTZ/s	40
Alma	Pixel CO_2	10 600		10 × 10		15–20%		30
Lasering	Mixto SX Slim E30	10 600	300	20 × 20	500	20–100%		30
MedArt	MedArt FrX	10 600	300	10 × 10	1660	7–20%		20
Deka/Cynosure	SmartXide DOT/Affirm	10 600	350	15 × 15	350	5–100%	5–100	30
Lutronic	Mosaic eCO_2	10 600	120, 300, 1000	14 × 14	2400	5–130%	200	30
Wavelight	Paxel	2 940		3 × 10				
Palomar	Lux 2940	2 940	300		600			
Cutera	Fractionated Pearl	2 940	300		200–1000			
Sciton	Profractional	2 940	250	20 × 20	1500	1.5–60%	2.3 cm^2/s	
Sciton	Profractional XC	2 940	430	20 × 20	1500	5.5 or 11%		
Alma	Pixel	2 940		11 × 11	<300	49 or 81	2	

MTZ, microthermal zone.

and 40 W systems. The nature of the 240 W square wave pulse of the UltraPulse makes it about eight times the power of competitive CO_2 laser systems. This is said to result in a cleaner ablation. The Active FX hand-piece has a spot size of 1.3 mm and ablates up to 300 µm of tissue (Figure 49.3). The Deep FX hand-piece has a 120 µm diameter spot size which can ablate tissue from superficial to up to 2 mm depending on the power density chosen as well as whether the individual pulses occur as a single, double, or triple pulse (Figure 49.4). The Deep FX is used to treat individual scars and/or wrinkles. This is followed by the Active FX which is used to treat the entire face, rejuvenating the epidermis.

We have evaluated the histologic and clinical effects of varying pulse energies and densities on e*x vivo* tissue as well as *in vivo* with the fractionated CO_2 laser (UltraPulse Encore Active FX™, Lumenis, Santa Clara, CA, USA). A distinct, stippled gray, fractional epidermolysis pattern is apparent

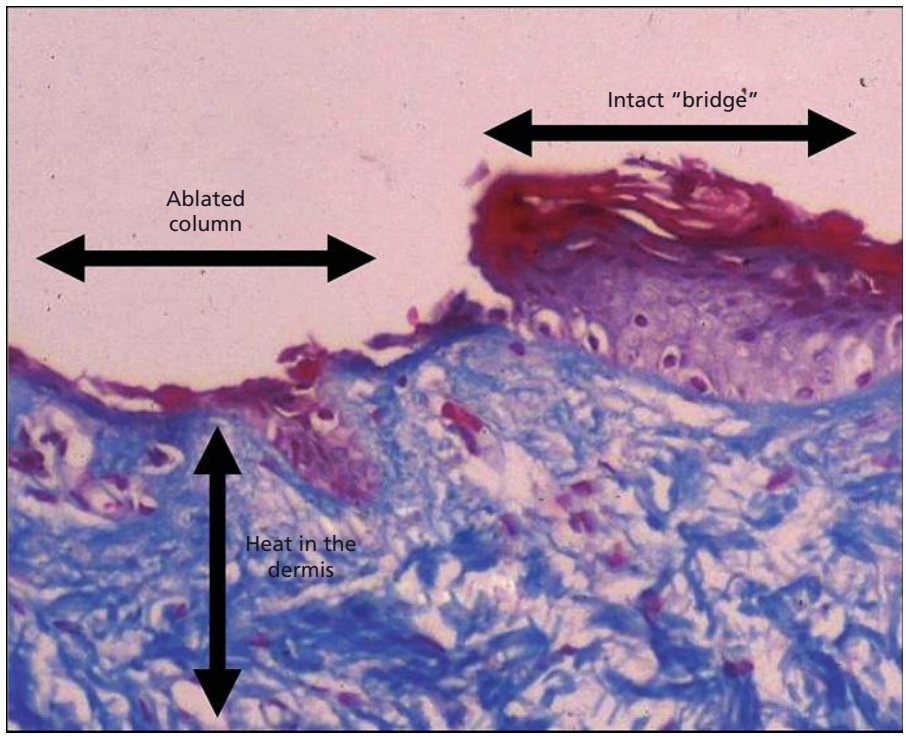


Figure 49.3 Histology of Active FX laser impulse at 100 mJ.

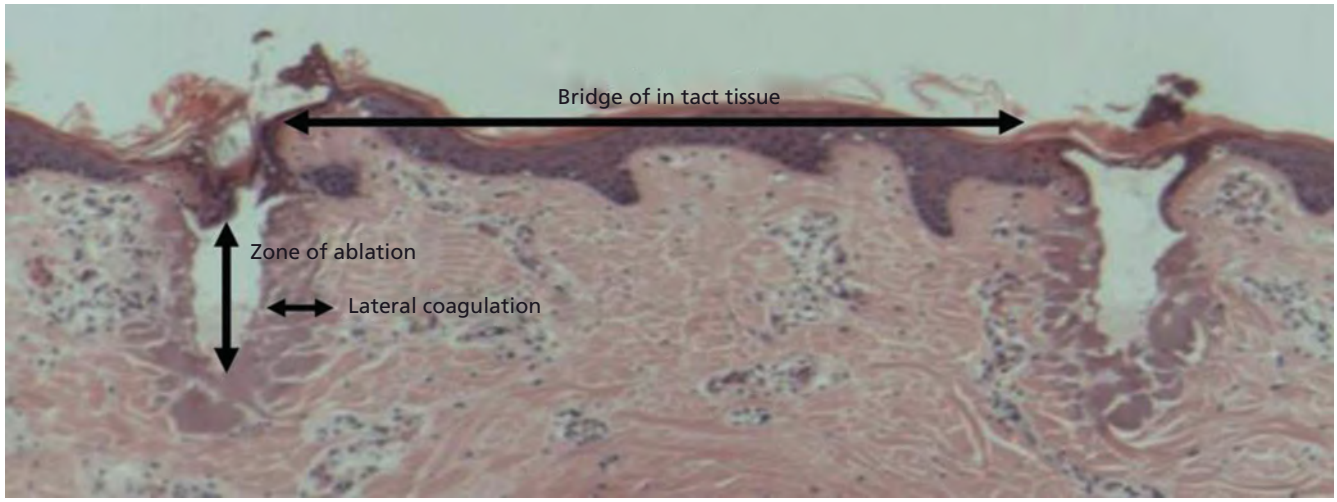


Figure 49.4 Histology of Deep FX laser impulse at 17.5 mJ. Zones of ablation are created, leaving bridges of intact tissue to aid in regeneration. Lateral and vertical coagulation stimulate a tissue regeneration response between the ablated columns.

Figure 49.5 Forty-year-old female treated with Active FX fractionated CO_2 laser with a 1.3 mm diameter spot size, density 2, 100 mJ: (a) before; (b) two months after treatment.

during the procedure followed by erythema. Erythema lasts for about 3 days for patients treated with –10% overlap and increases by approximately 1 day for each increased density setting. Edema persists for a little more than 1 day (Figure 49.5). The level of satisfaction at 1 month is relatively high, averaging 6 on a 1–10 scale.

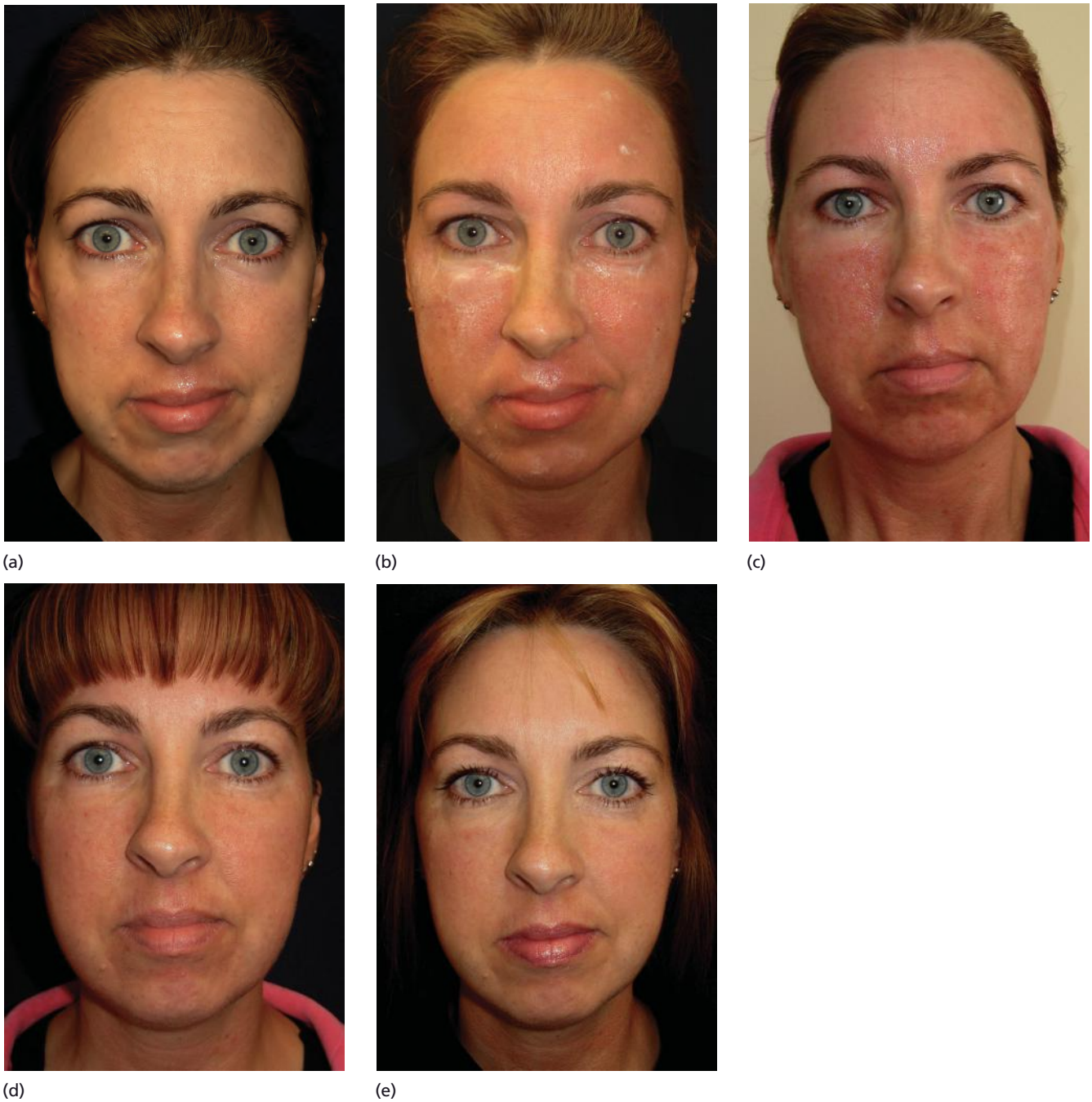
We find that it may take three separate treatments with the fractionated CO_2 laser to achieve the same results as non-fractionated CO_2 laser resurfacing (Figures 49.6 and 49.7). The advantage of the fractionated approach is that the procedure can be performed entirely under topical anesthesia supplemented with cold air cooling as opposed to standard CO_2 laser resurfacing which requires general anesthesia or the use of a large number of nerve blocks and/or tumescent anesthesia. In addition, postoperative healing is far easier with the fractionated approach. Patients do not require a Silon TSR dressing (Bio Med Sciences, Inc., Bethlehem, PA, USA) and do not have to be as diligent with vinegar water soaks. There is minimal serous exudate or crusting. Finally, patients are able to wear make-up 3–4 days post-procedure and are usually completely healed and look good without make-up within 5–7 days (Figure 49.8).

Weiss has conducted a split-face study to evaluate the efficacy of the Active FX Fractionated Laser compared to the 1550 nm Fraxel Er:YAG laser (Reliant Technologies, Mountain View, CA, USA). The Active FX was used at 80 mJ for a depth of 300 µm and the 1550 Fraxel was used at a final depth of 800 µm per microthermal zone (MTZ) with a density of 1000 MTZ/cm^2. The entire face is pretreated with topical anesthesia for 30 minutes and cold air cooling was used during treatment. Pain was higher with the 1550 nm side. Erythema lasted 1–2 days on the 1550 nm side and 4–6 days on the CO_2 side. The CO_2 side had an average of 75% improvement while the 1550 nm side had an average improvement of 25%.

We and others have not seen post-inflammatory hyperpigmentation (PIH) with the Active FX even in Asian patients and patients with type 4 and 5 skin. PIH has been reported with the fractionated 1550 nm lasers.

Fraxel Re:Pair – Reliant

The second-generation fractionated resurfacing laser from Reliant used a CO_2 laser instead of the 1550 nm Er:YAG laser. The spot size is 120 µm with a large treatment area of



(a) (b) (c)

(d) (e)

Figure 49.6 Forty-year-old female (same as in Figure 49.5) treated with Deep FX at 17.5 mJ density 1, 1 pass 3 months after Active FX treatment as above. (a) Immediately before; (b) immediately after treatment; (c) 1 day after treatment; (d) 2 days after treatment; (e) 2 months after treatment.

Figure 49.7 Fifty-one-year-old women treated with Deep FX at 15 mJ, density 1, 1 pass in the periorbital and perioral area followed by Active FX to the entire face at 100 mJ, density 2, 1 pass. Before and 2 months after treatment.

Figure 49.8 Forty-year-old patient (same as in Figure 49.5 with same laser parameters) treated with fractionated CO_2 laser: on day 3 before and after make-up application.

15 × 15 mm. Depth of laser effects has been reported to be 1.6 mm. At the time of this writing, there are no published papers on this system.

Mixto SX – Slim Evolution – Lasering

This low-powered fractionated CO_2 laser is usually used at a power between 8 and 15 W. This low-energy system has the advantage of causing only 1 day of erythema and fine, pinpoint crusting lasting for up to a week. No topical anesthesia or concurrent cold air cooling is recommended, and pain is minimal and "easily tolerated" with one pass (Figure 49.9).

A split-face study comparing the Mixto SX with a microfractional Er:YAG laser (Dermablade MCL 30, Aeslepion, Jena, Germany), with both systems using an energy density of 15 J/cm^2 without any anesthesia, showed a slightly higher improvement (15%) with the CO_2 as opposed to the Er:YAG systems without any difference in satisfaction scores. Microcrusting lasted 1 day less with the Er:YAG system.

This laser can also be used in a continuous mode at 30 W for cutting. In fractional mode, the scanner is delivered

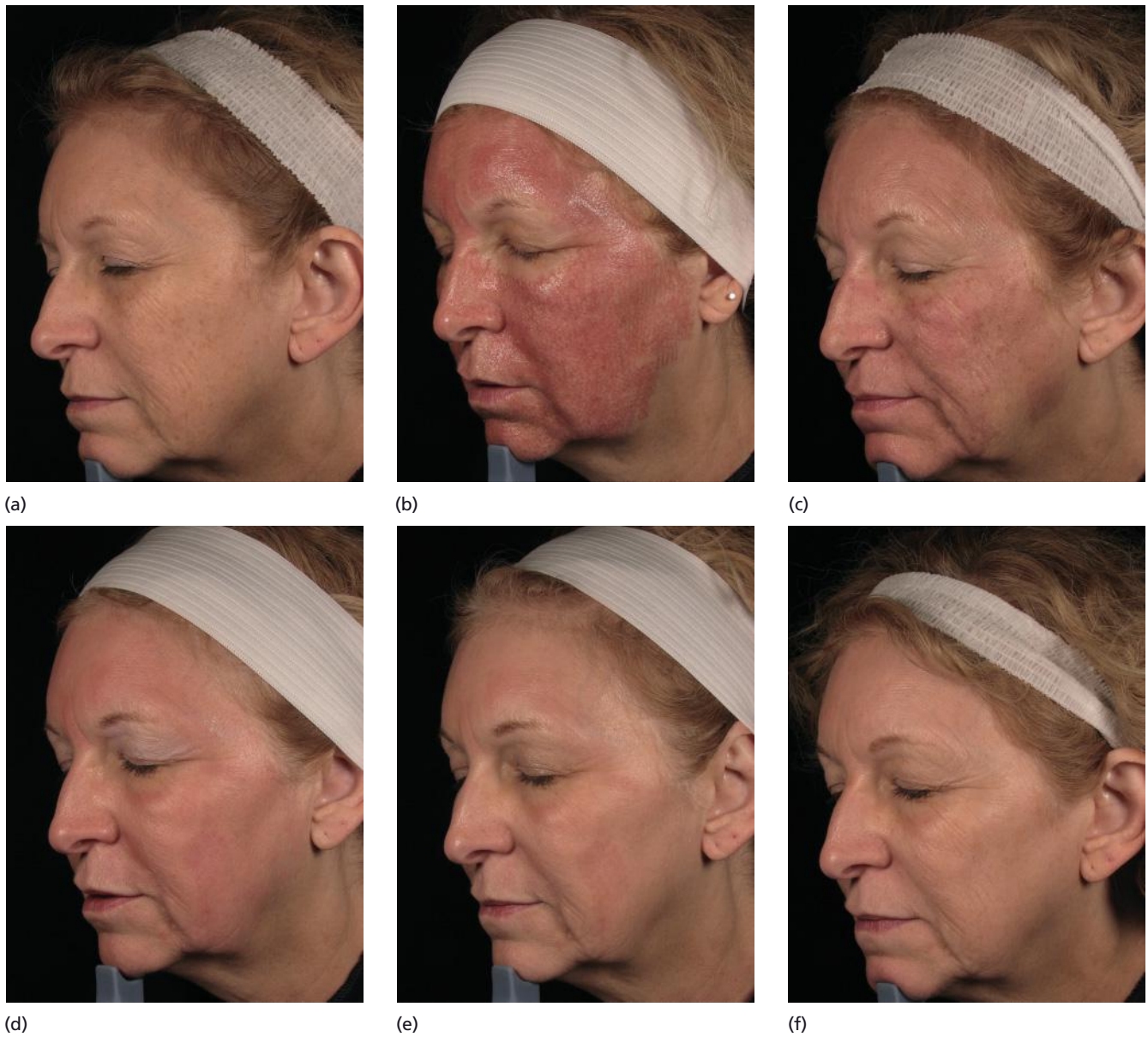


Figure 49.9 Patient treated with the SLIM E30 Mixto SX fractionated CO_2 laser. (a) Before treatment; (b) 1 day after treatment; (c) 3 days; (d) 7 days; (e) 2 weeks; (f) 8 weeks. (Courtesy of Dr. Jeffery Hsu.)

alternatively into four quadrants to produce thermal relaxation between impact spots.

Pixel CO_2 – Alma Lasers

The Pixel CO_2 fractionated laser (Alma Lasers Ltd., Caesarea, Israel) is a 30-W laser that fractionates the continuous duration CO_2 laser beam through a patented Pixel® microoptics lens array that divides the energy to 49 250 µm spots with a spacing of 1600 µm. The micro-injury sites are about 15–20% of the treatment area. Thermal effect goes approximately 300 µm deep at maximal energy. A burning sensation on the skin is said to last 1–3 hours. Re-epithelialization requires 8–10 days and patients may remain erythematous for 6 weeks to 3 months.

The Pixel® CO_2 OMNIFIT hand-piece is a separate device that can fit on to nearly any existing CO_2 laser designed for skin ablation or resurfacing. It converts any pulsed or continuous wave CO_2 laser into a fractionated skin resurfacing laser.

MedArt FrX – MedArt, Denmark

This 20-W CO_2 laser equipped with a scanner performs fractionated resurfacing with 36, 64, or 100 µm microthermal zones/cm^2. One study on the perioral area treated three

times using a 0.5 mm spot size and 12 W with a single pass produced histologic evidence of increased collagen without any noticeable improvement in wrinkles in 9 of 11 patients. Crusting lasted up to 15 days with erythema lasting 1–3 days.

SmartXide DOT – Deka, Italy, Novel Micro Ablative Affirm CO_2 Cynosure

The SmartXide DOT/Affirm CO_2 is the same fractionated laser sold by two subsidiaries of the company EIEn. While power up to 30 W accounts for depth of ablation of approximately 300–350 µm, dwell time (0.2–2.0 ms in microablative mode; 0.2–20.0 ms in standard mode) controls the width of the thermal pulse that is delivered directly after the microablation occurs.

A third setting space between laser impacts can be adjusted from 0.0 to 2.0 mm in order to change the laser from fractionated to fully ablative. The scan mode defines how each of the spots are laid out on the scanned surface. The "normal" option will sequentially place each spots. The "interlaced and autofill" options are especially programmed to minimize tissue overheating. In the interlaced mode, odd lines are scanned first followed by the even ones. In the autofill mode, the spots are randomly placed on the scanned area.

Like the Lumenis Active/Deep FX, the Affirm CO_2 user has the flexibility of selecting one of the six possible shape options (rectangle, triangle, hexagon, parallelogram, line, and point) to fit to the patient's anatomy. In addition, each shape can be modified in size (maximum scan area: 15 × 15 mm) and ratio (width/height).

Finally, the Affirm CO_2 operates without any consumables and comes with the option of a hand-piece that can be used for excision and ablation. As of this writing there are no published or unpublished investigations on this product but excellent results have been presented (Figure 49.10).

Mosaic Lutronic – eCO_2™ New Jersey – imported from Korea

The Lutronic eCO_2 is a multifunctional microfractional CO_2 laser with the ability to target the superficial epidermis or remodel collagen deep within the reticular dermis. The eCO_2 allows the user to select between several scan shapes and sizes, a sequential beam pattern or a non-linear randomized microbeam delivery pattern (known as Lutronic's Controlled Chaos Technology™ – a spray paint-like approach). The Controlled Chaos Technology minimizes thermal damage by spacing each beam further apart to reduce the collateral thermal effect of the laser beams and creates a more natural post-treatment look by non-sequentially placing the beams. There are dual operation modes, the Static Mode (a pulsed operating mode) and the Dynamic Mode (a continuous operating mode) used to "feather" the treatment to reduce the "checkerboard" appearance that is common with currently available fractional CO_2 devices (Figure 49.11). A Multiple Repetition Mode (also on the Lumenis Deep FX) enables even deeper penetration (successive shots of two to five) to create subdermal damage without the superficial

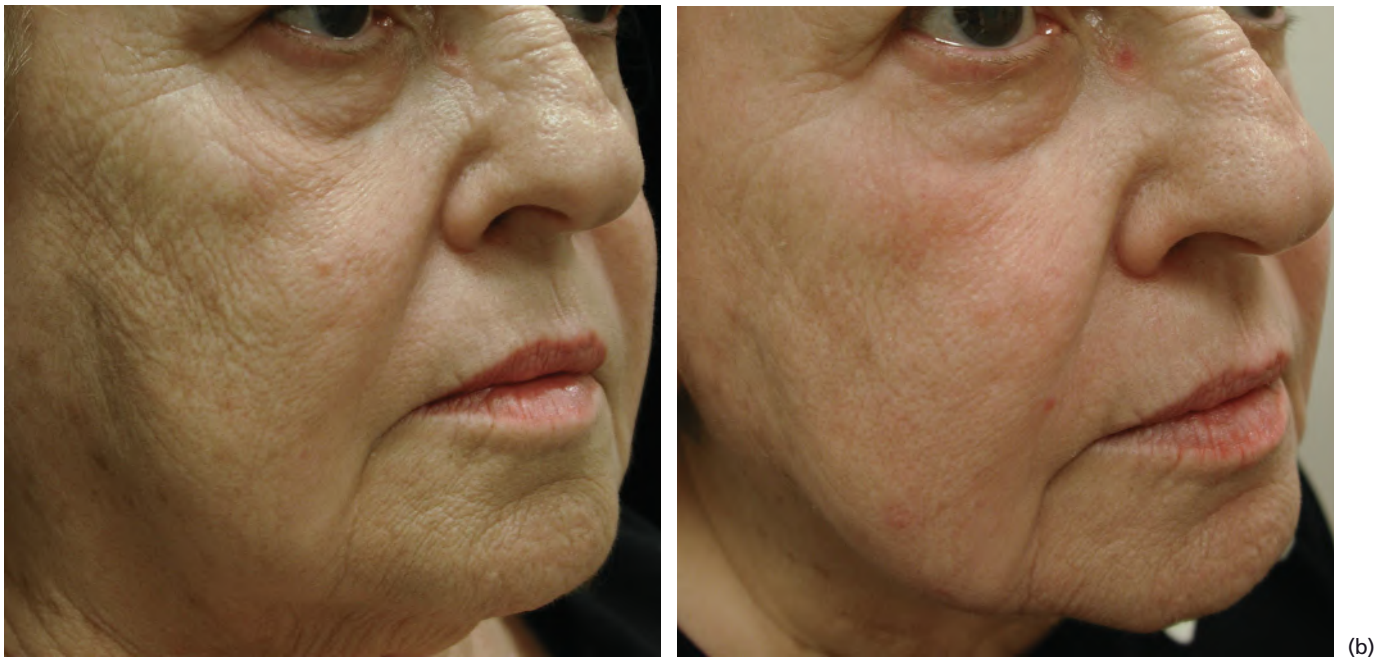


Figure 49.10 Patient treated with the Affirm CO_2 laser. (a) Before treatment; (b) 6 weeks after treatment. (Courtesy of Dr. Bruce Katz.)

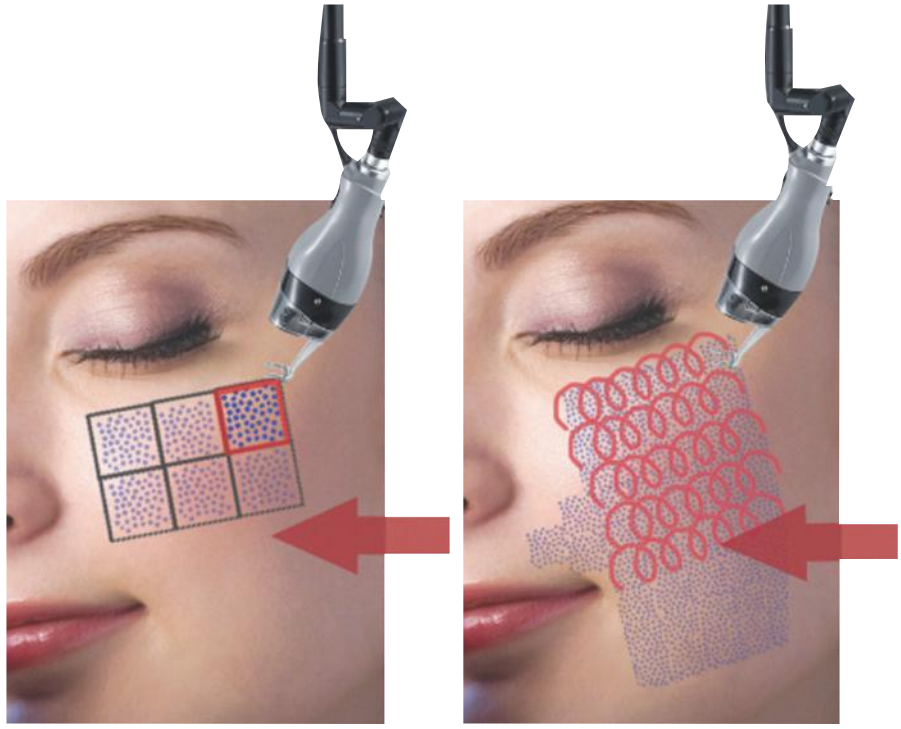


Figure 49.11 The Controlled Chaos Technology minimizes thermal damage by spacing each beam further apart to reduce the collateral thermal effect of the laser beams.

damage for greater skin tightening ability. The eCO_2 laser has a variable microbeam delivery speed, skin sensing treatment tips (safety feature that prevents laser firing without skin contact), and user-friendly treatment interfaces that enable real-time tracking of microbeam delivery (automatic total density counter) in dynamic mode.

There are three interchangeable treatment tips (120, 300, and 1000 µm), which include a pinpoint beam tip for traditional ablative skin resurfacing. The 120 µm beam size has a deep penetration depth (up to 2.4 mm) (Figure 49.12). There are no consumable tips for the eCO_2 laser. Patients are usually healed within 3–5 days post-treatment at 140 mJ of pulse energy (Figure 49.13).

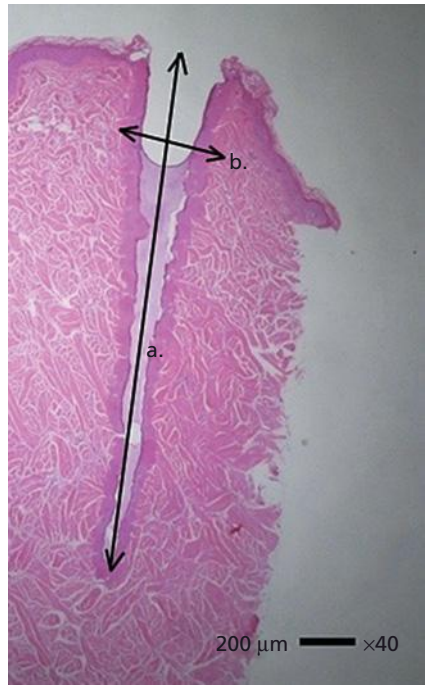


Figure 49.12 The 120 µm beam size has a deep penetration depth (up to 2.4 mm).

Sciton ProFractional and ProFractional-XC – Sciton

Sciton's ProFractional 2940 nm wavelength allows the user to optimize treatment depth, area coverage, and the ratio of ablation and thermal zone. The ProFractional module can selectively treat – in a single pass – from 1.5 to 60% of the skin area and from 25 to 1500 µm in depth. ProFractional-XC provides the same treatment depths and two fixed densities – 5.5 and 11% – and offers two additional features: superfast treatment speed and user-controlled thermal coagulation for increased collagen production. Thermal coagulation is achieved by using a long, low-power pulse that heats but does not vaporize tissue, immediately following a short, high-energy pulse for tissue ablation. ProFractional-XC allows the user to select and control the degree of the thermal damage independent of the ablation depth. With this tunable flexibility the user can adjust settings for different skin types and patient expectations and can emulate the thermal profile of CO_2 or other lasers (Figures 49.14–49.16).

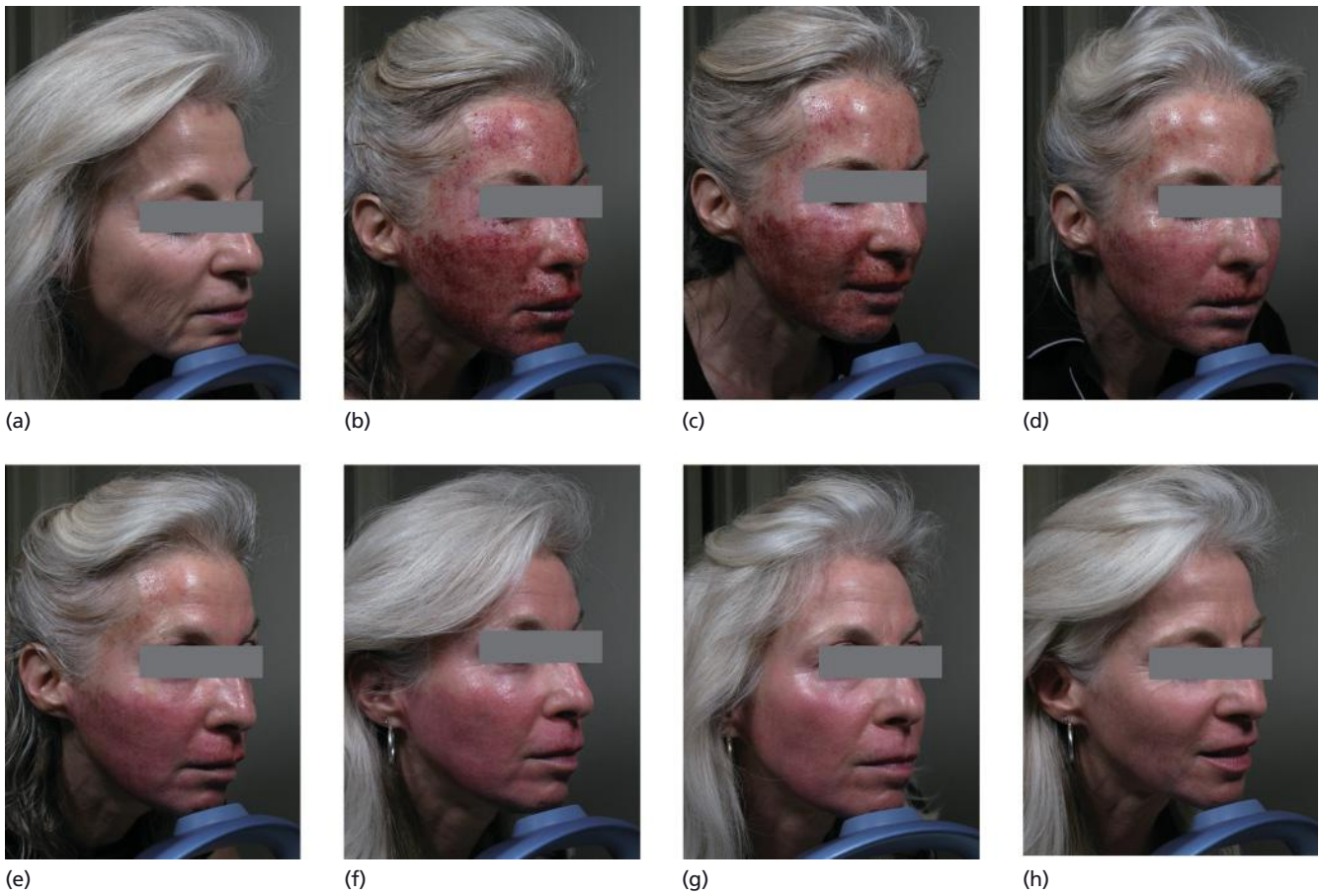


Figure 49.13 (a) Before treatment; (b) 1 day after treatment; (c) 2 days; (d) 3 days; (e) 4 days; (f) 5 days; (g) 1 week; (h) 4 weeks.

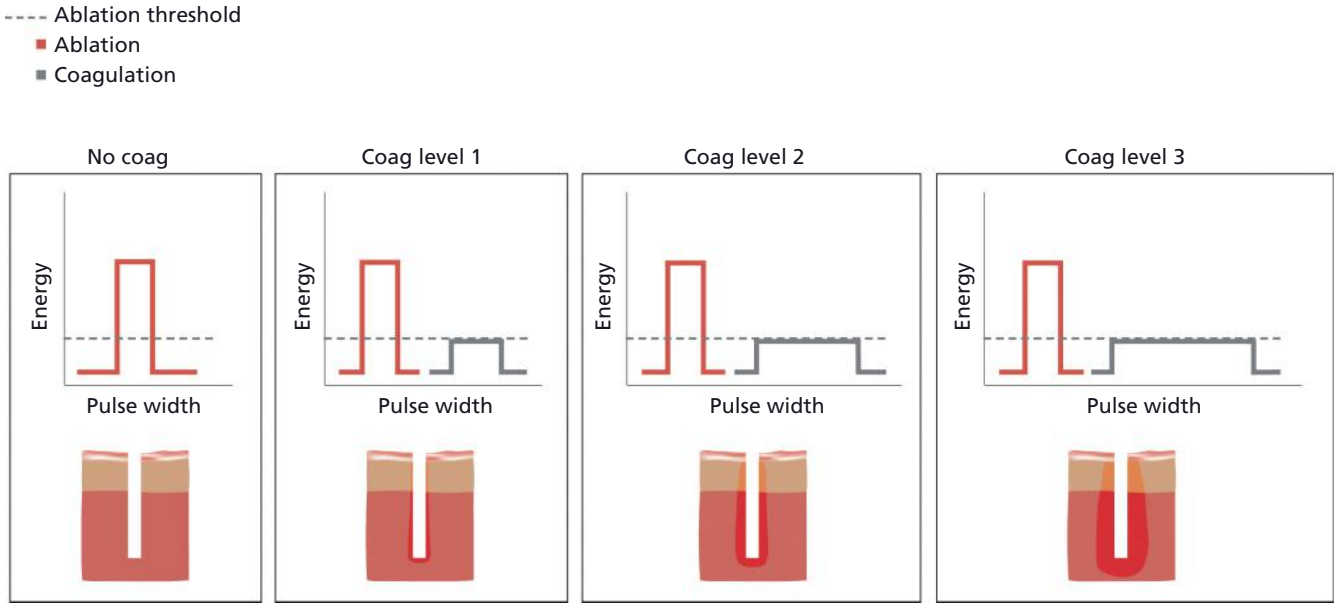
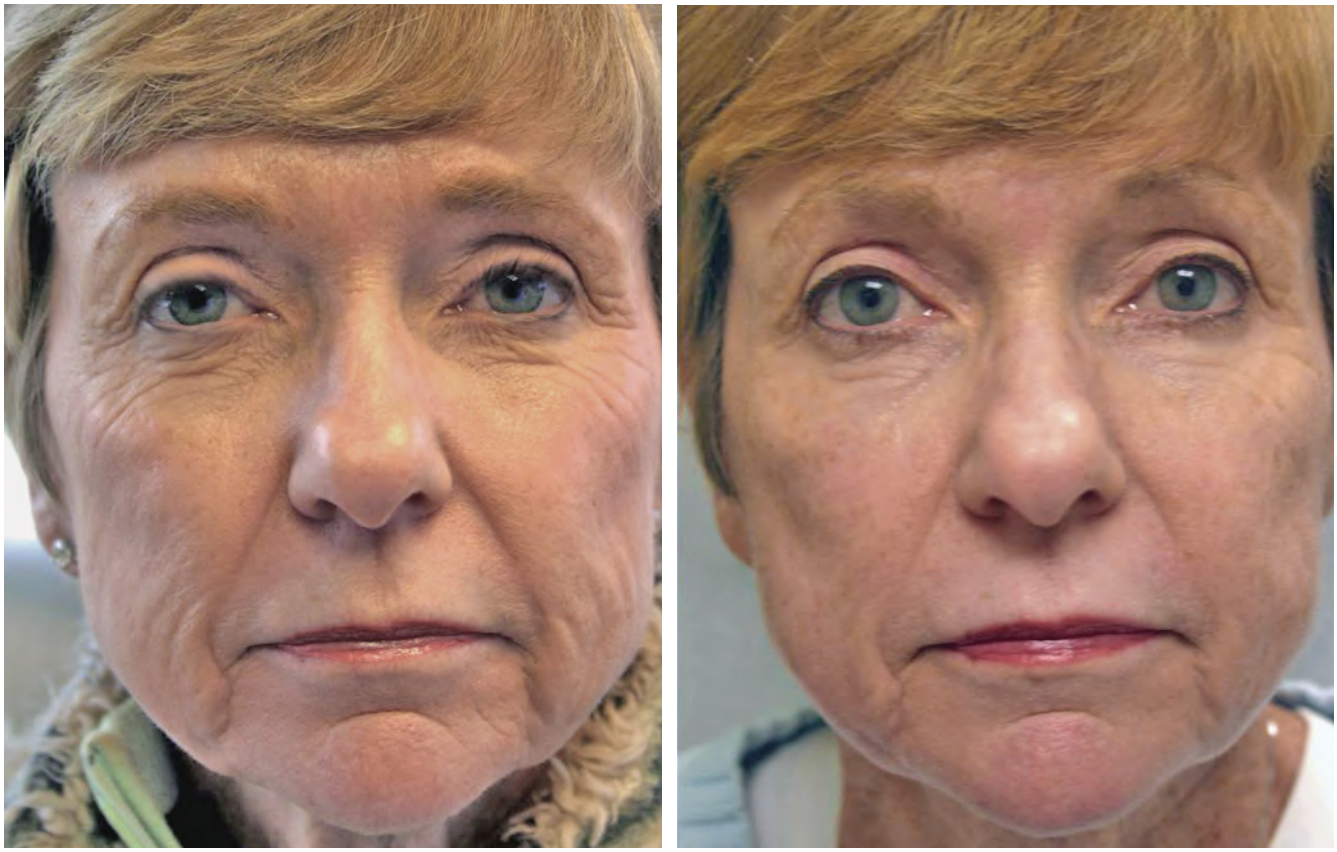
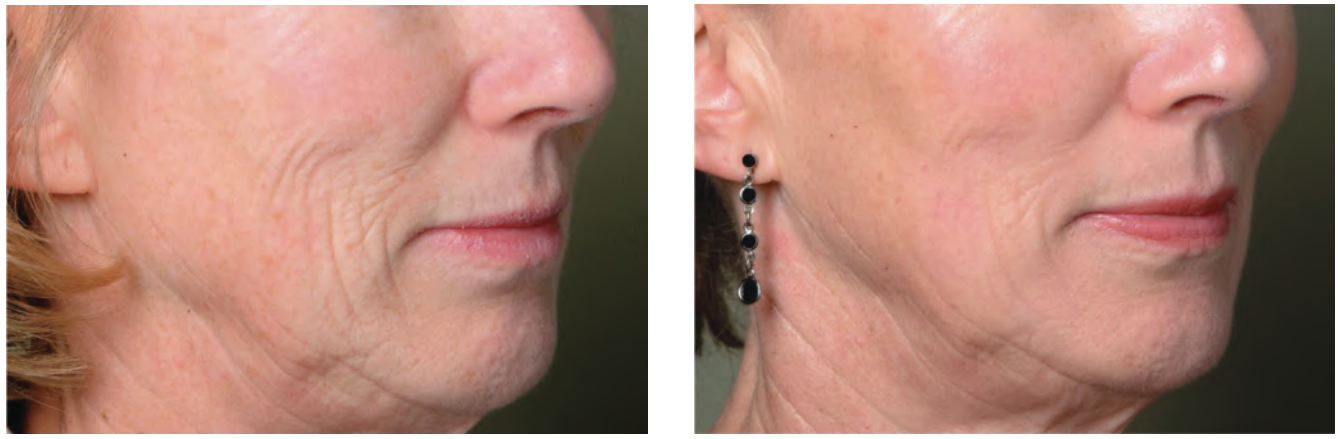


Figure 49.14 Diagramatic representation of non-specific thermal damage by controlling the pulse width of the Sciton Er:YAG laser. (Courtesy of Sciton, Inc.)



(a) (b)

Figure 49.15 Patient treated with the Sciton Profractional at 150 µm, 1.9%. (a) Before; (b) 4 weeks after treatment. (Courtesy of Dr. Michael Gold.)



(a) (b)

Figure 49.16 Patient treated with the Sciton Profractional-XC at 100 µm, 11%, 2 passes. (a) Before treatment; (b) 4 weeks after three treatments. (Courtesy of Dr. Kent Remington.)

Pixel 2940 – Alma

This fractionated Er:YAG laser delivers the laser beam via a hand-piece that splits the beam into various microbeams 150 µm in diameter using the same technology as the Pixel CO_2 laser. The 7×7 matrix with 49 microbeams with 150 µm in diameter yields energy density of up to 51 mJ/pulse per pixel in an area of $11 \times 11\,mm^2$. The 9×9 matrix produces 81 microbeams 150 µm in diameter, with 31 mJ/pulse per pixel which covers $11 \times 11\,mm^2$. The laser operates at energy of up to 2500 mJ/pulse and multiple passes are required to produce epidermal ablation and dermal effects. The degree of thermal effects is determined by the number of stacks

(stationary technique) or passes (non-stationary technique). No Zimmer or other cooling means is required during the procedure. An unpublished study found that erythema lasts 2–10 days (mean 3.6 days). An evaluation of 28 patients treated 1–4 times demonstrated excellent (21) and good (7) results.

Lux 2940 – Palomar

This fractionated Er:YAG laser splits the laser beam into micobeams 300 µm in diameter through a microlens array hand-piece. Biopsy demonstrates ablated columns extending 600 µm below the epidermis with an approximate 20 µm coagulation area. Re-epithelialization occurs by 12 hours with a mild inflammatory response persisting for 1 month (Figure 49.17).

Paxel – Wavelight, Germany

This fractionated, heated, punch ablation Er:YAG laser has recently been introduced. A 300 × 1000 µm grid is treated with 64–128 mJ/mm^2. Skin texture has been noted to occur with an increase in hyaluronic acid production in a limited unpublished study.

Fractionated Pearl – Cutera

This is the newest fractionated Er:YAG laser at the time of this writing. There is very limited experience with this

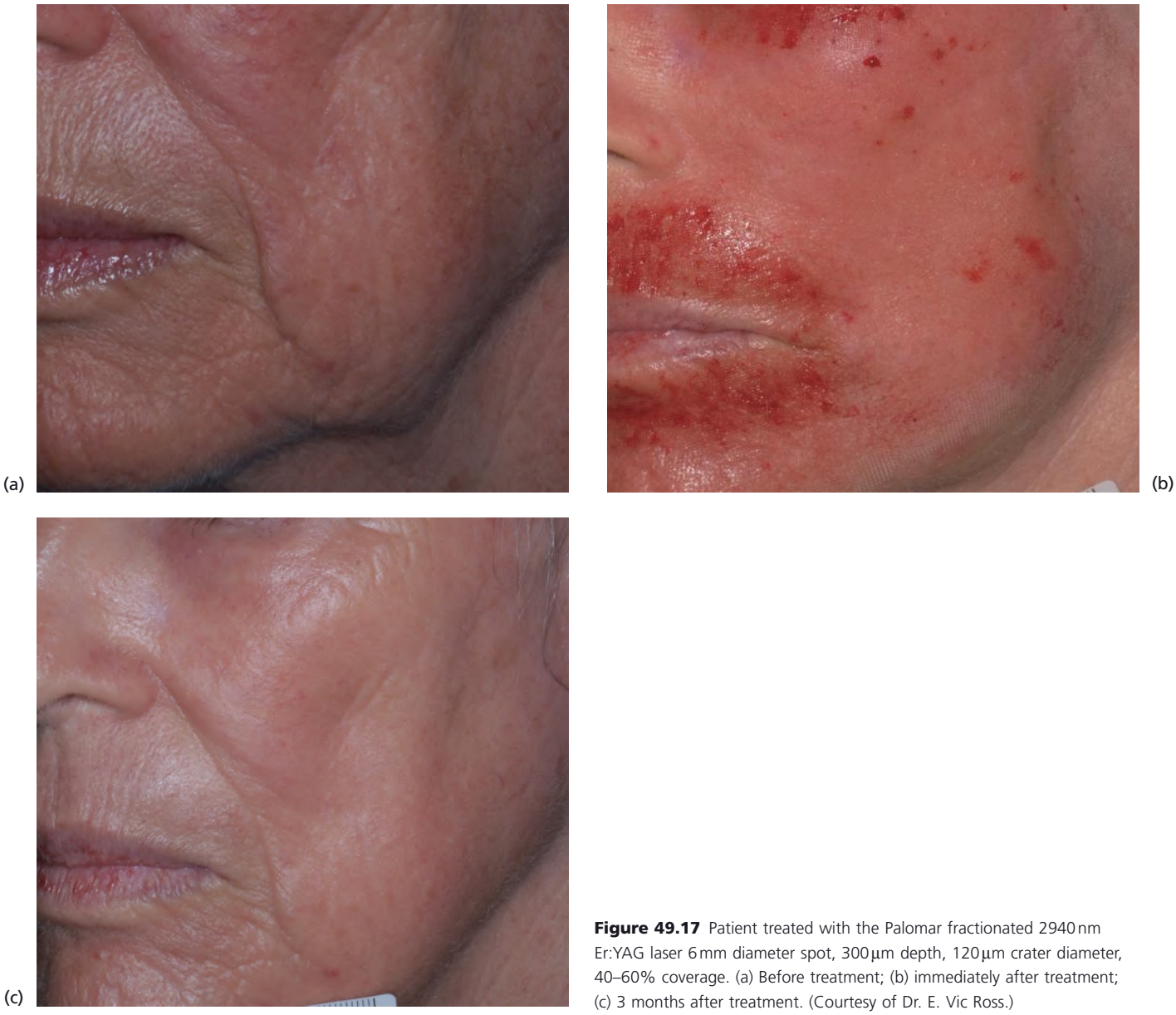


Figure 49.17 Patient treated with the Palomar fractionated 2940 nm Er:YAG laser 6 mm diameter spot, 300 µm depth, 120 µm crater diameter, 40–60% coverage. (a) Before treatment; (b) immediately after treatment; (c) 3 months after treatment. (Courtesy of Dr. E. Vic Ross.)

device. Ross notes that 300 μm holes can ablate 200–1000 μm depending on the energy fluence used.

Technique and procedures for fractionated laser treatment (Active/Deep FX)

Preoperative

Our experience with full-face ablative laser resurfacing has proven that preoperative treatment with topical retinoids, glycolic or depigmenting agents such as hydroquinones are not required to enhance treatment efficacy. At best, by pretreating the skin, both patient and physician can determine what products are easily tolerated and/or irritating to the skin. This may be beneficial if and when the physician prescribes the medical creams post-laser to treat hyperpigmentation or an acniform eruption. It does make sense to ensure that patients have adequate nutrition and vitamin stores to enhance healing and promote new collagen formation. I regularly recommend oral antioxidants and a multivitamin. No controlled clinical studies have yet to be performed to demonstrate the efficacy of this recommendation.

We have found that treating areas of hyperactive muscle movement, such as the lateral canthus, with a botulinium toxin neuromodulator 1 week before laser treatment will allow for uniform lamellar collagen deposition to occur. We do not recommend performing these injections at the same time as laser treatment because the resulting inflammation and edema from the laser may inactivate and/or promote migration of the neuromodulator from the intended site of injection.

Before treatment, patients wash their faces with a neutral cleanser. A topical anesthetic cream (2.5% lidocaine and 2.5% prilocaine (Pligalis, Galderma, Dallas TX, USA) is applied to the face for 30 minutes and wiped off just before treatment. We use the UltraPulse Encore™ Fractional CO_2 Laser System (Active/Deep FX, Lumenis Inc., Santa Clara, CA, USA), which emits a wavelength of 10 600 nm, with spot sizes of 1.25 and 0.12 mm in diameter. We always treat the face with a 5 °C cold air cooler (Zimmer) set at maximum flow. We initially use the Deep FX hand-piece with its 120 μm spot size at 15–25 mJ to treat areas of skin laxity and/or wrinkles and scars at a density of 1–2 with one to two passes. The entire face is then treated with one pass of the Active FX hand-piece with its 1.25 mm spot size at a fluence of 125 mJ, frequency of 100 Hz, pattern of 3 (square), size 7 mm, and density of 2. We always used the Cool Scan setting, which produces a randomized spot pattern allowing for extra cooling to occur between laser impacts and a repeat delay of 0.3 Hz. The mean duration for the entire procedure is 10–15 minutes.

Postoperative

Patients apply cold, wet compresses immediately post-treatment. They use Aquaphor healing ointment for 3 days until epithelial healing is complete and then a bland moisturizer such as Cetaphil cream (Galderma, Fort Worth, TX, USA) or Pryatine-6 cream (Senetek, Napa, CA, USA) four times a day until erythema has resolved. Patients wear a broadspectrum, zinc oxide containing sunscreen during the day under a mineral based make-up. At 3–4 weeks, when epidermal regeneration is complete with formation of an intact epidermal barrier, patients then use a topical antioxidant growth factor cream (2.5% CRS SpaMD Vitaphenol cream, Avidas Pharmaceuticals, Doylestown, PA, USA) to further stimulate fibroblastic formation of new collagen and elastic fibers. Sun protection with UVA and UVB blockers is continued.

Patients are seen 1 day, 1 week, and 1 month after the procedure and then every 3 months. A botulinium toxin neuromodulator is recommended to relax hyperactive muscles and allow continued collagen deposition every 3–4 months. If patients do not achieve the degree of improvement they would like, repeat treatments are scheduled every 6 months. Histologic studies of non-fractionated CO_2 and Er:YAG laser resurfacing patients demonstrated continued collagen production and improvement lasting up to 2 years after treatment. It is not know how long fibroblastic stimulation occurs after fractionated laser resurfacing, but 6 months seems to be a reasonable estimate.

Identification and management of complications

We recently performed a retrospective evaluation of 373 consecutive patients treated with the Active/Deep FX in our office. We found 4.6% incidence of an irritant reaction to postoperative topical therapy, 2.5% with acne lesions secondary to postoperative ointment, 1% incidence of erythema lasting > 4 days, 1% incidence of herpes simplex in patients not prophylactically treated with an antiviral that cleared with antiviral treatment, and importantly no patient with either postoperative hyperpigmentation or hypopigmentation. A recent split-face study on Chinese patients confirms our adverse effects profile as well as the lack of post-laser pigmentary alterations. Of note is that unlike fully ablative, non-fractionated CO_2 laser resurfacing, we have yet to see any patients with hypopigmentation. This could either be that we do not yet have long enough follow-up on a large enough patient group, or that fractionating epidermal and dermal ablation has a protective effect on epidermal melanocytes.

Conclusions

In our clinic from 2004–2007, we performed on average 75 full-face CO_2: Er:YAG laser resurfacing/year, 75 one pass Er:YAG laser resurfacings/year, and 150 Active/Deep FX

fractionated CO_2 laser resurfacings/year. In 2008 those numbers have changed with only 25 full-face CO_2: Er:YAG laser resurfacings, 35 one pass Er:YAG laser resurfacings/year, and 225 Active/Deep FX fractionated CO_2 laser resurfacings. Our advice to patients is to choose the procedure based on how much time they can take off from work and/or social events vs. the number of treatments that they are willing to undergo to achieve the expected results.

Patients with severe acne scarring or those with extensive photodamage, actinic keratoses, and/or acne scarring do best with deeper, non-fractionated laser resurfacing and do not achieve satisfactory results with less invasive procedures. We have found that severe acne scarring may require 2–3 treatments every 6 months to achieve optimal results. Full face CO_2: Er:YAG laser resurfacing usually gives excellent results for up to 10 years before patients request additional cosmetic procedures. Full-face Er:YAG laser resurfacing procedures have a more rapid healing and are best reserved for patients who need limited skin tightening but have extensive superficial photodamage. Full-face Er:YAG resurfacing can also be combined with spot Deep FX fractionated laser resurfacing over wrinkled areas or in areas that require skin tightening. Optimal results last approximately 5 years. Fractionated CO_2 laser resurfacings are usually given twice within a year to achieve optimal results. At this time our limited experience over 3 years of use does not allow an accurate prediction for the longevity of this procedure, but 5 years seems like a reasonable estimate.

Future advances in fractionated CO_2 laser resurfacings will incorporate a variety of spot size and energy densities in one hand-piece to allow for more rapid treatment with variation of laser depths as well as differing widths and depths of both flash vaporization and non-specific thermal damage. Incorporation of different laser wavelengths including but not limited to 2940 nm Er:YAG, 1064, 1320, 1440, and 1550 nm separately or together may also increase efficacy.

Further reading

Cassuto DA, Sadick NS, Scrimali L, Sirago P. (2008) An innovative device for fractional CO_2 laser resurfacing: a preliminary clinical study. *Am J Cosmet Surg* **25**, 97–101.

Christiansen K, Bjerring P. (2008) Low density, non-ablative fractional CO_2 laser rejuvenation. *Lasers Surg Med* **40**, 454–60.

Fitzpatrick RE, Goldman MP, Satur NM, Type WD. (1996) Pulsed carbon dioxide laser resurfacing of photoaged skin. *Arch Dermatol* **132**, 395–402.

Goldman MP. (2006) Carbon dioxide and erbium:YAG laser ablation. *Cutaneous and Cosmetic Laser Surgery*. Mosby-Elsevier, p. 162.

Goldman MP. (2006) Laser–tissue interactions. *Cutaneous and Cosmetic Laser Surgery*. Mosby-Elsevier. p. 5.

Goldman MP, Manuskiatti W, Fitzpatrick RE. (2000) Combined laser resurfacing with the ultrapulse carbon dioxide and Er:Yag lasers. In: Fitzpatrick RE, Goldman MP, eds. *Cosmetic Laser Surgery*. St. Louis: Mosby.

Goldman MP, Marchell N, Fitzpatrick RE, Tse Y. (2000) Laser resurfacing of the face with the combined CO_2/Er:YAG laser. *Dermatol Surg* **26**, 102–4.

Greene D, Egbert BM, Utley DS, Koch RJ. (1999) The validity of *ex vivo* laser skin treatment for histological analysis. *Arch Facial Plast Surg* **1**, 159–64.

Hantash BM, Bedi VP, Chan KF, Zachery CB. (2007) *Ex vivo* histological characterization of a novel ablative fractional resurfacing device. *Lasers Surg Med* **39**, 87–95.

Hobbs ER, Bailin PC, Wheeland RG, Ratz JL. (1987) Superpulsed lasers: minimizing thermal damage with short duration, high irradiance pulses. *J Dermatol Surg Oncol* **13**, 9.

Lapidoth M, Odo MEY, Odo LM. (2008) Novel use of erbium (2,940-nm) laser for fractional ablative photothermolysis in the treatment of photodamaged facial skin: a pilot study. *Dermatol Surg* **34**, 1048–53.

Lowe NJ, Lask G, Griffin ME. (1995) Skin resurfacing with the UltraPulse carbon dioxide laser: observations in 100 patients. *Dermatol Surg* **21**, 1025–9.

Manstein, D, Herron GS, Sink, RK, Tanner, H, Anderson RR. (2000) Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med* **320**, 2026–38.

Trelles MA, Velez M, Mordon S. (2008) Correlation of histological findings of single session Er:YAG skin fractional resurfacing with various passes and energies and the possible clinical implications. *Lasers Surg Med* (in press).

Chapter 50: Non-ablative resurfacing

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BASIC CONCEPTS

- Non-ablative resurfacing produces an injury requiring less recovery time than ablative resurfacing.
- Non-ablative lasers have been used to successfully treat rhytides, dyspigmentation, vascular changes, skin texture, laxity, and scarring.
- Non-ablative rejuvenation systems are composed of lasers, light sources, and radiofrequency devices.
- Each non-ablative system targets a different chromophore in the skin to produce different clinical results.

Introduction

In recent years there has been a progressive movement towards non-surgical interventions for facial rejuvenation. Ablative resurfacing with CO_2 and erbium:yttrium aluminum garnet (Er:YAG) lasers were first used to treat photodamaged skin in the 1980s and remain the gold standard today [1–5]. Yet, despite their effectiveness in treating photoaging, there has been a recent push for non-ablative treatment modalities with less down-time and fewer side effects.

Non-ablative lasers have been used to successfully treat rhytides, dyspigmentation, vascular changes, skin texture, laxity, and scarring [1,5,6]. The main goal of these systems is to selectively induce dermal damage, resulting in collagen remodeling and production while sparing the epidermis [1,3,6–8]. Many different systems have been used with this endpoint in mind (Table 50.1), and these are discussed in detail below.

Pathophysiology

Non-ablative rejuvenation systems are composed of lasers, light sources, and radiofrequency devices. Laser systems use energy in the infrared or near-infrared spectrum to target specific dermal chromophores, such as water, melanin, and hemoglobin. In contrast, radiofrequency devices produce heat in the dermis and subcutaneous tissue as a result of resistance to current flow through the tissue. Although the mechanisms of action are different, the end result is the same. Both the light sources and radiofrequency devices effectively heat the dermis eliciting a wound healing response without disturbing the integrity of the epidermis [1,5,9–11].

One of the main effects of photodamage and aging is a reduction in dermal collagen, and this is the target of non-ablative rejuvenation. It has been proven that thermal-induced injury to the dermis causes local release of inflammatory cytokines leading to the proliferation of fibroblasts which results in collagen synthesis [7,12–15]. *In vivo* mouse studies have been performed to evaluate collagen composition after treatment with various lasers, and they have all demonstrated a significant change in collagen and extracellular matrix [7,13].

A study by Liu *et al*. [7] compared the dermal collagen composition after treatment with various laser systems. This study confirmed that collagen I production is predominantly increased after non-ablative treatment with the pulse dye laser (PDL), 1320 nm neodymium:yttrium aluminum garnet (Nd:YAG) laser, and the long pulsed 1064 nm Nd:YAG laser. However, collagen type III was more significantly increased in those treated with the Q-switched 1064 nm Nd:YAG laser. These results not only support the theory of neocollagenesis, but also provide specific data on collagen composition and differences in laser systems. This study suggests that because of the predominant increase in collagen type III after treatment with the Q-switched Nd:YAG laser, it may be more effective in increasing the elasticity of the skin and giving a more youthful appearance.

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

Table 50.1 Lasers for facial rejuvenation.

Laser type	System name
Pulsed KTP	Gemini (Laserscope) Aura (Laserscope) Versapulse (Coherent/Lumenis) Diolite (Iridex)
Pulsed dye 585 nm	Cbeam (Candela) SPTL-1B (Candela) Photogenica V (Cynosure)
595 nm	Cynosure V-star (Cynosure-585/595) V-beam (Candela)
Intense pulse light	Quantum SR (Lumenis) Palomar Starlux (Palomar) Vasculight (Lumenis) Estelux/Medilux (Palomar) Aurora DS/Aurora SR (Syneron)
1320 nm Nd:YAG	Cool Touch I, II, and III (Cooltouch)
1064 nm QS Nd:YAG	Medlite IV Continuum (Biomedical) VersaPulse VPC (Lumenis)
1450 nm diode	Smoothbeam (Candela)
Er:glass 1540 nm	Aramis-Quantel (Quantel Medical)
Infrared light (1100–1800 nm)	Titan (Cutera Inc.)
Radiofrequency devices	
Monopolar	Thermacool TC (Thermage)
Unipolar and bipolar	Accent (Alma Laser)

KTP, potassium titanyl phosphate.

Non-ablative modalities

Many non-ablative systems have been evaluated for efficacy in facial rejuvenation. Results have been variable and often require multiple treatments in order to appreciate clinical improvement. The most effective treatment regimens are still being determined for facial rejuvenation, and the corresponding studies for each laser are discussed below. The most common lasers and parameter settings used today are outlined in Table 50.2.

Potassium titanyl phosphate 532 nm laser

The 532 nm potassium titanyl phosphate (KTP) laser is one of the many modalities used in facial rejuvenation (Figure 50.1). It is absorbed more intensely by melanin and hemoglobin, and so it is thought that fewer treatments are needed when targeting these components of photodamaged skin [2]. This laser has been shown to effectively target vascular and pigmentary change, skin texture, tightening, acne scars, and rhytides [5,15].

Lee [15] performed a 150 person study to compare the efficacy of the KTP laser alone, the long pulsed Nd:YAG alone, or the two modalities combined on collagen enhancement and photorejuvenation. After 3–6 treatments, all three groups showed statistically significant improvement in rhytides, skin toning and texture, reduction in redness, and improvement in dyschromia. Overall, the KTP laser-treated patients showed more improvement than the long pulsed Nd:YAG laser, but the combined treatment group was superior to either group alone. The combined group had a 70–80% improvement in redness and pigmentation, 40–60% improvement in skin texture, tone, and tightening, and a 30–40% improvement in rhytides. In addition to these findings, it was also noted that collagen remodeling continues for up to 6–12 months post-treatment, with slow regression in benefit thereafter. Although further studies are necessary, these results suggest that combined modalities may be superior at targeting various factors involved in photodamage and more effectively stimulate collagen production.

Pulse dye laser 585 or 595 nm

The PDL is a yellow light that targets oxyhemoglobin and melanin (Figure 50.2). It has been used to treat vascular changes and induce new collagen formation. It has been hypothesized that wavelengths targeting hemoglobin disrupt vascular endothelial cells resulting in cytokine release and subsequent collagen remodeling and production [5,16,17].

A group of 10 female patients, Fitzpatrick types I–IV, were treated in the periorbital area with the 595 nm flash lamp PDL [17]. One side of the face was treated with the following laser settings: 1.5 ms pulse, fluences of 5–6 J/cm^2, and a spot size of 7 mm. The contralateral side was treated with a 40 ms pulse duration, fluences of 8–11 J/cm^2, and a 7 mm spot size. Cryogen cooling was administered for 30 ms with a delay of 30 ms before treatment. Subjects were treated 1–2 times, and at their 6-month follow-up 70% treated had mild to moderate improvement overall. Sixty percent had equal improvement on both sides despite the different settings. Histologic and electron microscopic evaluation showed a significant increase in papillary dermal collagen, mainly type I.

Another study performed by Bernstein [16] evaluated the effects of treatment of sun-damaged skin with a 595 nm long pulse duration PDL. Ten subjects were treated with 10 ms pulse duration, fluences of 8–10 J/cm^2, and a 10 mm spot size. Improvements were evaluated 8 weeks after treatment with photograph comparison. Blinded physician evaluation of before and after treatment photographs rated improvement in wrinkles in 50%, facial veins improved in 82%,

Table 50.2 Non-ablative lasers.

Laser type	Wavelength (nm)	Fluences (J/cm^2)	Pulse duration	Spot sizes (mm)	Target
KTP (pulsed)	532	7–15	20–50 ms	2, 4, 10	Hemoglobin, melanin
PDL	585 595	3–6.5 6–12	350, 450 µs 6–10 ms	5, 7, 10 7, 10	Hemoglobin, melanin
IPL	550–1200	25–28	2.4, 4.0 ms		Hemoglobin, melanin, water (weak)
Nd:YAG	1320	17–22	200 or 350 µs	6, 10	Water
Nd:YAG (QS)	1064	2.5–7	5 ns	6	Hemoglobin, melanin, water
Diode	1450	8-14	160-260 ms	4, 6	water
Er:glass	1540	Up to 126	3.3	4, 5	water
Infrared light	1100–1800	30–40	170–200 pulses		–
Radiofrequency					
RF, monopolar	RF bipolar current	61.5–63.5 (adjusted for pain)	300–400 pulses	0.25, 1.0, 1.5, 3 cm	–
RF, unipolar	RF electromagnetic radiation	50–250			–
RF, bipolar	RF bipolar current	40–100			

IPL, intense pulse light; KTP, potassium titanyl phosphate; RF, radiofrequency; QS, Q-switched; PDL, pulsed dye laser.

Figure 50.1 Potassium titanyl phosphate laser.

Figure 50.2 Pulsed dye laser.

overall redness improved 80%, pigmentary change 61.4%, and a 25% improvement in pore size.

A small clinical trial was performed on 10 patients comparing the efficacy of a long pulse PDL (LPDL) with an intense pulsed light (IPL) on photodamaged facial skin [18]. When compared with the IPL, the LPDL showed greater improvement in lentigines (81% versus 62%), no significant difference in wrinkle reduction between the two groups, and fewer treatments were needed with the LPDL when compared with the IPL (three versus six).

In addition to using the PDL laser as a single agent in photorejuvenation, recent trends have shown effective

combination with aminolevulinic acid (ALA) in treatment of photodamaged skin. It is believed that PDL at 595 nm activates protoporphyrin IX, a photosensitizer, which accumulates in photodamaged cells, causing destruction of the cells, release of cytokines, and collagen repair [1]. This is a new and exciting area of research that offers another effective treatment modality for photorejuvenation.

Intense pulsed light

The IPL system emits light, with wavelengths of 550–1200 nm, which effectively targets melanin, hemoglobin, and water, to a lesser degree (Figure 50.3). The IPL device has been used in photorejuvenation to target vascular changes, pigmentary alteration, and mild rhytides [1,2,5,18,19]. Filters may be used with the IPL to target specific chromophores. Rapid improvement in overall appearance after IPL treatment is secondary to rapid and effective improvement of vascular and pigmentary change, rather than improvement in wrinkles [5]. As per Weiss *et al*. [2], shorter pulse duration and lower cutoff filters when using the IPL system result in significant improvement in pigmentary alteration.

Although not thought to be the most effective treatment modality for rhytides, some studies using the IPL have shown improvement [1,3,4,18,19]. Goldberg [3] and Goldberg and Cutler [19] evaluated the treatment of facial rhytides with an IPL system using a 645 nm cutoff filter. Thirty patients, skin types I–III, were treated 1–4 times over a 10-week period. Treatments were delivered using fluences of 40–50 J/cm^2, through bracketed cooling device with triple 7 ms pulses, and interpulse delay of 50 ms. At 6 months' follow-up, approximately 53% showed some improvement, 30% showed substantial improvement, and 17% showed no improvement.

Hedelund *et al*. [4] performed a study looking at the efficacy of IPL treatment for perioral rhytides in comparison with CO_2 ablative resurfacing. Twenty seven females, skin type II, with perioral rhytides were randomly treated with 3-monthly IPL sessions or one CO_2 laser ablation. The results showed a higher degree of patient satisfaction and significant improvement in rhytides with CO_2 laser resurfacing when compared with IPL rejuvenation. In addition to the more dramatic improvement seen with CO_2 resurfacing, side effects were also found to be significantly higher in this group. Patients treated with the CO_2 laser experienced milia, dyspigmentation, and persistent erythema, while the IPL group was not noted to have any side effects. Both groups showed long-term improvement in skin elasticity, although no significant improvement in wrinkles was seen in the IPL treatment group. Many physicians today advocate 3–6 treatments for significant improvement, which implies that the treatment course may not have been sufficient to produce notable results.

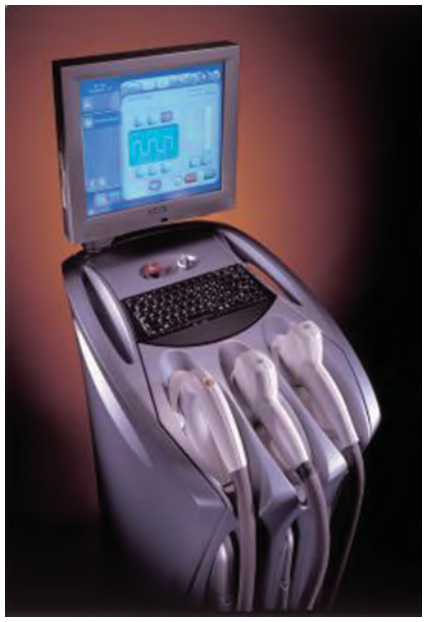

Figure 50.3 Intense pulsed light.

1320 nm Nd:YAG

One of the first laser systems to be developed for nonablative rejuvenation was the Nd:YAG 1320 nm laser (Figure 50.4) [20]. At this wavelength, energy is able to penetrate into the papillary and mid-reticular dermis, and it is absorbed by water associated with dermal collagen. There is a high water absorption and strong scattering in the dermis which allows for extensive dermal wounding [20]. The surface

Figure 50.4 1320 nm neodymium:yttrium aluminum garnet (Nd:YAG) laser.

cooling systems are present to protect the epidermis from involvement.

The 1320 nm Nd:YAG laser has been used to target acne scarring, photoaging, and rhytides with variable results [1–3,20,21]. As a result of its poor absorption by melanin, it can be used in all skin types without fear of pigmentary change [21]. When treating mild rhytides or acne scars, Weiss *et al*. [2] recommends using a fluence of 17–19 J/cm^2, a total of 25 ms of cooling (pre and post cooling at 10 ms and midcooling at 5 ms), with a fixed pulse duration of 50 ms, and 2–3 passes. When treating acne scars with this regimen, 30–50% improvement has been observed in about four of five patients, while 20% show no significant response.

According to a study performed by Rogachefsky *et al*. [21], the 1320 nm Nd:YAG laser is an effective modality to treat atrophic and mixed pattern facial acne scars. After treating 12 patients with 3-monthly sessions, optimal improvement was noted in atrophic acne scars; however, mixed acne scars also showed softening of sclerotic and shallow pitted scars. Sadick and Schecter [20] also confirm significant improvement in acne scars after treatment with the 1320 nm Nd:YAG, but they propose that six sessions is more effective than three laser sessions.

Figure 50.5 1064 nm Q-switched Nd:YAG laser.

Q-switched Nd:YAG 1064 nm laser

The Q-switched (QS) Nd:YAG 1064 nm laser has not only proven to be successful for treatment of tattoos, vascular, and pigmented lesions, but it has recently been used to treat rhytids, photodamage, and acne scars (Figure 50.5) [3,8,11,22]. This laser system is poorly absorbed by water, making deeper collagen damage more likely when compared with systems with other wavelengths [22]. It has been hypothesized that when compared with other non-ablative systems, the 1064 nm QS Nd:YAG laser is able to cause the most severe dermal damage and thus produce the greatest amount of collagen remodeling. This was confirmed in a mouse study which showed greatest improvement in skin elasticity after treatment with the QS Nd:YAG 1064 nm laser [13].

Another small study involving eight patients was performed to evaluate the effects of the QS 1064 nm Nd:YAG laser on facial wrinkles [22]. Treatments were performed monthly, for a total of 3 months, with a fluence of 7 J/cm^2, a 3 mm spot size, and two passes, with petechiae as the desired endpoint. In the end, six of the eight subjects demonstrated clinical improvement in rhytides.

The QS 1064 nm Nd:YAG laser has also been used to treat atrophic acne scars with notable success. In 11 patients who completed five treatment sessions with the QS 1064 nm Nd:YAG laser, significant improvement in facial acne scars was demonstrated [8]. After completing all five treatments, improvement was seen as early as 1 month, the greatest percentage improvement was noted at 3 months, and improvement had reached a plateau at 6 months. Another similar study used three-dimensional topography to quantify the efficacy of five QS 1064 nm Nd:YAG treatments on facial wrinkles and acne scars [11]. At 3 months post-treatment, a 61% improvement in surface topography was recorded, and it was maintained at the 6-month follow-up. These results, and others, have suggested that collagen remodeling and repair continues to occur for an extended period of time following the last treatment [1,3,8,11].

Erbium:glass 1540 nm

The erbium:glass (Er:glass) 1540 nm laser has been used to treat perioral and periorbital rhytides with mild to moderate end results [1,3,12,23]. Fournier *et al*. [23] studied the effects of the Er:glass laser on 42 patients treated at 6-week intervals for a total of five sessions. Profilometry, ultrasound, and photography were used to rate clinical improvement after the final treatment. All patients reported improvement in quality and appearance of their skin at 6 months. Notable findings showed an increase in dermal thickness by 17%, a reduction of anisotropy by 44.8%, and an overall improvement in clinical appearance.

An additional 35-month study was conducted to assess the long-term benefits of treatment with the Er:glass 1540 nm laser on facial rhytides [12]. Eleven patients with periorbital and perioral rhytides were treated with a series

of five treatments at 6-week intervals. Approximately half of the patients also received two additional maintenance treatments at 14 and 20 months. Treatments were performed with settings of 8 J/cm^2, three stacked pulses at 2 Hz repetition rates for periorbital and five stacked pulses for perioral sites, and a 4 mm spot size. It was demonstrated that for all 11 patients treated, the improvement in collagen anisotropy measurements showed a reduction in rhytides of 51.7% at 14 months, and 29.8% at 35 months. Overall patient satisfaction was 70% at approximately 2.5 years. Based on both of the aforementioned studies, the Er:glass 1540 nm laser appears to effectively stimulate collagen remodeling with long-term results.

1450 nm diode laser

The 1450 nm diode laser targets water-containing tissue to stimulate collagen remodeling and production. It has been used to treat periorbital and perioral rhytides, and facial acne scars (Figure 50.6) [1–3,24,25].

A previous study was performed with the 1450 nm diode laser to assess the efficacy of treatment on facial rhytides and the associated side effects [25]. Twenty patients underwent 2–4 monthly treatment sessions focusing on perioral and periorbital wrinkles. Each session consisted of treatment of one side of the face with laser and cryogen and the other side with cryogen alone. The laser settings were: frequency of 0.5–1.0 Hz, pulse width of 160–260 ms, pre, post, and intermediate cryogen cooling of 40–80 ms total, and a 4 mm spot size. At 6 months after the final treatment, 13 of the 20 laser/cryogen treated sites showed some improvement, while none of the cryogen only sites showed any improvement. It also showed that periorbital wrinkles showed greater improvement when compared with the perioral sites.

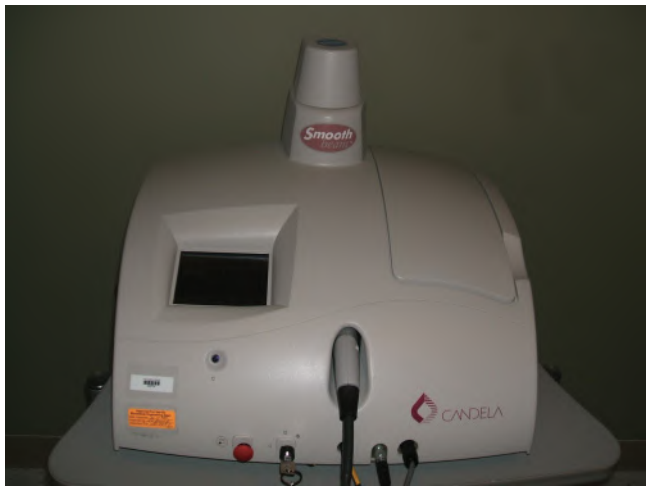

Figure 50.6 1450 nm diode laser.

In addition to wrinkles, the 1450 nm diode has been used to treat atrophic acne scars with minimal side effects. Tanzi *et al*. [24] performed a comparison study treating 20 patients with mild to moderate atrophic acne scars with the 1320 nm Nd:YAG on half of the face and the 1450 nm diode laser on the contralateral side. Three-monthly treatments were performed, and only modest improvement in facial scarring was seen among both groups at 6 months. Yet, greater overall clinical improvement and patient satisfaction was seen in the 1450 nm diode laser sites. Increase in dermal collagen and improvement in skin texture was found in both groups. Minimal side effects were reported.

Infrared light devices (1100–1800 nm)

A new, non-ablative, broad spectrum infrared device, emitting wavelengths 1100–1800 nm, has been recently introduced for the treatment of photoaged skin. Improvement in skin laxity and rhytides is believed to result from volumetric heating of water in the dermis which leads to tissue contraction [1,26,27]. A large component of facial aging is the development of skin laxity. With this in mind, a study was conducted to evaluate the efficacy of a filtered infrared light device in the treatment of skin laxity with ptosis of the lower face and neck [27].

Thirteen females, with a mean age of 64 years, were treated from the nasolabial folds to the preauricular area, and from the malar prominence to the clavicle. The parameters used were fluences of 30–36 J/cm^2, 230–440 pulses per session, pulse duration up to 11 s, a spot size of 1.5 × 1.0 cm, and cooling of the epidermis to 40 °C. Treatments were administered monthly for a total of two treatments. Improvement was seen clinically in 11 of 12 patients who completed the study. Significant improvement in submental and submandibular definition was noted. The most dramatic improvement was seen in those with loss of definition because of excess skin hanging separately from deeper soft tissue. Continued improvement was noted beyond the 1 month follow-up visit. Mild erythema was the only side effect seen, and it resolved within 30 minutes after treatment.

A recent small study was performed on nine women, skin types III–IV, with variable photodamage [26]. Half of the subjects received a one time treatment to the face, while the other group had two monthly treatments. The laser parameters were: fluences of 30–40 J/cm^2 and 170–200 pulses. Overall, both subjects' and investigators' assessments of pre-procedural and post-procedural appearances found significant improvement in elasticity, pore size, dyschromia, wrinkles, and overall texture. Also, the improvement in elasticity, rhytides, and skin texture were more evident in the group treated twice. This study showed promising results but was limited to an 8-week timespan and small study

Table 50.3 Advanced non-ablative resurfacing.

Laser/RF device	Treatment locations	Fluence	Pulse duration/pulse number	Spot size
1320 nm Nd:YAG	Photodamaged dorsal hands	13–18 J/cm^2	50 ms macropulse (stacked 350 μs micropulses)	10 mm
Infrared light device (1100–1800 nm)	Neck skin laxity	30–36 J/cm^2 (adjusted for pain level)	11 s Total pulses 230–440	1.5 cm
Monopolar RF (Thermacool)	Upper arm skin laxity			3 cm
Unipolar RF device (Accent XL)	Upper thigh, buttocks, abdominal cellulite	150–170 W	30 s	

RF, radiofrequency.

population. More studies will need to be performed to determine the role of new infrared light devices in the field of facial rejuvenation.

Radiofrequency devices

Radiofrequency (RF) devices have become another widely accepted method of non-ablative rejuvenation. The Food and Drug Administration (FDA) has approved the RF devices for the treatment of periorbital rhytides [9,10].

Advanced approaches

In addition to facial rejuvenation, several of these devices have also been evaluated for use in photoaging and tightening of other anatomic sites (Table 50.3) [26,28,29,31]. Early studies and preliminary results have suggested that non-ablative resurfacing may play a significant part in non-facial rejuvenation and tightening. Yet, further results are necessary to determine how important they will be in this rapidly growing field.

For example, a small case series was performed using the 1320 nm Nd:YAG laser to treat photoaging hands [29]. After six monthly treatments, four of the seven patients showed mild to moderate improvement in smoothness, reduced wrinkles, and more even pigmentation. Subjective improvement was reported by six of the seven patients at 6 months. Although this study was small, the results showed statistically significant, although mild, improvement in photoaged hands.

RF and infrared light devices have also been used in an attempt to treat skin laxity in non-facial areas with variable findings [27,30,31]. Although non-ablative tightening results may not be as effective as surgical interventions, significant improvement has been found. A small trial using an infrared light device showed improvement in neck contour and excess skin in 11 of the 12 patients who completed the study [27]. Early results from the use of a monopolar radiofrequency device on upper arm contouring have shown improvement in circumferential size of 36 of 70 patients treated at a 4-month follow-up [31]. Further long-term results are still expected to follow. Other trials are underway looking at the use of RF devices on tightening of thighs and enhancement of gluteal definition.

Table 50.4 Side effects of non-ablative laser resurfacing.

Transient erythema and edema (most common)
Pain/discomfort
Purpura (KTP and PDL)
Temporary hyperpigmentation
Petechiae/pinpoint bleeding (1064 nm QS Nd:YAG)
Burning and vesiculation (rare)
Crusting
Edematous papules, 1–7 days (1450 nm diode)

KTP, potassium titanyl phosphate; PDL, pulse dye laser; QS, Q-switched.

Complications

One of the major benefits of all non-ablative rejuvenation modalities is the low risk of potential complications involved with treatments. The most common side effect found among all non-ablative lasers, light devices, and RF devices is mild transient erythema and edema which commonly resolves within hours to days [1–3,6,8–10, 12,16,17,20,23–25]. Although complications are rare, temporary side effects have been recorded and are listed in Table 50.4.

Conclusions

Non-ablative rejuvenation is a relatively new and exciting field in esthetic dermatology. Many different devices are currently being used to treat changes associated with photoaging, such as rhytides, skin laxity, vascular changes, and pigmentary alterations. Although ablative resurfacing and surgical intervention remain the gold standard, non-ablative systems offer an alternative option with less down-time and risk of complications. These devices selectively target the dermis, inciting a wound healing response locally, while sparing the epidermis from harm. Dermal collagen remodeling, production, and repair are upregulated as a result of this selective targeting. Multiple lasers, light sources, and RF devices have been used to induce significant neocollagenesis with measurable success. Yet despite the significant histologic changes noted, the clinical enhancement is often subtle with mild to moderate improvement over time. As a result, it is important to give patients realistic expectations when performing non-ablative rejuvenation. The most effective devices and treatment parameters for photorejuvenation have yet to be determined, but continued enthusiasm in this field gives hope for continued research and success.

References

1 Alexiades-Armenakas MR, Dover JS, Arndt KA. (2008) The spectrum of laser skin resurfacing: nonablative, fractional, and ablative laser resurfacing. *J Am Acad Dermatol* **58**, 719–37.

2 Weiss RA, Weiss MA, Beasley KL, Munavalli G. (2005) Our approach to nonablative treatment of photoaging. *Lasers Surg Med* **37**, 2–8.

3 Goldberg DJ. (2003) Lasers for facial rejuvenation. *Am J Dermatol* **4**, 225–34.

4 Hedelund L, Bjerring P, Egekvist H, Haedersdal M. (2006) Ablative versus non-ablative treatment of perioral rhytides: a randomized controlled trial with long-term blinded clinical evaluations and non-invasive measurements. *Lasers Surg Med* **38**, 129–36.

5 Sadick NS. (2003) Update on non-ablative light therapy for rejuvenation: a review. *Lasers Surg Med* **32**, 120–8.

6 Bosniak S, Cantisano-Zilkha M, Purewal BK, Zdinak LA. (2006) Combination therapies in oculofacial rejuvenation. *Orbit* **25**, 319–26.

7 Liu H, Dang Y, Wang Z, Chai X, Ren Q. (2008) Laser induced collagen remodeling: a comparative study *in vivo* on mouse model. *Lasers Surg Med* **40**, 13–9.

8 Friedman PM, Jih MH, Skover GR, Payonk GS, Kimyai-Asadi A, Geronemus RG. (2004) Treatment of atrophic facial acne scars with the 1064 nm Q-switched Nd:YAG laser. *Arch Dermatol* **140**, 1337–41.

9 Bogle MA, Ubelhoer N, Weiss RA, Mayoral F, Kaminer FS. (2007) Evaluation of the multiple pass, low fluence algorithm for radiofrequency tightening of the lower face. *Laser Surg Med* **39**, 210–7.

10 Narins DJ, Narins RS. (2003) Non-surgical radiofrequency facelift. *J Drug Dermatol* **2**, 495–500.

11 Friedman PM, Skover GR, Payonk G, Kauvar AN, Geronemus RG. (2002) 3D *in vivo* optical skin imaging for topographical quantitative assessment of non-ablative laser technology. *Dermatol Surg* **28**, 199–204.

12 Fournier N, Lagarde JM, Turlier V, Courrech L, Mordon S. (2004) A 35-month profilometric and clinical evaluation of non-ablative remodeling using a 1540 nm Er:glass laser. *J Cosmet Laser Ther* **6**, 126–30.

13 Dang Y, Ren Q, Li W, Yang Q, Zhang J. (2006) Comparison of biophysical properties of skin measured by using non-invasive techniques in the KM mice following 595 nm pulsed dye, 1064 nm Q-switched Nd:YAG and 1320 nm Nd:YAG laser non-ablative rejuvenation. *Skin Res Technol* **12**, 119–25.

14 Keller R, Belda Junior W, Valente NY, Rodrigues CJ. (2007) Nonablative 1064 nm Nd:YAG laser for treating atrophic facial acne scars: histologic and clinical analysis. *Dermatol Surg* **33**, 1470–6.

15 Lee MW. (2003) Combination 532-nm and 1064-nm lasers for noninvasive skin rejuvenation and toning. *Arch Dermatol* **139**, 1265–76.

16 Bernstein EF. (2007) The new-generation, high-energy, 595 nm, long pulse-duration pulsed-dye laser improves the appearance of photodamaged skin. *Lasers Surg Med* **39**, 157–63.

17 Goldberg DJ, Sarradet D, Hussain M, Krishtul A, Phelps R. (2004) Clinical, histologic, and ultrastructural changes after nonablative treatment with a 595-nm flashlamp-pumped pulsed dye laser: comparison of varying settings. *Dermatol Surg* **30**, 979–82.

18 Kono T, Groff WF, Sakurai H, Takeuchi M, Yamaki T, Soejima K, *et al*. (2007) Comparison study of intense pulsed light versus a long-pulse pulsed dye laser in the treatment of facial skin rejuvenation. *Ann Plast Surg* **59**, 479–83.

19 Goldberg DJ, Cutler KB. (2000) Nonablative treatment of rhytids with intense pulsed light. *Lasers Surg Med* **26**, 196–9.

20 Sadick NS, Schecter AK. (2004) A preliminary study of utilization of the 1320-nm Nd:YAG laser for the treatment of acne scarring. *Dermatol Surg* **30**, 995–1000.

21 Rogachefsky AS, Hussain M, Goldberg DJ. (2003) Atrophic and a mixed pattern of acne scars improved with a 1320-nm Nd:YAG laser. *Dermatol Surg* **29**, 904–8.

22 Goldberg DJ, Silapunt S. (2000) Q-switched Nd:YAG laser: rhytid improvement by non-ablative dermal remodeling. *J Cutan Laser Ther* **2**, 157–60.

23 Fournier N, Dahan S, Barneon G, Rouvrais C, Diridollou S, Lagarde JM, *et al*. (2002) Nonablative remodeling: a 14 month clinical ultrasound imaging and profilometric evaluation of a 1540 nm Er:glass laser. *Dermatol Surg* **28**, 926–31.

24 Tanzi EL, Alster TS. (2004) Comparison of a 1450-nm diode laser and a 1320-nm Nd:YAG laser in the treatment of atrophic facial scars: a prospective clinical and histologic study. *Dermatol Surg* **30**, 152–7.

25 Goldberg DJ, Rogachefsky AS, Silapunt S. (2002) Non-ablative laser treatment of facial rhytides: a comparison of 1450-nm diode laser treatment with dynamic cooling as opposed to treatment with dynamic cooling alone. *Lasers Surg Med* **30**, 79–81.

26 Ahn JY, Han TY, Lee CK, Seo SJ, Hong CK. (2008) Effect of a new infrared light device (1100–1800 nm) on facial lifting. *Photodermatol Photoimmunol Photomed* **24**, 49–51.

27 Goldberg DJ, Hussain M, Fazeli A, Berlin AL. (2007) Treatment of skin laxity of the lower face and neck in older individuals with a broad-spectrum infrared light device. *J Cosmet Laser Ther* **9**, 35–40.

28 Sadick NS, Alexiades-Armenakas M, Bitter P Jr, Hruza G, Mulholland RS. (2005) Enhanced full-face skin rejuvenation using synchronous intense pulsed optical and conducted bipolar radiofrequency energy (ELOS): introducing selective radiophotothermolysis. *J Drugs Dermatol* **4**, 181–6.

29 Sadick N, Schecter AK. (2004) Tilization of the 1320-nm Nd:YAG laser for the reduction of photoaging of the hands. *Dermatol Surg* **30**, 1140–4.

30 Alexiades-Armenakas M. (2006) Rhytides, laxity, and photoaging treated with a combination of radiofrequency, diode laser, and pulsed light and assessed with a comprehensive grading scale. *J Drugs Dermatol* **5**, 731–8.

31 Goldberg DJ, Hussain M, Fazeli A, *et al*. (2007) Monopolar radiofrequency tightening of upper arm skin laxity: a multicenter study. *Laser Surg Med* (Suppl 19), 19.

Chapter 51: Microdermabrasion

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BASIC CONCEPTS

- Microdermabrasion is a superficial resurfacing procedure that utilizes a particulate to remove the stratum corneum.
- Microdermabrasion has been used to improve acne, scarring, photodamage, textural changes, stretch marks, and hyperpigmentation.
- All Fitzpatrick skin types can be treated with microdermabrasion.
- The primary advantage of microdermabrasion is the minimal post-procedure down-time.
- Contraindications to microdermabrasion include impetigo, herpes simplex, verruca plana, or other skin infections.

Introduction

Microdermabrasion is a superficial skin resurfacing procedure, in which the stratum corneum is partially or completely removed by light abrasion, to correct or improve skin imperfections [1]. This non-invasive procedure is used to treat a variety of skin conditions including acne, acne scars, hyperpigmentation, striae, photodamage, and texturally rough skin (Table 51.1) [2–7]. Microdermabrasion can be used on young and mature skin and is safe for all Fitzpatrick skin types. It is used to treat a variety of anatomic skin sites including the face, neck, chest, back, arms, elbows, knees, and hands. It is sometimes used in combination with chemical peels, non-ablative resurfacing, or other skin rejuvenation procedures.

First developed in Italy in 1985, it has become an extremely popular form of resurfacing. In 2007, it was one of the top five esthetic procedures performed in the USA; 829 658 microdermabrasion procedures were performed [8]. Despite the popularity of microdermabrasion there is a dearth of well-designed studies documenting the short-term and long-term efficacy of microdermabrasion.

Microdermabrasion units

Multiple microdermabrasion units are available throughout Europe and the USA, with a wide range of features for physician-directed use. Despite the diversity of units, there are several common components to most systems: a pump, tubing, wand, vacuum, and crystals (Table 51.2).

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

Different methods of microdermabrasion include mechanical abrasion from jets of aluminum oxide or zinc oxide crystals, fine organic particles, or wands with a roughened surface. Some newer machines include more than one method. Aluminum oxide is the most commonly used abrasive in microdermabrasion. It is a relatively chemically inert abrasive that does not cause allergic skin reactions, such as eczema or itching. Other crystals can also be used for microdermabrasion and these include sodium chloride, sodium bicarbonate, and magnesium oxide crystals [9]. Generally, these alternative particles are not as abrasive as aluminum oxide. Instead of crystals, some newer techniques use diamond-tipped devices that abrade the skin. Such devices have tips made of diamond chips of varied size and coarseness for different types of skin and varied levels of resurfacing.

Procedure

During the microdermabrasion procedure microcrystals are deposited on the skin via short, rapid strokes of the wand. A tube contained within the wand simultaneously aspirates the crystals and skin debris. Particle flow rate and vacuum pressure determine the volume of particles impacting the skin. The depth of the treatment is determined by several factors, including the strength of the flow of crystals, speed of movement of the wand, and the number of times the device passes over the treatment area [10]. Slower movement of the wand (allowing longer contact of the abrasive crystals with the skin) and more passes increase the depth of microdermabrasion. The treatment is typically performed in a series of 4–12 weekly or biweekly visits taking 20–30 minutes. The series can be significantly longer, particularly for acne scarring.

Table 51.1 Indications for microdermabrasion.

Acne
Hyperpigmentation
Melasma
Post-inflammatory
Oily skin
Enlarged pores
Photodamage
Texturally rough skin
Wrinkles

Table 51.2 Components of microdermabrasion units.

Pump	To generate a high pressure stream of non-absorbable crystals
Tube	To deliver the crystals to the wand (hand-piece)
Wand	To contain the crystals
Vacuum	To remove the spent crystals
Crystals	For exfoliating

Skin physiology and histopathology

Several studies have assessed the physiologic changes, barrier function, and histopathologic alterations induced by microdermbrasion. In general, most of these studies have been performed in small numbers of patients. In spite of the differences in methodologies, protocols, machines, pressures, number of passes, and biopsy sites, data suggest physiologic and histologic trends [1].

Epidermal barrier function

Epidermal barrier changes induced by aluminum oxide and sodium chloride microdermabrasion were initially reported by Rajan and Grimes [9]. Eight patients were treated in a split-face study. One side of the face was treated with aluminum oxide and the other side with sodium chloride microdermabrasion. Transepidermal water loss (TEWL), stratum corneum hydration, skin pH, and sebum production were measured at baseline, 24 hours, and 7 days after treatment. At 24 hours, TEWL increased for both aluminum oxide and sodium chloride microdermabrasion. After 7 days, there was a decrease in TEWL values to less than baseline ($p < 0.05$), suggesting improved epidermal barrier function. In addition, both aluminum oxide and sodium chloride microdermabrasion showed an increase in stratum corneum hydration after 24 hours, which increased significantly by day 7 on the sodium chloride-treated side. No difference was seen in pH or sebum production. The results suggested that changes in TEWL and hydration enhance lipid barrier function. Such barrier alterations may result in the improved texture and overall appearance of microdermabraded skin.

Davari *et al*. [11] also demonstrated changes in skin barrier function. Their study evaluated the extent of skin barrier function changes in relation with the number of microdermabrasion passes. A series of six microdermabrasion treatments using aluminum oxide crystals were performed in 10 patients. One side of the face was treated with two passes of microdermabrasion and the other side was treated with three passes, randomly. Stratum corneum hydration, sebum secretion, and skin pH were measured before and after the procedure for all sessions, and also at 1 and 4 weeks after the last treatment. Significantly higher sebum content and stratum corneum hydration were observed on the side of the face treated with three passes, suggesting that the higher number of passes has a significant effect on lipid barrier restoration. In addition, significant increases in ceramide levels in the stratum corneum have been observed following the first and second microdermabrasion session. By the third or fourth treatment levels returned to normal [12]. The increase in activating protein 1 (AP-1) and NF-κB following microdermabrasion may also influence ceramide levels via cell signaling pathways [13].

Molecular effects

It has been suggested that microdermabrasion activates dermal remodeling or the wound healing cascade. Karimipour *et al*. [13] assessed the molecular alterations following a single microdermabrasion treatment to buttock skin. They reported that transcription factors (AP-1 and NF-κB), primary cytokines (interleukin 1β [IL-1β] and tumor necrosis factor α [TNF-α]) and matrix metalloproteinases (interstitial collagenase, stromelysin-1, and gelatinase B) increase rapidly after a single microdermabrasion treatment. However, no significant alterations in stratum corneum structure were noted. The authors suggested that the increase in matrix metalloproteinases could:

1 Result in matrix remodeling and new collagen deposition; or

2 Remove damaged collagen and allow skin to regain its normal tension.

Histopathologic effects

Histologic changes have been observed in both the epidermis and dermis (Table 51.3). The most significant change is an increase in the thickness of the epidermis. In a series of six microdermabrasion treatments in 10 patients, Freedman *et al*. [3] showed that after three passes, the epidermal thickness increased from $45 \pm 4\,\mu m$ to $62 \pm 10\,\mu m$ ($p < 0.01$), and

to 65 ± 7 μm ($p < 0.01$) after an additional three passes. In the Hernandez-Perez and Ibiett [14] study, the epidermal thickness increased from 0.01 to 0.06 mm in some patients, and to 0.01 mm in one patient. Other studies also demonstrated an increase in the epidermal thickness [7,15].

Other epidermal alterations improved by microdermabrasion include polarity of cells, basal cell liquefaction, horny plugs, and atropic changes [14]. In addition, more regular distribution of melanosomes, less melanization, flattening of the rete pegs, and basal cell hyperplasia had been reported (Figure 51.1) [3,7].

Dermal changes include an increase in papillary dermal thickness, as demonstrated by Freedman *et al.*, from 81 ± 8 μm to 108 ± 11 μm ($p < 0.01$) after three treatments and to 114 ± 9 μm after an additional three. The treated areas showed hyalinization of the collagen fibers in the papillary dermis; the fibers were thicker, more tightly packed, and orientated horizontally. An increase in elastic fibers was seen at the junction of the reticular and papillary dermis after three treatments. After six treatments, the density of the elastic fibers in the reticular dermis increased. These new fibers were more vertically orientated and of normal caliber. After treatment, the blood vessels appeared ecstatic with the presence of a perivascular infiltrate. Fibroblasts were more conspicious, larger, and more densely distributed within the dermis, especially around the dermal capillaries. Recent interest in the impact of topical antioxidants on the skin has shown that the addition of a polyphenolic antioxidant serum to a facial microdermabrasion regimen also enhances clinical and histologic changes [16].

Table 51.3 Histologic changes caused by microdermabrasion.

Epidermal
Increased thickness
Decreased melanization
Alteration of rete ridges
Variable epidermal changes
Decreased liquefaction of basal cells
Improved polarity
Variable dermal changes
Increased dermal thickness
Increased collagen
Increased elastin
Mononuclear infiltrates
Vascular ectasia

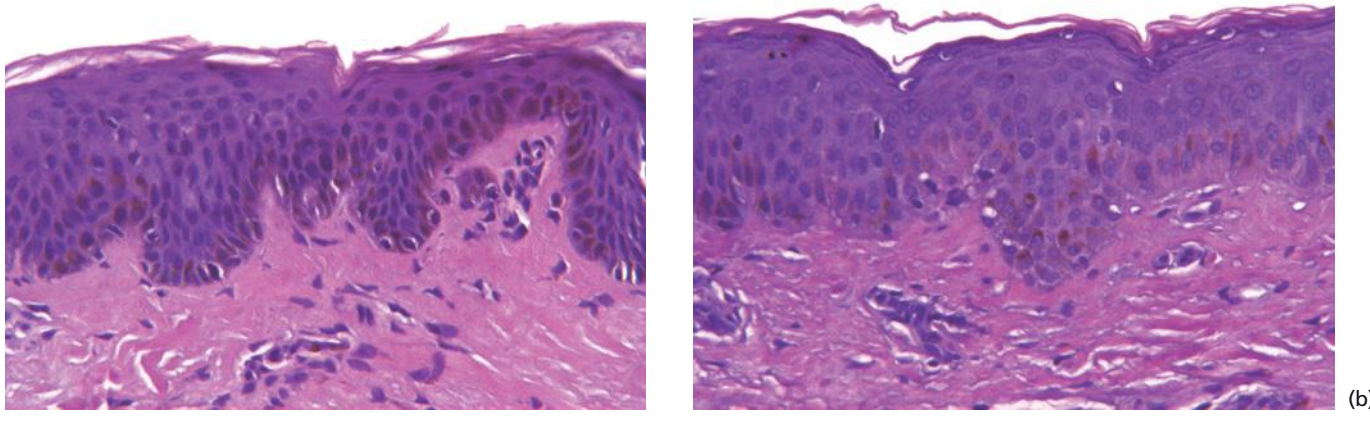
Contraindications

Relative contraindications to the use of microdermabrasion include rosacea and telangiectasia, which may be exacerbated. Absolute contraindications include active infections such as impetigo, flat warts, and herpes simplex [17–19]. The active use of isotretinoin is also contraindicated.

Indications for microdermabrasion

Acne

Microdermabrasion is most effective when treating superficial skin conditions such as acne (Figure 51.2). In a study by Lloyd [2], the role of microdermabrasion in the treatment of patients with acne was studied. Twenty five patients with grade II–III acne received eight microdermabrasion treatments (Parisian Peel microdermabrasion unit used at a pressure of 26.67 mmHg initially and then increased as tolerated)



(a) (b)

Figure 51.1 (a) Baseline biopsy. (b) Biopsy after a series of four microdermabrasion treatments performed at 1 week intervals. Note: No change in thickness of the stratum corneum; however, marked improvement in the polarity of epidermal cells, some increase in epidermal thickness and improvement in dermal collagen.

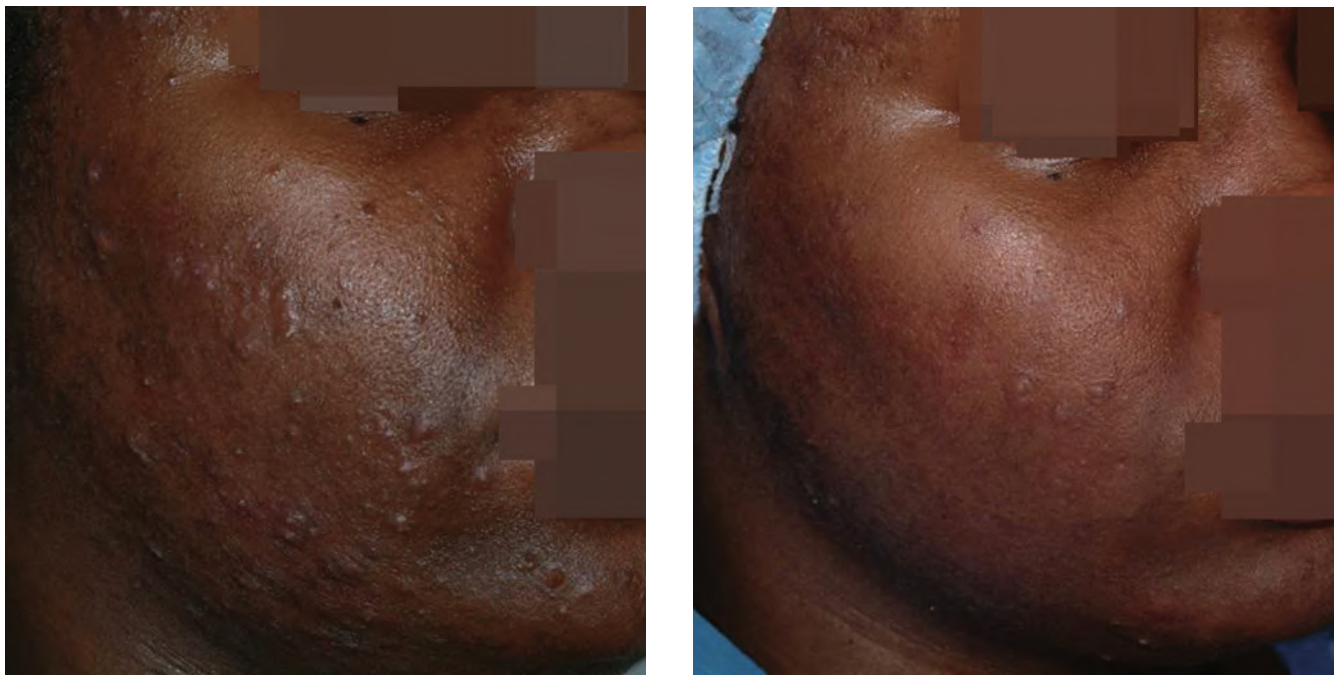


Figure 51.2 Patient with moderate acne treated with a series of five microdermabrasions in combination with oral antibiotics. Treatments at 2-week intervals.

at weekly intervals. Throughout the treatment, patients continued taking their oral antibiotics and topical acne treatment. Photographs were taken before and after treatment, and evaluated for clinical improvement. Twenty-four patients completed the study: 38% (9 of 24) achieved excellent results, 34% (8 of 24) had good results, 17% (4 of 24) had fair results, and 12% (3 of 24) had poor results. Ninety-six percent of patients were pleased with their results. The most prominent improvement was noted with post-inflammatory acne changes and the overall skin quality. No adverse effects were noted during the procedure. The treatment was well tolerated. The only side effect was erythema, which resolved within 24 hours. No controls were included in this investigation.

Scars

The effectiveness of this technique in the treatment of facial scarring was first demonstrated in 1995 by Tsai *et al*. [5]. They treated 41 patients with facial scarring with an average of 9.1 treatments. Facial scars included acne, burns, varicella, and post-traumatic scars. A Harvey 91 microdermabrasion unit with a pressure setting of 76 mmHg was used. All patients had "good to excellent" improvement.

The study showed that patients with acne scars require longer treatment (mean, 15.19 times) than those with traumatic or surgical scars (mean, 4 times) to achieve clinical improvement ($p < 0.001$). Multiple passes and numerous treatments are often needed. This is probably because most acne scars are depressed and surgical and traumatic scars are elevated – depressed lesions are more difficult to treat than elevated ones.

Hyperpigmentation

Albeit commonly used to treat disorders of hyperpigmentation, only a few published reports describe the use of microdermabrasion in the treatment of hyperpigmentation [4,7,20]. Cotellessa *et al*. [4] evaluated the efficacy of microdermabrasion alone or in combination with 15% trichloroacetic acid (TCA) for treatment of patients with multiple hyperpigmented macules of the face. A total of 20 patients were treated. Eight (40%) had complete clearing of the pigmentation after four to eight treatments; 10 (50%) had partial clearance; and two patients (10%) had no improvement after eight treatments. When patients were treated with both TCA peels and microdermabrasion, fewer treatments (four to six) were required to clear or partially clear pigmentation, 50% and 40%, respectively. No serious side effects were observed.

Other studies have also reported improvement in mottled and diffuse hyperpigmentation [1,7,21]. Data from the Vitiligo and Pigmentation Institute suggest that microdermabrasion is an effective and well-tolerated treatment for disorders of hyperpigmentation in all racial ethnic groups (Figure 51.3). Conditions treated included melasma, post-inflammatory hyperpigmentation, and the dyschromias of photoaging.

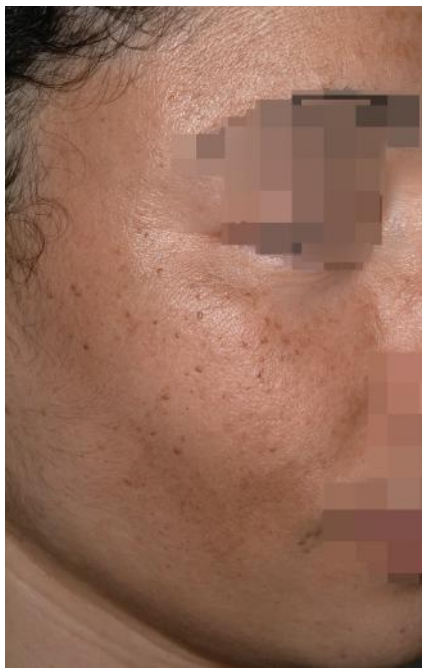
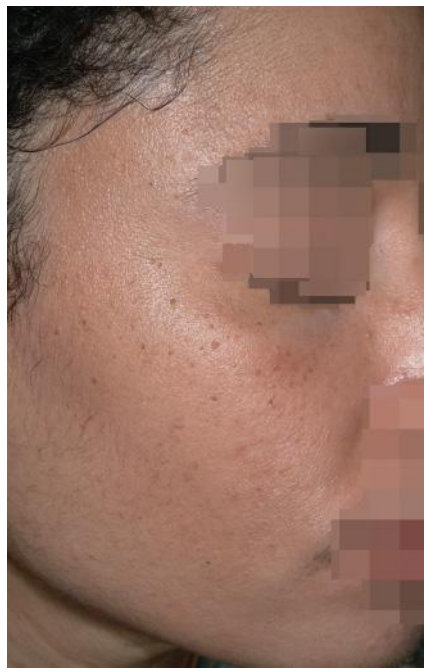
(a)   (b)

Figure 51.3 Patient with melasma and textural changes treated with four microdermabrasions and hydroquinone 4%. (a) Before. (b) After.

Photodamage

Microdermabrasion is well suited for patients with early photodamage, especially those with Glogau photaging classes I and II. In a study to evaluate the effect of microdermabasion on photodamaged skin, 10 patients with Fitzpatrick skin types I–III and photodamage (Glogau scale II and III) were treated once a week for five to six treatments using a Parisian Peel [6]. The face was treated with four passes at a pressure of 30 mmHg, while the periorbital skin received two passes at a pressure of 15 mmHg. Clinical responses, skin surface roughness, topography, elasticity, stiffness, compliance, temperature, sebum content, and histology were analyzed. Nine patients completed at least five treatments.

Clinical analysis showed mild improvement in the majority of patients. Immediately after treatment, skin temperature increased and sebum content decreased. There was a temporary increase in skin roughness. Dynamic skin analysis showed a decrease in skin stiffness and increase in skin compliance. The authors suggest that the observed changes in skin characteristics are consistent with increased blood flow and mild abrasion. Biopsies showed slight orthokeratosis and flattening of rete ridges and a perivascular mononuclear cell infiltrate, edema, and vascular ectasia in the upper reticular dermis. There was no change in collagen or elastin content.

Other studies addressing photodamage have also shown improvements in skin roughness, mottled pigmentation, and overall global improvement in the treated skin areas [7,21]. Hernandez-Perez and Ibiett [14] treated seven women, six with Glogau's photoaging class II and one with Glogau's photoaging class III. Five microdermabrasion treatments were carried out on each patient, at weekly intervals, three complete passes per treatment. Clinical parameters assessed were oily skin, dilated pores, fine wrinkles, thick skin, and general appearance. Skin biopsies were taken before and after treatment. All patients showed clinical and histopathologic improvements in all parameters assessed. Clinical improvement was considered 'good to excellent.' Patients also reported improved self-esteem.

Striae

Microdermabrasion is occasionally used to treat striae. However, patients should be advised that this treatment is aggressive in order to reach the level of the papillary dermis and can cause erythema and hyperpigmentation.

Comparison of microdermabrasion and chemical peeling

Chemical peeling and microdermabrasion are both popular resurfacing procedures that exfoliate the skin. While microdermabrasion works well on superficial skin imperfections, chemical peels may be more effective on skin defects such

as deeper scars and wrinkles. The aftercare and down-time are also longer with more aggressive peeling agents.

Unlike microdermabrasion, the depth of wounding induced by chemical peeling is determined by the strength of the peeling agent. Superficial peels target the stratum corneum to the papillary dermis. They include glycolic acid, salicylic acid, Jessner's solution, and trichloroacetic acid (TCA) 10–30%. Medium depth peels penetrate to the upper reticular dermis and the protype is TCA 35–50%, whereas deeper peels penetrate to the mid-reticular dermis (phenol).

Glycolic acid peels were compared with microdermabrasion in a right–left controlled assessment [20]. Ten patients were enrolled in this split-face, unblinded, randomized trial. One side of the face was treated with a series of 20% glycolic acid peels on a weekly basis, and the opposite side was treated simultaneously with microdermabrasion. Patients' self-analysis revealed that seven patients perceived greater improvement on the side treated with microdermabrasion. Physician investigator ratings found no differences between microdermabrasion or the side with glycolic acid. Furthermore, photographic comparisons by investigators did not reveal treatment-related differences. The investigators could not differentiate pre- and post-treatment photographs. However, both procedures were well tolerated.

The efficacy and safety of microdermabrasion followed by a 5% retinoic acid peel was compared with the effects of a 5% retinoic acid peel alone in six patients with photodamage. The authors reported improvement in texture, pigmentation, and overall skin appearance. The combination group showed slightly greater improvement [22].

A recent study compared the immunohistologic and ultrastructural changes induced by chemical peeling and microdermabrasion [23]. Fifteen patients were treated by weekly microdermabrasion for 2 months while 15 were treated with weekly chemical peeling using either glycolic acid 70% or Jessner's solution. Biopsies were pereformed 1 week before treatment and 1 week after treatment. Skin treated with both chemical peels and microdermabrasion showed an increase in epidermal thickness, dermal vascular ectasia, and densely arranged collagen fibers compared with untreated skin. Skin changes were very similar but milder in the group treated by microdermabrasion [23].

Advantages and disadvantages

There are several microdermabrasion benefits. One of the most noteworthy is that there is no "down-time" after treatment, unlike chemical peels. Microdermabrasion is a relatively painless and safe procedure; the patient perceives immediate improvement in skin tone, texture, and pigmentation (Figure 51.4). Retinoids and other exfoliation therapies can be continued up to the day of the procedure without incurring significant irritation. However, the effectiveness of microdermabrasion is limited for deeper skin conditions,

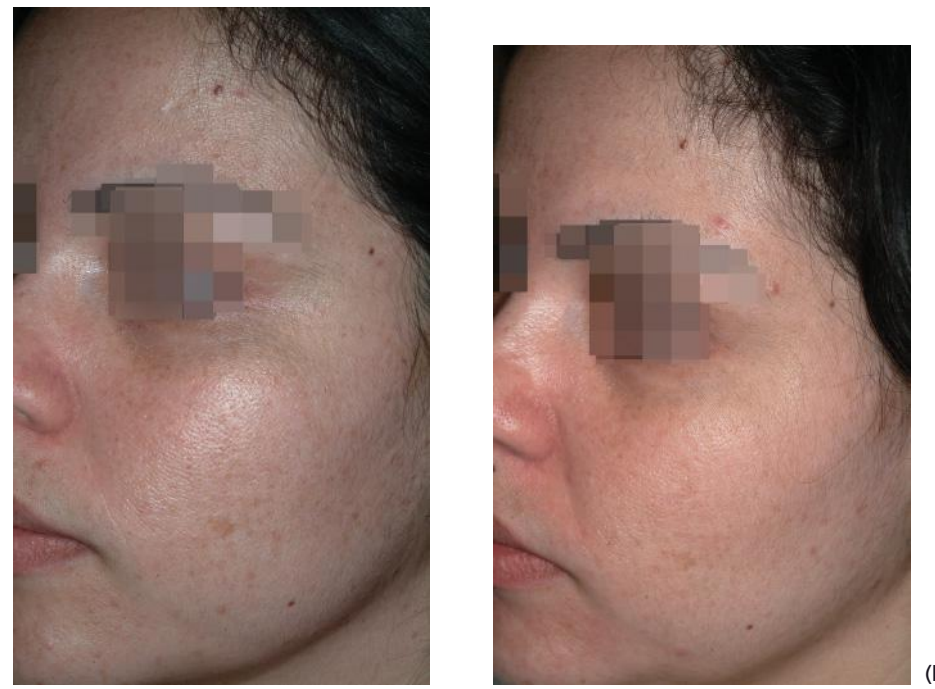


Figure 51.4 Patient with mottled pigmentation, oily skin, and textural changes treated with a series of five microdermabrasions. (a) Before. (b) After.

such as deep wrinkles and scars, which are currently best treated with other resurfacing techniques. Deeper injury increases complications and recovery time along with effectiveness. Microdermabrasion can be combined with other skin resurfacing procedures or chemical peels [4].

Complications and side effects

Although microdermabrasion is considered a safe procedure with few reported side effects [2,5,6,7,14], complications can occur. The most common include mild erythema and increased sensitivity, but these are transient and resolve within a few hours [6,7]. Post-inflammatory hyperpigmentation and streaking can occur from intense pressure of the hand-piece. Petechia and purpura are also complications of aggressive treatment. Post-treatment hyperpigmentation has also been reported and is more likely with aggressive treatment on patients with higher Fitzpatrick skin types (IV–VI) [5].

Ocular complications can occur if microcrystals enter the eye. These include eye irritation, chemosis, photophobia, and punctate keratitis [24]. Patients must wear protective eyewear during the procedure. Cross-contamination can occur when using mircrodermabrasion equipment. Shelton reported that bloody material was present on the wand after performing microdermabrasion on a patient with acne scaring, indicating that it is not sufficient to sterilize the distal cap of the wand or to use disposable caps. The operator must therefore ensure that cross-contamination does not occur. An unusual case of a severe urticarial reaction immediately following aluminum oxide microdermabrasion has been reported [25].

Conclusions

Microdermabrasion is considered a safe, non-invasive procedure for resurfacing the skin and is used to treat a variety of skin problems and is suitable for all skin types. However, despite its popularity by patients and physicians alike, there remains a dearth of robust scientific evidence about the efficacy and long-term safety of this procedure. However, the few studies published suggest that both patients and physicians have reported benefits from microdermabrasion: improved texture, pigmentation, improvement in acne scarring, photodamage, and appearance of treated skin as well as improved self-esteem. Most studies were performed on small patient groups where protocols and the variety of units used differed. Further, multicentered, randomized studies are needed to confirm the long-term benefits of this popular and widely used procedure for skin rejuvenation.

References

1 Grimes P. (2005) Microdermabrasion. *Dermatol Surg* **31**, 1160–5.
2 Lloyd J. (2001) The use of microdermabrasion for acne: a pilot study. *Dermatol Surg* **27**, 329–31.
3 Freedman BM, Rueda-Pedraza E, Waddell SP. (2001) The epidermal and dermal changes associated with microdermabrasion. *Dermatol Surg* **27**, 1031–4.
4 Cotellessa C, Peris K, Fargnoli M, Mordenti C, Giacomello RS, Chimenti S. (2003) Microabrasion versus microabrasion followed by 15% trichloroacetic acid for treatment of cutaneous hyperpigmentations in adult females. *Dermatol Surg* **29**, 352–6.
5 Tsai RY, Wang CN, Chan HL. (1995) Aluminum oxide crystal microdermabrasion. *Dermatol Surg* **21**, 539–42.
6 Tan MH, Spencer JM, Pires LM, Ajmeri J, Skover G. (2001) The evaluation of aluminum oxide crystal microdermabrasion for photodamage. *Dermatol Surg* **27**, 943–9.
7 Shim E, Barnette D, Hughes K, Greenway HT. (2001) Microdermabrasion: a clinical and histopathologic study. *Dermatol Surg* **27**, 524–30.
8 American Society for Aesthetic Plastic Surgery. (2007) Procedure Survey, Dermasurgery Trends and Statistics. Available from http://www.surgery.org/press/statistics.php
9 Rajan P, Grimes P. (2002) Skin barrier changes induced by aluminum oxide and sodium chloride microdermabrasion. *Dermatol Surg* **28**, 390–3.
10 Grimes P. (2008) *Aesthetics and Cosmetic Surgery for Darker Skin Types*. Lippincott Williams and Wilkins.
11 Davari P, Gorouhi F, Jafarian S, Dowlati Y, Firooz A. (2008) A randomised investigator-blind trial of different passes of microdermabrasion therapy and their effects on skin biophysical characteristics. *Int J Dermatol* **47**, 508–13.
12 Lew Bl, Cho Y, Lee MH. (2006) Effect of serial microdermabrasion on the ceramide level in the stratum corneum. *Dermatol Surg* **32**, 376–9.
13 Kamimipour DJ, Kang S, Johnson T, Orringer JS, Hamilton T, Hammerberg C, *et al*. (2006) Microdermabrasion with and without aluminum oxide crystal abrasion: a comparative molecular analysis of dermal remodeling. *J Am Acad Dermatol* **54**, 405–10.
14 Hernandez-Perez E, Ibiett EV. (2001) Gross and microscopic findings in patients undergoing microdermabrasion for facial rejuvenation. *Dermatol Surg* **27**, 637–40.
15 Rubin M, Greenbaum S. (2000) Histological effects of aluminum oxide microdermbrasion on facial skin. *J Aesthet Dermatol* **1**, 237–9.
16 Freedman B. (2009) Topical antioxidant application enhances the effects of facial microdermabrasion. *J Dermatolog Treat* **20**, 82–7.
17 Clark C. (2001) New directions in skin care. *Clin Plast Surg* **28**, 745–50.
18 Bernard R, Beran S, Rusin L. (2000) Microdermabrasion in clinical practice. *Clin Plast Surg* **27**, 571–7.
19 Warmuth I, Bader R, *et al*. (1999) Herpes simplex infection after microdermabrasion. *Cosmet Dermatol* **12**, 13.
20 Alam M, Omura N, Dover J, Arndt KA. (2002) Glycolic acid peels compared to microdermabrasion: a right–left controlled trial of efficacy and patient satisfaction. *Dermatol Surg* **28**, 475–9.

21 Hexsel D, Mazzuco R, Dal'Forno T, Zechmeister D. (2005) Microdermabrasion followed by a 5% retinoid acid chemical peel vs a 5% retinoid acid chemical peel for the treatment of photoaging: a pilot study. *J Cosmet Dermatol* **4**, 111–6.

22 Hussein MR. (2008) Chemical peeling and microdermabrasion of the skin: comparative immunohistological and ultrastructural studies. *J Dermatol Sci* **52**, 205–22.

23 Cotellessa C, Peris K, Onorati M. (1999) The use of chemical peelings in the treatment of different cutaneous hyperpigmentations. *Dermatol Surg* **25**, 450–4.

24 Morgenstern K, Foster J. (2002) Advances in cosmetic oculoplastic surgery. *Curr Opin Ophthalmol* **13**, 324–30.

25 Farris P, Rietschel R. (2002) An unusual acute urticarial response following microdermabrasion. *Dermatol Surg* **13**, 324–30.

Chapter 52: Dermabrasion

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BASIC CONCEPTS

- Dermabrasion involves mechanically removing the epidermis and papillary dermis, creating a newly contoured open wound to heal by second intention.
- The most common indications for dermabrasion are for the improvement of cystic acne scarring, post-surgical scar revision, and enhanced contouring of partial thickness Mohs defects.
- Patients must have realistic expectations of the anticipated improvement, possible side effects, and potential complications of dermabrasion prior to treatment.
- Proper technique is paramount in order to avoid intraoperative complications.
- Vigilance during the postoperative period is important in order to recognize complications at an early stage and prevent long-term sequelae.

Introduction

Dermabrasion involves mechanically resurfacing the skin with an abrasive tip driven by a high-speed rotary hand engine. Either a wire brush or diamond fraise may be used as the abrading tip to create an open wound that will heal by second intention. An irregular or scarred cutaneous surface may be surgically abraded in order to achieve a more regular plane, or a more gradual transition between different planes, thereby improving skin contour. This chapter discusses the dermabrasion technique.

Mechanism of action

Fundamentally, the skin can be subdivided into three layers: epidermis, dermis, and subcutaneous tissue. The dermis is further subdivided into the more superficial papillary dermis, containing both a finely woven meshwork of collagen interdigitating with the epidermal rete as well as the superficial vascular plexus, and the deeper reticular dermis, composed of thick bundles of predominantly type I collagen [1]. Resurfacing, by definition, involves iatrogenic removal of one or multiple layers of the skin to create a cutaneous wound. Dermabrasion mechanically removes the epidermis and papillary dermis, creating a partial thickness wound to heal by second intention. The well-characterized, yet complex, wound healing response is triggered, involving transforming growth factor β (TGF-β) driven myofibroblastic deposition of new type I and III collagen and subsequent remodeling in the dermis [2]. Additionally, TGF-β, keratinocyte growth factor (KGF), and epidermal growth factor (EGF) stimulate re-epithelialization from both underlying skin appendages and adjacent epithelialized skin [2].

When properly performed, the irregularly contoured or actinically damaged epidermal and papillary dermal layers are removed, and second intention wound healing occurs. The clinical result is a smoother, more evenly contoured surface, with fewer irregularities in the form of acne scars, rhytides, keratoses, or step-off transitions.

Indications

The most common indications for dermabrasion are desired improvement of acne scars, traumatic and surgical scars, rhinophyma, deep rhytides, and partial thickness Mohs defects [3]. However, dermabrasion is also indicated for improvement of actinic keratoses, seborrheic keratoses, angiofibromas, syringomas, solar elastosis, epidermal nevi, and tattoo removal [4].

With regard to acne scarring, even in the era of laser devices, fractionated delivery approaches, and non-invasive "tissue-tightening" procedures, dermabrasion remains an important tool in the combination approach to the improvement of cystic acne scarring. While the shallow and wide, undulating, or "rolling" type acne scars are better treated with subcision, dermal grafts, fillers, or fractionated laser devices, the slightly deeper and narrower "box-car" type

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acne scars that demonstrate step-off vertical borders respond best to mechanical dermabrasion. Additionally, the deepest and narrowest "ice-pick" type acne scars respond best to dermabrasion subsequent to punch excisions, punch grafts, or trichloroacetic acid (TCA) cross-destruction.

For traumatic and surgical scars, the thickness, contour, and overall appearance is routinely improved with postoperative dermabrasion. Also known as "scar abrasion," this procedure is best performed 6–8 weeks after the initial surgery or wounding event [5]. When performed during this 6–8 week window, the late proliferative and early remodeling phases of wound healing are interrupted and partially "reset," resulting in an improved final cosmetic result.

While several modalities, including wire loop electrosurgery and CO_2 laser resurfacing, have been described for the treatment of rhinophyma, dermabrasion remains unmatched in the operator's ability to re-establish the complex contour of the many cosmetic subunits of the nose. Furthermore, although CO_2 resurfacing, erbium:yttrium aluminum garnet (Er:YAG) resurfacing, and deep chemical peels may improve facial rhytides, dermabrasion proves as efficacious or more efficacious at removal of both fine and moderate facial rhytides, with a slightly lower risk of permanent hypopigmentation.

Finally, dermabrasion proves to be an incredibly useful technique in the armamentarium of the Mohs surgeon. Thin carcinomas in cosmetically sensitive or high-risk areas can often be completely removed with a shallow Mohs layer to the level of the superficial reticular dermis. After clearance, these partial thickness defects, particularly on the nose and scalp, may lend themselves to healing by second intention rather than primary closure, yet with slightly increased risk of an evident contour discrepancy or sharp pigmentary transition. Dermabrasion of the edges surrounding the partial thickness Mohs defect greatly improves the final contour by replacing the steeply beveled wound edge with a more gradual slope. Additionally, dermabrading the remainder of an involved cosmetic subunit of the nose results in a less obvious scar by placing the pigmentary demarcation lines at the less perceptible subunit boundaries.

Advantages and disadvantages

Compared with fully ablative resurfacing with the CO_2 and Er:YAG lasers, dermabrasion demonstrates similar or greater efficacy for the treatment of scars, rhytides, and precancerous lesions, with less postoperative erythema and more rapid re-epithelialization. While newer, fractionated delivery protocols result in even less erythema and quicker re-epithelialization than dermabrasion, their efficacies for the improvement of scars, rhytides, and precancerous lesions do not currently match that seen with mechanical dermabrasion. Dermabrasion has also been shown to be more efficacious than 5-fluorouracil for the treatment of actinic keratoses [6].

The major disadvantage of dermabrasion compared with the above modalities is that it is much more operator-dependent. Unlike laser and light devices, the depth of penetration is not preprogrammed. Successful treatment relies not only on the physician's knowledge of the modality and application settings, but also on his or her skilled execution. In the novice's hands, dermabrasion exhibits a narrower window or buffer between effective treatment depth and inappropriate scarring depth. However, this is quickly overcome with experience.

Patient selection and preoperative consultation

The most important components of the preoperative consultation are determining the patient's specific motivation for resurfacing and establishing realistic expectations regarding the treatment outcome. The ultimate goal of any resurfacing treatment should be an improvement of the given defect rather than a complete eradication. Dermabrasion consistently achieves 30–50% improvement in the appearance of deep acne scars and rhytides, but the patient who seeks and expects the elimination of all scars and rhytides will rarely be satisfied. Reviewing before and after photographs with the patient during consultation, particularly when considering full cosmetic unit or full-face dermabrasion, may foster realistic expectations for improvement.

The preoperative consult should also include a complete history addressing bleeding disorders, prior herpes simplex infection, impetigo, keloidal or hypertrophic scarring, koebnerizing conditions, prior isotretinoin therapy, and immunosuppression. The risk:benefit ratio of an iatrogenically induced wound is unfavorable in patients who are immunosuppressed, who have a history koebnerizing conditions such as lichen planus and psoriasis, or who demonstrate a propensity towards keloidal or hypertrophic scar formation. Because of an increased risk of scarring in patients on isotretinoin, dermabrasion should be delayed until 6 months after finishing an oral retinoid course [7]. Caution should also be exercised when planning to dermabrade patients who have recently undergone extensive procedures involving the area to be dermabraded, such as a facelift, as a robust blood supply is necessary for appropriate wound healing. Many surgeons prefer to wait 6 months after a facelift before subsequent dermabrasion.

Antiviral prophylaxis should be instituted in those with a history of herpes simplex outbreak in the area to be spot dermabraded or in those who are undergoing full-face or multiple cosmetic unit dermabrasion. The antiviral agents acyclovir or valcyclovir may be used, and patients should remain on prophylactic therapy for 10 days after the

procedure (50 mg valacyclovir b.i.d. for 10 days). Similarly, antibacterial prophylaxis with an antistaphylococcal agent should be instituted in those with a history of impetigo.

Particular attention should also be paid to the Fitzpatrick skin type of the patient. Fitzpatrick skin types IV, V, and VI are much more prone to both postoperative hyperpigmentation and permanent, clinically significant hypopigmentation, the latter of which may not appear for several months following the procedure.

Preoperative photographs are highly recommended, and should include a frontal view, 45° and 90° views from both sides, and a close-up view of the areas to be treated. Additionally, all preoperative and postoperative expectations should be discussed. The patient should particularly be made aware of the nature of the postoperative recovery routine, which includes extensive facial dressings with multiple changes over several days, and clinically apparent erythema for several weeks.

Instrumentation

With mechanical dermabrasion, a diamond fraise or wire brush abrading tip is driven by a handheld engine at speeds of 15 000–30 000 rotations per minute. Current hand engines include the Osada, Ram, and Urawa Kohgyo Acrotorque hand-pieces. The classic Bell hand engine is no longer available from the manufacturer, but may occasionally be found as a refurbished item through select vendors.

Diamond fraises come in a range of shapes and sizes, such as pears, cones, bullets, and wheels, and also vary in coarseness from fine to extra coarse. Alternatively, the wire brush is a 3.0–5.0 mm wide × 17.0 mm diameter wheel with steel bristles radiating from the center in a clockwise fashion when viewed from the shaft (Figure 52.1). The wire brush is the most aggressive type of end piece and can be more technically difficult to master, yet it is considered more efficacious by those experienced with its use. The microlacerations created with the wire brush are the most efficient means of removing the nodules of rhinophyma, the thick plaques of hypertrophic scars, and deep acne scars.

Figure 52.1 Wire brush abrading wheel with steel bristles radiating from the center in a clockwise fashion.

Standard technique

Treating surgical scars, rhinophyma, and partial thickness Mohs defects provides an excellent point of entry into the practice of dermabrasion prior to practicing advanced techniques such as full-face dermabrasion. If the treatment area is limited in size, local anesthesia (1% lidocaine with epinephrine 1:100 000) or tumescent technique is adequate. When treating the entire nose, a ring block may achieve an appropriate degree of anesthesia. Prior to abrasion, the area to be treated is cleansed with a 4% chlorhexidine solution.

The body of the hand engine is grasped in the palm of the dominant hand with four fingers, allowing the thumb to project along the neck for stabilization (Figure 52.2). Finger position is similar to a "thumbs-up" sign or to that seen when gripping a golf club, yet the hand and instrument are pronated, with the palm facing downward. Freon 114 refrigerant spray (Frigiderm, Delasco, Council Bluffs, IA, USA) is applied to the treatment area in an amount necessary to achieve a 5–10 s thaw time, during which time abrasion is performed on the frozen area. Refrigerant spray accomplishes two important functions: decreasing pain by cryoan-

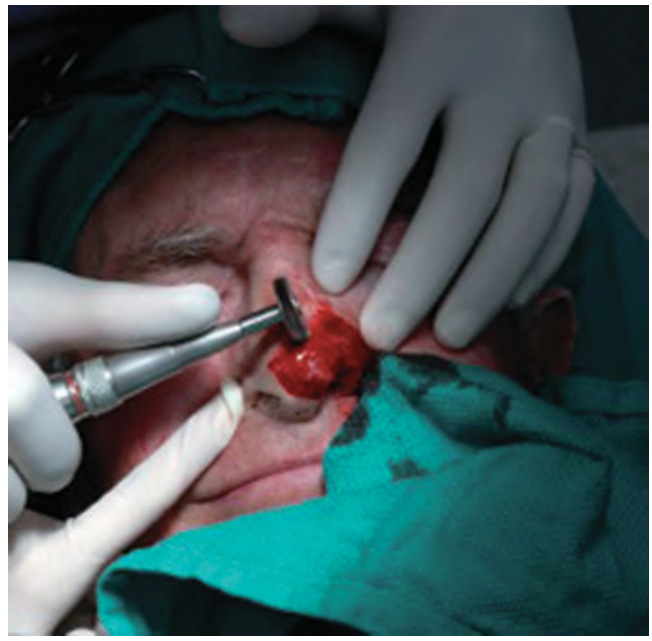

Figure 52.2 Dermabrasion of multiple cosmetic subunits of the nose showing operator hand position and three-point retraction by physician's non-dominant hand and two hands of assistant.

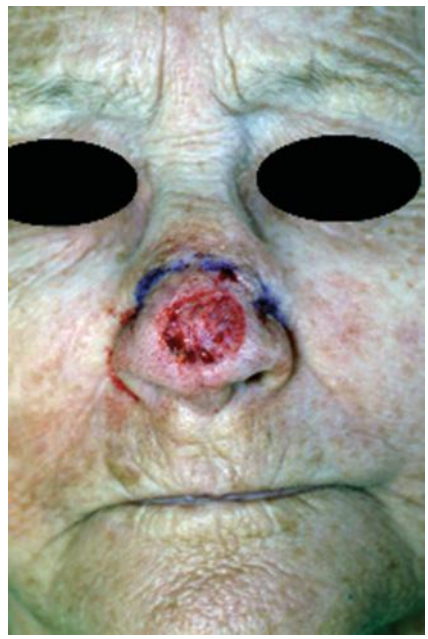

Figure 52.3 Female patient after two stages of Mohs micrographic surgery for removal of basal cell carcinoma of the nasal tip. Tumor has been cleared and defect depth remains in the superficial reticular dermis. Surgical marking notes superior border of nasal supratip subunit.

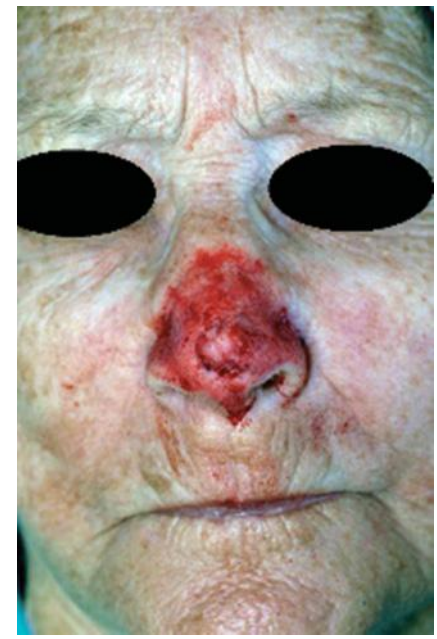

Figure 52.4 Same patient as in Figure 52.3 after wire brush dermabrasion of the remaining nasal tip and surrounding cosmetic subunits. Area will now heal with improved contour and pigment match.

esthesia and a providing a firm substrate upon which to achieve recontouring.

Immediately after freezing, three-point retraction is obtained by the two hands of the surgical assistant and the non-dominant hand of the surgeon. The frozen skin is thus stabilized by retraction, and the lesion is recontoured with the wire brush rotating in a counter-clockwise direction (with the angle of the radiating bristles) as determined from the point of view of the body of the hand engine. The wire brush is passed over the treatment area in an arciform motion with the long axis perpendicular to the rotating hand-piece (parallel to the body of the hand engine). Counter-clockwise rotation of the wire brush offers a less aggressive technique of wire brush surgery that is especially well suited for spot dermabrasion of Mohs defects or surgical scars without cryoanesthesia (Figures 52.3 and 52.4). With counter-clockwise rotation, the radiating bristles are less prone to gouge unfrozen skin. This counter-clockwise direction of rotation is also useful when dermabrading free margins of the face such as the lips and nasal alae, in order to prevent the inadvertent "grabbing" of tissue by the rotating wire brush when dermabrading from the right side with the dominant right hand.

Regular pinpoints of bleeding signal abrasion to the level of the papillary dermis. As depth increases to the reticular dermis, the bleeding foci become larger, and frayed collagen bundles become apparent. Surgical scars will frequently disintegrate upon abrasion, which is a desirable endpoint. Contouring should often include "feathering" or graduating zones of treatment around the central scar to provide a smooth transition between different planes and improved pigment transition. Alternatively, the treatment zone may be stopped at the border of a cosmetic unit or carried to an inconspicuous endpoint such as 1.0 cm beyond the mandible.

Advanced technique

While local or tumescent anesthesia may be adequate for scar or spot dermabrasion, full-face abrasion of acne scarring or rhytides is best accomplished with a combination of oral (p.o.) or intramuscular (i.m.) light sedation, nerve blocks, and cryoanesthesia. A standard regimen consists of 50–75 mg meperidine i.m., 25 mg hydroxyzine i.m., and 5–10 mg diazepam p.o. or sublingual 30–60 minutes prior to the start of the procedure. After a chlorhexidine prep, nerve blocks to the supratrochlear, supraorbital, infraorbital, and mental nerves may also be performed.

In contrast to the counter-clockwise rotation typically utilized for less aggressive dermabrasion, more experienced practitioners may opt to use a clockwise rotation of the abrasive wire brush. Rotation in a clockwise direction occurs against the angle of the radiating wire bristles and causes the tip to pull away from the thumb rather than driving toward it. Deeper planing and recontouring are possible with clockwise rotation, but this direction is much less forgiving. Additionally, clockwise rotation utilized by a

dominant right hand increases the risk that free margins of the face, such as lips and nasal alae, will be "grabbed" by the rotating bristles rather than brushed away, resulting in unintentional, deeper abrasion in these areas.

When performing full-face dermabrasion, beginning at the periphery of the cheek or mandible and working toward the center of the face allows the practitioner to avoid gravity dependent bleeding as the procedure progresses. A surgical towel, surgical cap, or petrolatum may also be used to help prevent entanglement of hair at the periphery of the treatment area. Surgical towels are also preferable to cotton gauze as sponges on the surgical field, as gauze becomes more easily entangled in the wire brush and hand engine.

Postoperative wound care

Gauze soaked with 1% lidocaine with 1:100 000 epinephrine may be immediately applied to the post-abraded area for a period of 5–10 minutes to assist with hemostasis. A closed technique, layered bandage is then applied, composed of a semi-permeable hydrogel dressing (Vigilon, CR Bard, Inc., Covington, GA, USA, or Second Skin, Spenco Medical Corp., Waco, TX, USA) in contact with the wound, a non-adherent dressing (Telfa™, Covidien, Mansfield, MA, USA) above, and paper tape or surgical netting to secure the bandage in place. Semi-permeable hydrogel dressings provide two important advantages over other types of dressings: decreased patient discomfort in the postoperative period and decreased time to re-epithelialization by up to 40% [8]. The dressing should be changed daily for 3–5 days. If full-face dermabrasion has been performed, it is usually most convenient to have the patient return to the office for dressing changes during this period. For smaller areas, the patient may change the bandage at home. After 3–5 days, the patient begins an open wound care technique at home. 0.25% Acetic acid soaks (1 tablespoon white vinegar into 1 pint of warm water) are followed by topical petrolatum ointment until re-epithelialization is complete, usually 7–10 days after the procedure. Strict adherence to this regimen reduces the risk of both secondary infection and scarring.

If full-face dermabrasion is performed, a short course of oral or intramuscular steroids may also be given immediately after the procedure to help reduce facial swelling. Swelling is an anticipated consequence of full-face dermabrasion and may be expected to resolve over several weeks to a few months. All previously prescribed antivirals and antibacterials should be instituted or continued, and patients should be given a prognosis and expected recovery timeframe. Once re-epithelialization has occurred, sunscreens and sun avoidance should be strictly adhered to for several weeks in order to minimize post-procedure pigment alteration. Makeup may be used to cover erythema after re-epithelialization.

Complications

The most common complications encountered after dermabrasion are milia and acne flares (Table 52.1). These minor

Table 52.1 Complications of dermabrasion with suggested treatment.

Complication	Comment	Treatment
Milia and acne flare	Most common	Expression, topical retinoids, oral antibiotics
HSV "breakthrough" infection	Intensely painful erythematous lesions at 7–10 days	Increase antiviral dose (1 g valcyclovir t.i.d. for 7–10 more days)
Bacterial infection	Persistently painful erythematous lesions	Culture and begin empiric therapy with antistaphylococcal antibiotic
Fungal infection	Persistently painful erythematous lesions	Culture and begin empiric therapy with anticandidal agent
Hyperpigmentation	Usually transient	4–8% hydroquinone for 4–8 weeks
Hypopigmentation	Delayed onset, usually permanent	Camouflaging makeup, possibly 308 nm excimer laser
Scarring	Persistent erythema in the absence of infection	Treat early and repeatedly Topical steroids Intralesional steroids Pulsed dye laser

side effects should be anticipated, and may be treated by comedone expression, topical tretinoin, and oral antibiotics.

Infection, pigment alteration, and scarring are the more portentous complications that may be encountered after dermabrasion. Vigilance in the immediate postoperative period is necessary to identify these complications at an early stage and institute treatment. Herpes simplex infection may still occur while the patient is on a prophylactic antiviral dose, and clinically manifests as painful (out of proportion to healing phase), erythematous lesions 7–10 days post-procedure. Larger doses of antiviral medications are then necessary for treatment (1 g valcyclovir t.i.d. for 7–10 more days). Bacterial and fungal infections may likewise produce persistently painful, erythematous lesions. Lesions should be cultured and empiric therapy with an antistaphylococcal or anticandidal agent, or both, should be implemented as warranted by clinical suspicion.

Transient, postoperative hyperpigmentation is a common complication, usually beginning 4–6 weeks after dermabrasion. 4–8% Hydroquinone, or formulations containing hydroquinone, tretinoin, and a mild steroid, should be implemented at the earliest signs of hyperpigmentation and continued for 4–8 weeks.

A more difficult complication to treat is hypopigmentation. While not quite as common as with fully ablative CO_2 laser resurfacing, nearly one-third of patients will develop permanent hypopigmentation after full-face wire brush dermabrasion. Furthermore, such hypopigmentation often does not develop until several months post-procedure. Female patients may camouflage such hypopigmentation with makeup, but male patients have fewer options for improvement. The 308 nm excimer laser has been shown to improve hypopigmented scars and vitiligo, and may be an option for improvement after dermabrasion [9]. True hypopigmentation should be differentiated from the pseudo-hypopigmentation seen when resurfaced skin without actinic damage simply appears lighter than the surrounding actinically damaged skin.

Finally, persistent erythema in the absence of infection is the harbinger of scar formation. Scars should be treated early and proactively in order to minimize sequelae. Flat, erythematous scars may be managed by topical steroids, or steroid-impregnated tape (Cordran, Aqua Pharmaceuticals, LLC, West Chester, PA, USA) worn nightly. However, indurated scars also require intralesional corticosteroid injections and/or pulsed dye laser treatments on a regular basis. These may be repeated every few weeks until stabilization and improvement occur.

Conclusions

With the armamentarium of resurfacing modalities increasing, mechanical dermabrasion remains an important dermasurgical procedure, particularly for the improvement of cystic acne, post-surgical scars, and partial thickness Mohs defects. Selecting appropriate patients and establishing realistic treatment goals are prerequisites. Small areas may be easily and safely treated with proper technique, and these demonstrate a rapid recovery. Although experience and skill are necessary in order to avoid serious complications with full-face dermabrasion, its efficacy for the treatment of acne scarring and deep rhytides currently remains unmatched for the patient who is willing to endure the resultant recovery period. Close follow-up during the postoperative period is important in order to recognize and treat the most serious potential complications of infection and scarring at the earliest stages. While new technologies continue to emerge, mechanical resurfacing will likely remain an essential and unmatched modality for scar improvement into the foreseeable future.

References

1 Murphy GF. (1997) Histology of the skin. In: Elder D, Elenitsas R, Jaworsky E, Johnson BL, eds. *Lever's Histopathology of the Skin*, 8th edn. Philadelphia, PA: Lippincott, pp. 42–3.

2 Kirsner RS. (2008) Wound healing. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*, 2nd edn. Spain: Elsevier, pp. 2147–58.

3 Campbell RM, Harmon CB. (2008) Dermabrasion in our practice. *J Drugs Dermatol* **7**, 124–8.

4 Roenigk HH Jr. (1977) Dermabrasion for miscellaneous cutaneous lesions (exclusive of scarring from acne). *J Dermatol Surg Oncol* **3**, 322–8.

5 Yarborough JM Jr. (1988) Ablation of facial scars by programmed dermabrasion. *J Dermatol Surg Oncol* **14**, 292–4.

6 Coleman WP 3rd, Yarborough JM, Mandy SH. (1996) Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg* **22**, 17–21.

7 Rubenstein R, Roenigk HH Jr, Stegman SJ, Hanke CW. (1986) Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol* **5**, 280–5.

8 Pinski JB. (1987) Dressings for dermabrasion: new aspects. *J Dermatol Surg Oncol* **13**, 673.

9 Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, Geronemus RG. (2004) The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. *Arch Dermatol* **140**, 955–60.

Part 4: Skin Modulation Techniques

Chapter 53: Laser-assisted hair removal

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BASIC CONCEPTS

Current options for hair removal include shaving, epilation, depilatories, electrolysis, and, more recently, lasers.

- Lasers are fast, safe, and effective when used appropriately.
- Selective photothermolysis is the key concept in laser hair removal.
- By varying specific parameters such as wavelength, pulse duration, and fluence, certain specific chromophores may be targeted while protecting other tissues.
- Melanin is the main endogenous chromophore in hair follicles.
- In permanent hair reduction, heat from the laser must spread from the hair shaft to the bulb and the bulge of the hair.
- Adverse effects reported after laser-assisted hair removal include erythema, perifollicular edema, crusting, vesiculation, hypopigmentation, and hyperpigmentation.

Introduction

The use of lasers for hair removal, or photoepilation, is becoming increasingly popular. According to the American Society for Aesthetic Plastic Surgery (ASAPS), nearly 11.7 million cosmetic surgical and non-surgical procedures were performed in the USA in 2007. ASAPS, which has been collecting multispecialty procedural statistics since 1997, notes the number of cosmetic procedures has increased 457% [1]. Laser hair removal is one of the top, non-surgical, cosmetic procedures with 1 412 657 performed in 2007.

Hair removal is of great interest because excess hair, especially in those with hypertrichosis or hirsutism, can be socially and psychologically troubling [2]. The psychosocial importance of hair is great, as noted by patient distress over both hair loss and excess hair [3]. Current options for hair removal include shaving, epilation, depilatories, electrolysis, and, more recently, lasers [4]. All of these hair removal methods possess side effects, yet lasers are fast, safe, and effective when used appropriately. The concept of laser hair removal was defined in 1998 by the US Food and Drug Administration (FDA). Following this, manufacturers were given permission to use the term "permanent hair reduction" in their materials. The FDA definition of permanent hair reduction included "long-term, stable reduction in the number of hairs regrowing after a treatment regimen." Thus, permanent hair removal does not imply the total elimination of hairs [5], but rather a significant reduction in growth rate. Complete hair loss is defined as a lack of regrowing hairs, which can be temporary or permanent. However, permanent hair loss is defined as lack of regrowing hair indefinitely. Hair removal with lasers produces complete but temporary hair loss for 1–3 months [6].

Biology of hair follicles

Hair is a skin appendage, present on the entire body except for the palms and soles. There are approximately 5 million hair follicles on the adult body with a density of 40–800/cm^2. They are made of keratin fibers supported by specialized dermal structures. Hair is formed from the matrix epithelial cells at the base of the hair follicle. The hair matrix is contained in the hair bulb, which is the deep bulbous portion of the hair follicle that surrounds the dermal papilla. The bulge of the hair is the reservoir for hair stem cells. In permanent hair reduction, heat from the laser must spread

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Table 53.1 Hair cycles for various body sites.

Body site	Anagen (%)	Telogen (%)	Anagen duration (months)	Telogen duration (months)	Follicular depth (mm)
Scalp	85	15	24–72	3–4	3–5
Upper lip	65	35	3–4	1–2	1–2
Axillae	30	70	3–4	2–3	3–4
Arms	20	80	2–4	2–4	2–3
Legs	20	80	5–7	3–6	3–4
Bikini area	30	70	1–3	2–3	3–4

from the hair shaft to the bulb and the bulge of the hair. Heating only the hair matrix is not sufficient for permanent hair reduction.

There is no formation of new hair follicles throughout life, so, as the body expands, the density decreases. Hair changes throughout our lifetime. A single follicle can form several different types of hairs ranging from lanugo in preterm newborns to vellus hairs in children to terminal hairs in adults. Lanugo is fine, non-pigmented hairs present at birth. Vellus hairs are fine, short, non-pigmented hairs known as "peach fuzz." Terminal hairs are the thick, usually pigmented, hairs of the scalp and secondary sexual areas. Terminal hairs are the targets of photoepilation.

Hair does not grow continuously, but instead grows in three phases: anagen, catagen, and telogen. The anagen phase is known as the growth phase. Catagen is the transition phase. Telogen is the resting phase. The cycle for scalp hairs is not only asynchronous but lasts 3–5 years. The duration of the hair cycle varies depending on body location (Table 53.1). Photoepilation is most effective during certain phases of the hair growth cycle.

The regulation of hair growth is influenced by genetic factors and hormones, particularly androgens. The function of hair, while primarily psychosocial, serves to protect from mechanical, thermal, and UV damage [3]. Thus, hair removal is important for appearance and not functional reasons. The basic concepts of laser-assisted hair removal are discussed next.

Basic concepts of laser-assisted hair removal

Selective photothermolysis is the key concept in laser hair removal, known as photoepilation. Photoepilation causes thermal destruction of the hair follicle and its associated stem cells at the hair bulge. By varying specific parameters such as wavelength, pulse duration, and fluence, certain specific cutaneous chromophores may be targeted while protecting other tissues [7]. Whether the hair is in telogen at the time of removal is important, because only anagen hairs are sensitive to photothermolysis. Because melanin is the main chromophore in hair follicles, the corresponding wavelength spectrum would range from UV to near-infrared light. Longer wavelengths are preferred, because the chromophore lies deep in the skin and the penetration of light increases with wavelength.

The specific target in laser hair removal is melanin and the light emitted must be within the absorption spectrum of melanin, which is 250–1200 nm [8]. Melanin is an endogenous chromophore found in the hair bulb, bulge, and shaft. Thus, in the range of 600–1100 nm, deep dermal melanin absorption may be used for selective photothermolysis of hair follicles [9].

A drawback to the use of lasers for hair removal, especially in those with darker skin, is that melanin resides in the epidermis. This is problematic because epidermal melanin can interfere with photoepilation by distracting the laser energy, but can also lead to certain side effects, such as epidermal damage and pigmentation. Thus, proper preoperative management is essential to achieving superior results.

Preoperative management

Discrepancy can exist between patient expectations for laser-assisted hair removal and the actual effects of such a treatment. Open communication must exist between the care provider and the patient. Preoperative management for laser hair removal consists of three main steps: history and physical examination, counseling, and preparatory instructions (Table 53.2). First, an accurate patient history must be taken focusing on patient's expectations, current medications, scarring risk, and local infection including history of herpes virus infection in the area of treatment. Along with a complete history, a thorough physical examination is vital.

Table 53.2 Preoperative and postoperative procedures for hair removal.

History	Preoperative care (4 weeks prior to treatment)	Preoperative care (day before treatment)	Day of treatment	Postoperative care
Conditions that may cause hypertrichosis: hormonal, familial, drug, tumor	Sunscreen application	Shave area to be treated	Clean and remove make-up from area to be treated	Ice packs
History of HSV perioral and genitalis	Bleaching cream (hydroquinone) to those with darker skin	When indicated, start prophylactic antiviral	Apply topical anesthetic cream to treatment area 1–2 h prior to treatment	Avoid sun exposure and trauma
History of keloids/hypertrophic scarring	No plucking, waxing, or electrolysis	When indicated, start prophylactic oral antibiotic		Mild topical steroid creams (if necessary)
Previous treatment modalities	Shaving or depilatory creams may be used			Prophylactic antiobiotics/antivirals completed
Current medications				

HSV, herpes simplex virus infection.

Table 53.3 Step-by-step technique for hair removal.

Skin preparation	Visibility	Treatment fluence	Technique	Cooling
Remove anesthetic cream, makeup	Treatment grid or Seymour light in order to prevent skipped areas and double treatment	Ideal treatment parameters individualized for each patient, increase fluence carefully while monitoring for adverse effects	Slightly overlapping laser pulses are delivered with a predetermined spot size and highest tolerable fluence to obtain best results	Cooling gel applied prior to pulses if device is not equipped with cooling feature

The physical examination should assess the aspects of the patient's skin color, health condition, hair color, hair diameter, and hair density.

Following the workup of the patient, a counseling session is necessary. The patient must be advised that 4–6 weeks prior to laser treatment no plucking or other hair removal methods can be used in the treatment areas. Shaving and depilatory creams may be used as these methods do not remove the hair root, which is targeted by the laser. In addition, sun exposure and tanning should be limited. Bleaching of the skin with retinoic acid or hydroquinone can lighten the skin prior to laser treatment. Topical anesthetic creams or cryogenic sprays may be applied to the treatment area to reduce discomfort during the procedure. Cold compresses are also effective in reducing discomfort, erythema, and edema at the treatment area.

The skin surface must be thoroughly cleansed of all makeup, anesthetic creams, and other applicants immediately prior to laser treatment. This may be done with a gentle cleanser, followed by a cloth, and should be allowed to dry completely.

Laser systems are dangerous hazards to the eye. Because there are high concentrations of melanin in the iris and in the retina, these areas are highly susceptible to damage by laser light. Every person in the room during laser treatment should wear protective eyewear that is certified for the wavelength of the laser in use. Because the patient usually lies supine, he or she may require full occlusive eye protection to prevent laser light from entering underneath a sunglasses or goggle type of protective eyewear [6].

Description of techniques

Long pulsed 694 nm ruby laser

The long pulsed ruby laser was the first widely used laser for hair removal (Table 53.3). This laser has the shortest wavelength at 694 nm of all the available lasers for hair reduction. It is absorbed the best by melanin but has the shortest penetration depth. Thus, this would mean that the ruby laser is the most effective at hair removal, but has the greatest potential for epidermal injury. A cooling hand-

piece is used concomitantly during treatment to reduce the risk of injury by lowering the skin's temperature. This laser is ideal for those with light skin and dark hair, and penetrates the skin by only 1–2 mm. This laser is not recommended in darker skin types.

In a study demonstrating the efficacy of the ruby laser, 48 areas of unwanted facial and body hair from 25 patients with blonde, brown, or black hair were treated with the long pulsed ruby laser at fluences of 10–40 J/cm^2. Hair regrowth was measured at 4 weeks after the first treatment, 4 weeks after the second treatment, 4 weeks after the third treatment, and 16 weeks after the third treatment by counting the number of terminal hairs compared with baseline pretreatment values. The mean percent of regrowth after the first treatment was 65.5%, 41% after the second treatment, and 34% after the third treatment. Overall, regardless of skin type or targeted body region, patients who underwent three treatment sessions demonstrated an average 35% regrowth in terminal hair count [10].

Long pulsed 755 nm alexandrite laser

The long pulsed alexandrite laser has a wavelength of 755 nm. This longer wavelength allows deeper penetration into the dermis with less absorption by epidermal melanin. This causes less adverse side effects such as pigmentation in darker skin patients. This laser is still typically used for patients with lighter skin types, but can also be used in those with darker skin. The adverse effects of this laser, when used on patients with darker skin types, can include blistering, crusting, and alterations of pigment, even when skin cooling devices are used. In patients classified as having the darkest skin, residual hypopigmentation or hyperpigmentation is the rule with the alexandrite laser.

Long pulsed 800 nm diode laser

The 800 nm diode laser is comparable to the 755 nm alexandrite laser, and has become more popular along with the neodymium:yttrium aluminum garnet (Nd:YAG) laser for treating patients with darker skin types. The diode laser is more effective for laser-assisted hair removal in patients with dark skin because of the higher absorption by melanin than is seen with the Nd:YAG laser. Still, temporary adverse effects have been reported with the use of the diode laser in the form of postinflammatory hyperpigmentation when used on individuals with dark skin.

A retrospective study of 313 consecutive laser-assisted hair removal treatments was conducted on a total of 23 patients (22 women, 1 man) with 58 anatomic areas by means of an alexandrite laser. The long pulsed alexandrite system was used at a 755 nm wavelength to deliver fluences ranging 17–25 J/cm^2 through a 10 mm spot size. The results showed that patients who undergo more treatment sessions achieve a higher rate of hair reduction; although this may be concomitant with an increase in the incidence of adverse effects. The benefit of more laser treatments should be balanced with the risk of occurrence of side effects in each patient [11].

1064 nm Nd:YAG laser

The 1064 nm Nd:YAG has the longest wavelength and deepest penetration amongst the aforementioned laser systems available. It is not very well absorbed by melanin, but is sufficient in achieving selective photothermolysis and has superior penetration. This laser is able to penetrate the skin to 5–7 mm, a depth at which most of the target structures lay. Furthermore, the combination of a low melanin absorption and deep penetration leads to less collateral damage to the melanin-containing epidermis. These features make this particular laser the safest method to treat all skin types, especially darker skinned patients (Figure 53.1). Unfortunately, while this laser may be the safest, it is not the most effective. In a study by Bouzari *et al*. [12], hair reduction by the long pulsed Nd:YAG, alexandrite, and diode lasers were compared. They found

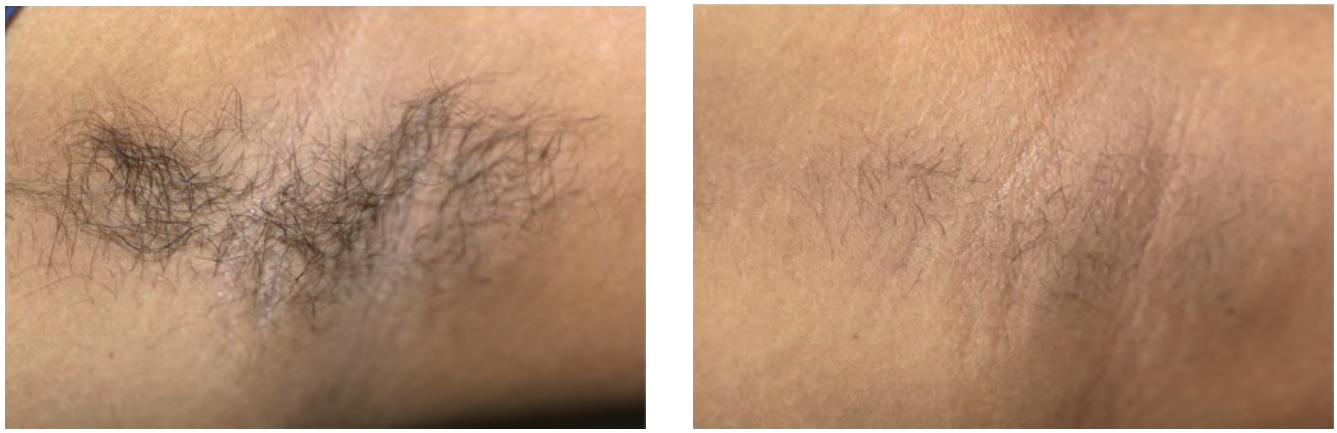


Figure 53.1 (a) Pretreatment of the right axillary area with coarse hair. (b) Only fine hair exists after 3 months after five treatments with a 1064 nm Nd:YAG laser.

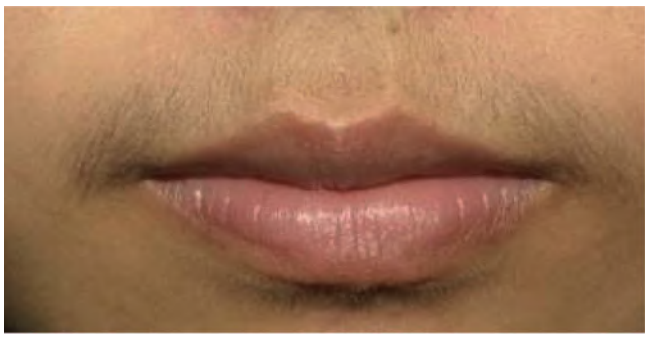
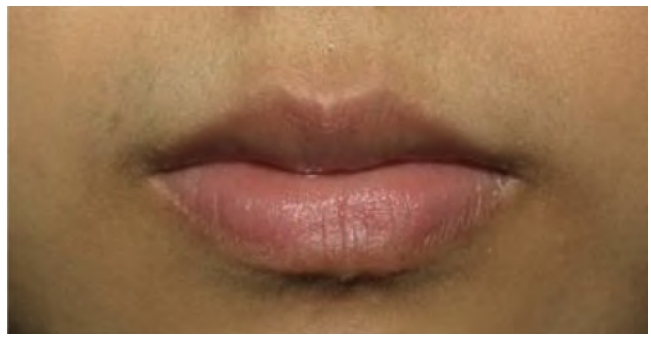
(a)   (b)

Figure 53.2 (a) Pretreatment of the upper lip area. (b) Seven weeks after two treatments with intense pulsed light (IPL) system.

that after 3 months, the Nd:YAG was the least effective of the three.

Intense pulsed light

The intense pulsed light (IPL) system is not a laser, but has recently entered the hair removal realm as a competent contender. It has been used for virtually all of the same indications as laser systems. IPL systems utilize a xenon bulb as a light source, which produces polychromatic light with wavelengths of 515–1200 nm. This is in contrast to laser light sources, which produce monochromatic light of a specific wavelength. Light emitted by the bulb passes through a filter that excludes shorter wavelengths which may severely damage skin. The ability to "tune" the wavelength of light emitted by these systems gives IPL systems the advantage of versatility. Using different filters, a pulsed light system could mimic any number of laser systems, allowing the operator to treat many different conditions amenable to light therapy, including, of course, the removal of unwanted hair (Figure 53.2).

Radiofrequency combinations

Radiofrequency devices have been combined with both IPL and diode lasers to provide optimal hair removal treatments to a wider range of skin types. The combinations are considered safe for patients with darker skin types because the radiofrequency energy is not absorbed by melanin in the epidermis. This technology, termed electro-optical synergy (ELOS) has a dual mechanism of heating the hair follicle with electrical energy (radiofrequency) and heating the hair shaft with optical energy.

Other removal methods for non-pigmented hair

Meladine, a topical melanin pigment, has been studied in Europe with interesting results. The liposome solution dye, which is sprayed on, is selectively absorbed by the hair follicle and not the skin. This in turn gives the follicles a temporary boost of melanin to optimize laser hair removal treatments. Clinical studies in Europe have shown vast permanent hair reduction in patients who used meladine prior to treatment. However, other studies have found meladine to only offer a delay of hair growth as opposed to permanent hair reduction [6].

Another option for non-pigmented hair removal is photodynamic therapy. A photosensitizer such as 5-aminolevulinic acid (5-ALA) is used because non-pigmented hair lacks a natural chromophore. In a study conducted to compare the 6-month hair removal efficacy of a combined pulsed light bipolar radiofrequency device with and without pretreatment using topical 5-ALA, researchers found that an average terminal white hair removal of 35% was observed at 6 months after treatment with the combined pulsed light bipolar radiofrequency device. When pretreatment with topical 5-ALA was provided the average hair removal of terminal white hairs was found to be 48%. This finding can be explained by the fact that light exposure activates the 5-ALA, which leads to the formation of reactive oxygen elements and slows for hair follicle destruction [13].

Postoperative management

Postoperative management consists of reducing pain and minimizing edema. This can be done using ice packs. Mild topical steroid creams can also be used to decrease redness. Antibiotics should be given if epidermal injuries occur during the procedure.

Complications

Although there is no obvious advantage of one laser system over another in terms of treatment outcome (except the Nd:YAG laser, which is found to be less efficacious, but more suited to patients with darker colored skin), laser parameters

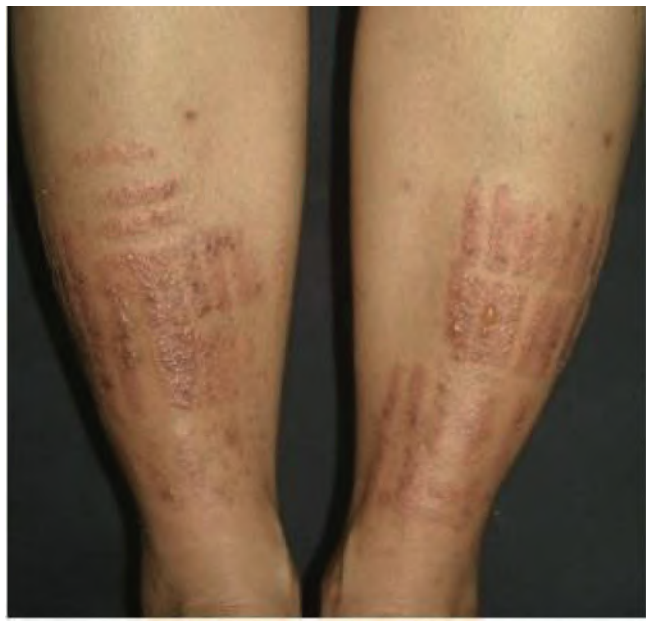


Figure 53.3 Blister formation 3 days after treatment with IPL system.

may be important when choosing the ideal laser for a patient. Adverse effects reported after laser-assisted hair removal including erythema and perifollicular edema, which are common, and crusting and vesiculation of treatment site, hypopigmentation, and hyperpigmentation (depending on skin color and other factors) (Figure 53.3).

Most complications are generally temporary. The occurrence of hypopigmentation after laser irradiation is thought to be related to the suppression of melanogenesis in the epidermis (which is reversible), rather than the destruction of melanocytes. Methods to reduce the incidence of adverse effects include lightening of the skin and sun avoidance prior to laser treatment, cooling of the skin during treatment, and sun avoidance and protection after treatment. Proper patient selection and tailoring of the fluence used to the patient's skin type remain the most important factors in efficacious and well-tolerated laser treatment. While it is generally believed that hair follicles are more responsive to treatment while they are in the growing (anagen) phase, conflicting results have also been reported. There is also no consensus on the most favorable treatment sites [14]. In addition, patients should be cautious and not use numbing agents on large areas of their body for prolonged periods of time as this can lead to adverse reactions.

Future directions

Laser hair removal is not FDA approved to be marketed as a permanent hair removal treatment. Further, manufacturers may not claim that laser hair removal is either painless or permanent unless the FDA determines that there are sufficient data to demonstrate such results. Several manufacturers received FDA permission to claim, "permanent reduction," not "permanent removal" for their lasers. This means that although laser treatments with these devices will permanently reduce the total number of body hairs, they will not result in a permanent removal of all hair.

There is a new laser hair removal device that the FDA has approved for at home use and over-the-counter sales. This new device is known as TRIA. SpectraGenics announced clearance from FDA for their patented hand-held laser hair removal device designed for at-home use. The TRIA is the first hair removal laser to enter the US home-based device market, an industry projected to grow exponentially over the next 3 years.

Conclusions

Up to 22% of women in North America have excessive or unwanted facial hair. Men also feel compelled to rid themselves of unwanted body hair, as dictated by popular culture and appearance anxieties. Excessive facial hair can negatively impact on one's quality of life. Prior options to hair removal have been painful, tedious, resulted in frustrated clients, and caused short-term effects. With the advent of laser technology, laser and light systems have becomes some of the most popular procedures. While this is still not a permanent solution to hair removal, is a safe, fast, and effective method for hair reduction.

References

1 American Society for Aesthetic Plastic Surgery (ASAPS). (2007) ASAPS 2007 Cosmetic Surgery National Data Bank Statistics. http://www.surgery.org/download/2007stats.prf Accessed 2008 Aug 20.

2 Nouri K, Trent JT. (2003) Lasers. In: Nouri K, Leal-Khouri S, eds. *Techniques in Dermatologic Surgery*. St. Louis: Mosby, pp. 245–58.

3 Rassner G. (2004) *Atlas of Dermatology*. Philadelphia, PA: Lea & Febiger, pp. 224–6.

4 Olsen EA. (1999) Methods of hair removal. *J Am Acad Dermatol* **40**, 143–55.

5 Food and Drug Administration. (1998) FDA docket K980517. July 21.

6 Dierickx C, Crossman M. (2005) Laser hair removal. In: Golderg DJ, ed. *Lasers and Lights*, Vol. 2. China: Elsevier-Saunders, pp. 61–76.

7 Anderson RR, Parrish JA. (1983) Selective photothermolysis: precise microsurgery by selective abdorption of pulsed radiation. *Science* **220**, 524–7.

8 Battle EF, Hobbs LM. (2003) Lasers in dermatology: four decades of progress. *J Am Acad Dermatol* **49**, 1–31.

9 Mandt N, Troilius A, Drosner M. (2005) Epilation today: physiology of the hair follicle and clinical photoepilation. *J Investig Dermatol Symp Proc* **10**, 271–4.

10 Williams R, Havoonjian H, Isagholian K, Menaker G, Moy G. (1998) Clinical study of hair removal using the long-pulsed ruby laser. *Dermatol Surg* **24**, 837–42.

11 Bouzari N, Nouri K, Tabatabai H, Abbasi Z, Firooz A, Dowlati I. (2005) The role of number of treatments in laser-assisted hair removal using a 755-nm alexandrite laser. *J Drugs Dermatol* **4**, 573–8.

12 Bouzari N, Tabatabai H, Abbasi Z, Firooz A, Dowlati Y. (2004) Laser hair-removal: comparison of long-pulsed Nd:YAG, long-pulsed aleandrite, and long-pulsed diode alsers. *Dermatol Surg* **30**, 498–502.

13 Goldberg DJ, Marmur ES, Hussain M. (2005) Treatment of terminal and vellus non-pigmented hairs with an optical/bipolar radiofrequency energy source: with and without pre-treatment using topical aminolevulinic acid. *J Cosmet Laser Ther* **7**, 25–8.

14 Liew SH. (2002) Laser hair removal: guidelines for management. *Am J Clin Dermatol* **3**, 107–15.

Chapter 54: Radiofrequency devices

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BASIC CONCEPTS

- Radiofrequency devices have been introduced for non-surgical skin tightening of facial and non-facial skin.
- The mechanism of action of these devices involves an initial immediate collagen contraction and a secondary wound healing response producing collagen deposition and remodeling with skin tightening over time.
- Radiofrequency devices can be divided into monopolar and bipolar categories.
- Monopolar radiofrequency utilizes an electrical current passed from the radiofrequency energy source through a monopolar electrode in the hand-piece and the current continues through the patient to the grounding pad, which completes the circuit.
- Bipolar radiofrequency in conjunction with light and vacuum offer more superficial treatments, and, most recently, a combined unipolar and bipolar radiofrequency device has been introduced with control of depths of radiofrequency energies.

Introduction

Radiofrequency devices have been introduced for non-surgical skin tightening of facial and non-facial skin. The mechanism of action of these devices involves an initial immediate collagen contraction and a secondary wound healing response producing collagen deposition and remodeling with skin tightening over time. There has been a great deal of controversy surrounding the use of these devices when they were first introduced for non-surgical skin tightening. With the advent of newer protocols utilizing lower energies and multiple passes, the safety and efficacy of radiofrequency devices is increasing.

Radiofrequency devices

Radiofrequency devices can be divided into monopolar and bipolar categories (Table 54.1). Monopolar radiofrequency utilizes an electrical current passed from the radiofrequency energy source through a monopolar electrode in the hand-piece and the current continues through the patient to the grounding pad, which completes the circuit. The Thermage device is an example of monopolar radiofrequency. Bipolar radiofrequency devices employ a closed system and are usually combined with other sources. Examples include systems using bipolar radiofrequency and light (electro-optical synergy systems), bipolar radiofrequency and vacuum, and a combination of unipolar and bipolar radiofrequency to deliver different depths of radiofrequency current to the skin.

Monopolar radiofrequency

Monopolar capacitive radiofrequency was the first commercially available device to be introduced for non-surgical skin tightening and is the most widely studied. The generation of heat occurs because of natural tissue resistance to the movement of electrons within a radiofrequency field which creates heat relative to the amount of current and time. The different components of skin (dermis, fat, subcutaneous tissue, muscle, and fibrous tissue) have varying resistance to the movement of radiofrequency energy. For example, the fibrous septa are heated more than the surrounding subcutaneous tissue.

Controlled radiofrequency pulses selectively heat zones of the dermis and deeper tissue with the use of cryogen delivery to protect and cool the epidermis. A pressure-sensitive tip prevents the non-uniform application of energy to the skin and the cryogen delivery minimizes epidermal compromise and assists in comfort of the procedure.

The initial approach to utilize monopolar radiofrequency for skin tightening employed very high fluencies with one to two treatments. The discharge time was slow and the protocol was to utilize the highest tolerable fluence with a single pass over the entire treated area. With this protocol, the results were modest at best with significant pain. Moreover, the discharge time of the tip was slow at 5–6 seconds. In addition to significant discomfort and high variability in efficacy, infrequent reports of subcutaneous tissue

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Table 54.1 Examples of radiofrequency devices.

Device	Mechanism
Thermacool (Solta Medical)	Unipolar radiofrequency
Aluma (Lumenis)	Bipolar radiofrequency
ELOS devices (Syneron)	Bipolar radiofrequency
Accent (Alma lasters)	Unipolar and bipolar radiofrequency

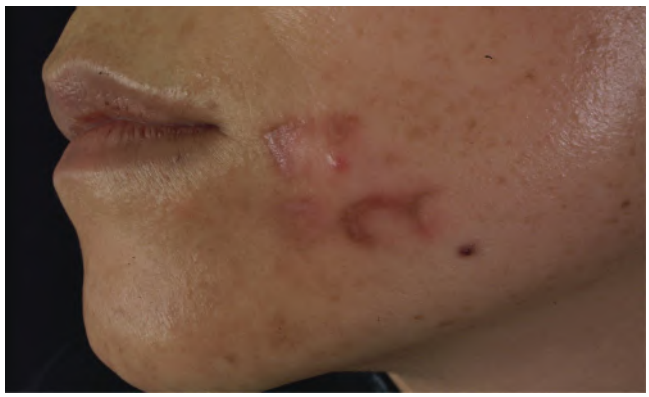

Figure 54.1 Subcutaneous atrophy from unipolar radiofrequency using old protocol with high fluencies.

depressions were reported (Figure 54.1). As a result, the treatment received much skepticism and criticism.

The Thermacool device utilizes monopolar radiofrequency energy with a maximal output of 225 J/cm^2 with a peak temperature 2–3 mm beneath the surface. Upon activation of the device, a cooling system which uses a cryogen spray is activated and internally precools the electrode. The cryogen continues to be delivered during (parallel cooling) and after (post-cooling) the energy delivery. The initial treatment cycle consisted of 6 seconds but the newer protocol is about 2 seconds.

A new protocol was developed to overcome these limitations based on observations and studies demonstrating that low fluence delivery with multiple passes of monopolar radiofrequency can produce a more reproducible clinical endpoint. Histologic correlations to these findings demonstrated greater collagen denaturation at multiple passes using lower energies. In addition, lower energies produced less discomfort and greater patient satisfaction. A consensus panel published these findings with the following criteria:
1 Use of patient feedback about heat sensation as a valid and preferred method for selecting the optimal amount of energy;
2 Use of multiple passes at moderate energy settings to yield consistent efficacy; and
3 Treatment to a clinical endpoint of visible tightening and contouring for maximizing predictability and long-term results.
With the original treatment protocol (single pass and high fluence) 26% of patients showed immediate tightening and 54% showed delayed tightening. With the new protocol, 87% showed immediate tightening and 92% noted tightening after 6 months, with 94% of patients of the patients showing satisfaction.

The largest studied areas for monopolar radiofrequency are the midface, lower face, and neck. The technique with the new protocol utilizes a tip that can deliver up to 900 pulses using multiple low fluence passes (typically 450 per each side of the face and neck). Treatments are administered without any topical anesthesia or intravenous sedation, as patient feedback is critical for outcomes. Up to 10 passes are performed using this algorithm.

The greatest challenge in all skin tightening modalities is patient selection and setting expectations. Because three-dimensional changes are often difficult to capture in two-dimensional photography, it is imperative to have a detailed and thorough consultation to set realistic expectations. In our practice, we perform a detailed consultation to discuss the realistic goals of monopolar radiofrequency and emphasize the variability in results. Standardized photography is absolutely critical with standardized lighting and angles to capture subtle changes. Our criteria for patient selection include the following:
1 Patients who are absolutely averse to any surgical procedures for laxity such as rhytidectomy.
2 Patients who have had rhytidectomy and are showing signs of laxity.
3 Patients who are not surgical candidates because of risks associated with surgery.
4 Post-surgical patients who still show some laxity.
5 Off face loose skin, for which there are no other options.
We also offer this procedure to candidates who seek subtle body contouring, with emphasis on the word subtle.

Complications

Complications with monopolar radiofrequency are rare. With the old protocol, subcutaneous depressions were seen. Common transient side effects include mild erythema and edema. Slight tenderness post-treatments have been reported. Lack of proper contact with the skin can produce burns. With the new protocol, there have been no reports of permanent complications. All skin types can be treated, as radiofrequency is truly color blind and does not compete with melanin chromophores. There have been no reports of postinflammatory hyperpigmentation.

Future directions

New directions for monopolar radiofrequency are the introduction of several new tips to address specific areas. These

include tips for eyelid rejuvenation and large area body contouring. Eyelid rejuvenation has been one of the most exciting and innovative developments in monopolar radiofrequency tips. A shallow 0.25 cm^2 tip is utilized which delivers heat more superficially than the medium depth tips utilized for facial and body areas. Plastic corneoscleral shields are placed prior to treatment. Ideal candidates for eyelid treatment include patients with mild to moderate dermatochalasis and good skin tone and patients who have previously had blepharoplasty and show signs of skin laxity. With low fluence and multiple pass protocol, upper eyelid tightening and reduction of hooding has been seen in over 80% of patients. The newest addition to the tip armamentarium is the large diameter deep tip for large body areas. One of the limitations of treating large body areas has been the amount of time required for treatments. Recently, a 16 cm^2 deep tip was introduced which has shortened the treatment time by 50%. This allows for more efficient treatments of large body areas such as abdomen, buttocks, and flanks.

Summary

Monopolar radiofrequency, in summary, is the most widely studied modality for non-surgical skin tightening. The initial protocol has been modified with a low energy multiple pass algorithm to reduce discomfort and achieve more predictable outcomes. While midface and lower neck were the initial areas for treatments, the advent of varying depth tips has expanded the use for the treatment of eyelids and off face areas such as the abdomen, buttocks, and flanks. The biggest challenge in treatment outcomes is predictability of results, which are variable. Therefore, a thorough consultation setting realistic patient expectations and "underpromising" results are key for optimal outcomes. It is imperative to emphasize that these procedures are not a subsititute for surgery and will not address severe laxity.

To further enhance outcomes of monopolar radiofrequency treatments, combination therapy approaches are being investigated. Most recently, we have initiated combining non-ablative fractional resurfacing, monopolar radiofrequency, and dermal fillers. Combination therapy is becoming the mainstay of treatments for a variety of non-surgical procedures. The combined non-ablative fractional resurfacing and monopolar radiofrequency procedure has been coined "Thermafrax," with the fractional resurfacing addressing dyschromia, superficial rhytids, and the monopolar radiofrequency addressing laxity. The treatments can be performed on the same day or as staged procedures. The radiofrequency treatments are performed first, as patient feedback is necessary and anesthesia cannot be used. This is followed by non-ablative fractional resurfacing. Dermal fillers are performed last for any volume depletion. Facial and non-facial skin can be effectively treated with this approach. Hand rejuvenation with combination of monopolar radiofrequency, non-ablative fractional resurfacing, and dermal fillers is becoming increasingly popular, with each modality complementing the other – radiofrequency addressing laxity, fractional resurfacing addressing dyschromia and photodamage, and fillers addressing volume loss (Figure 54.2).

Bipolar radiofrequency and light

The second commercially introduced modality for non-invasive skin tightening employed the combination of bipolar radiofrequency and light energy devices (900 nm diode laser in a single pulse or broadband light in the 700–2000 nm wavelength in a single pulse). The theory behind the use of two technologies is the safer delivery of radiofrequency energy, with the optical component enabling the bipolar

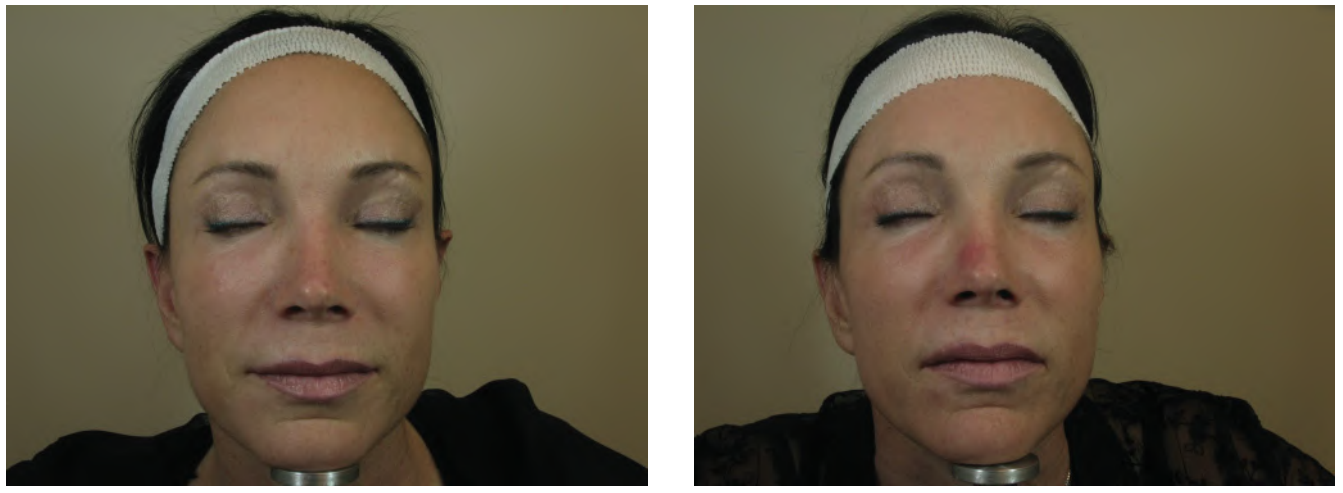

Figure 54.2 (a) Pre-Thermage and Fraxel laser. (b) Post-Thermage and Fraxel laser.

radiofrequency energy to concentrate where the optical energy has selectively heated the target. Optical energy levels of 30–50 J/cm^2 with radiofrequency levels of 80–100 J/cm^2 are utilized in this mode. Three to four passes are usually performed and, unlike monopolar radiofrequency, 3–5 treatment sessions are necessary, as opposed to a single treatment.

The main indication for bipolar radiofrequency and light combination devices is diminution of superficial rhytids. There may be some subtle tissue tightening. There is much controversy regarding the synergistic effects of light and radiofrequency energies. The use of lower optical energies makes this a safe device in all skin types. However, because the radiofrequency energy does not penetrate very deep into the skin, tissue arcing can occur with improper technique, resulting in scar formation.

The majority of published clinical studies using these devices have focused on the treatment of mild to moderate rhytids with modest improvement. The amount of energy penetration with these devices does not produce deep volumetric heating and subsequent tightening compared with monopolar radiofrequency.

Bipolar radiofrequency and vacuum

Bipolar radiofrequency with vacuum was introduced to reduce discomfort associated with radiofrequency devices. The bipolar radiofrequency energy with an accompanying vacuum apparatus allows the tissue into the vacuum and targets the radiofrequency energy to the deep dermis. Less energy is necessary for treatment efficacy, as the vacuum brings the electrodes closer to the dermis, with the additional benefit of reducing pain. The main indications for this technology are subtle improvement of fine rhytids and tissue tightening.

Unipolar and bipolar radiofrequency device

Different depths of radiofrequency energy can be delivered to the skin – bipolar for more superficial heating and unipolar for deeper heating. It is a closed system and does not require grounding, as monopolar radiofrequency. Published data are limited and there is some evidence in the reduction of the appearance of cellulite and subtle tissue tightening.

Conclusions

Non-surgical tissue tightening has evolved considerably since its first introduction. Monopolar radiofrequency using a new treatment algorithm remains the gold standard of radiofrequency, with the largest series of published papers, longest clinical experience, and modifications for optimal outcomes. Bipolar radiofrequency in conjunction with light and vacuum offers more superficial treatments, and, most recently, a combined unipolar and bipolar radiofrequency device has been introduced with control of depths of radiofrequency energies.

The greatest challenge in all modalities of radiofrequency treatments is predictability of outcomes. Patient selection with a thorough consultation reviewing realistic expectations is key for successful outcomes. The development of newer algorithms with standardized protocols is allowing for more reproducible outcomes in using these devices for non-surgical skin tightening.

Further reading

Alster TS, Tanzi E. (2004) Improvement of neck and cheek laxity with a nonablative radiofrequency device: a lifting experience. *Dermatol Surg* **30**, 503–7.

Biesman B, Baker SS, Carruthers J, Silva JL, Holloman EL. (2006) Monopolar radiofrequency treatment of human eyelids: a prospective multicenter efficacy trial. *Lasers Surg Med* **38**, 890–8.

Doshi SN, Alster TS. (2005) Combination radiofrequency and diode laser for treatment of facial rhytids and skin laxity. *J Cosmet Laser Ther* **7**, 11–5.

Dover JS, Zelickson BD. (2007) 14 physician multispecialty consensus panel. Results of a survey of 5700 patient monopolar radiofrequency facial skin tightening treatments: assessment of a low energy multiple pass technique leading to a clinical endpoint algorithm. *Dermatol Surg* **33**, 900–7.

Emilia del Pino M, Rosado RH, Azuela A, Graciela Guzmán M, Arqüelles D, Rodríguez C, *et al.* (2006) Effect of controlled volumetric tissue heating with radiofrequency on cellulite and the subcutaneous tissue of the buttocks and thighs. *J Drugs Dermatol* **5**, 714–22.

Fitzpatrick R, Geronemus R, Goldberg D, Kaminer M, Kilmer S, Ruiz-Esparza J. (2003) Multicenter study of noninvasive radiofrequency for periorbital tissue tightening. *Lasers Surg Med* **33**, 232–2.

Fritz M, Counters JT, Zelickson BD. (2004) Radiofrequency treatment for middle and lower face laxity. *Arch Facial Plast Surg* **6**, 370–3.

Gold MH. (2007) Tissue tightening: a hot topic utilizing deep dermal heating. *Drugs Dermatol* **6**, 1238–42.

Gold MH, Goldman MD, Rao J, Carcamo JS, Ehrlich M. (2007) Treatment of wrinkles and elastosis using vacuum assisted bipolar radiofrequency heating of the dermis. *Dermatol Surg* **33**, 303–9.

Jacobson LG, Alexiades-Armenakis M, Bernstein L, Geronemus RG. (2003) Treatment of nasolabial folds and jowls with a noninvasive radiofrequency device. *Arch Dermatol* **139**, 1371–2.

Lack EB, Rachel JD, D'Andrea L, Corres J. (2005) Relationship of energy settings and impedance in different anatomic areas using a radiofrequency device. *Dermatol Surg* **31**, 1668–70.

Sadick NS. (2005) Combination radiofrequency and light energies: electro-optical synergy technology in esthetic medicine. *Dermatol Surg* **31**, 1211–7.

Weiss RA, Weiss MA, Munavalli G, Beasley KL. (2006) Monopolar radiofrequency facial tightening: a retrospective analysis of efficacy and safety in over 600 treatments. *J Drugs Dermatol* **5**, 707–12.

Yu CS, Yeung CK, Skek SY, Tse RK, Kono T, Chan HH. (2007) Combined infrared light and bipolar radiofrequency for skin tightening in Asians. *Lasers Surg Med* **39**, 471–5.

Chapter 55: LED photomodulation for reversal of photoaging and reduction of inflammation

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BASIC CONCEPTS

- Photomodulation uses of non-thermal light treatments to regulate the activity of cells rather than to invoking thermal wound healing mechanisms.
- Photomodulation stimulates cells to perform certain functions using light packets that are low energy and enhance cell metabolism.
- LED arrays for photomodulation are useful for collagen stimulation, textural smoothing, and reduction of inflammation.

Introduction

Photorejuvenation encompasses many procedures using light or laser-based technology to reverse the effects of photoaging. Photoaging, a huge component of which is dermal collagen degeneration, is compounded by environmental damage including smoking, pollutants, and other insults causing free radical formation. Non-ablative photorejuvenation refers to the controlled use of thermal energy to accomplish skin rejuvenation without disturbance of the overlying epidermis and with minimal to no down-time. Currently employed non-ablative modalities include primarily intense pulsed light (IPL), visible wavelengths including pulsed dye laser (PDL), and 532 nm green light (KTP laser) [1]. Various infrared wavelengths with water as the target are used for remodeling dermal collagen. Because absorption by melanin is negligible, these devices can be used for all skin types and these include 1064, 1320, 1450, and 1540 nm [2,3]. The primary mechanism of action is thermal injury either by heating the dermis to stimulate fibroblast proliferation or by heating blood vessels for photocoagulation [4–6]. The newest way to deliver these wavelengths is by fractionating the dose through microlenses that allow microthermal zones surrounded by normal skin [7].

A non-thermal mechanism, which represents a fundamental change in thinking, is the theory of photomodulation. This concept involves the stimulation of cells to perform certain functions using light packets that are low energy and stimulate cell metabolism. This novel approach to photoaging uses non-thermal light treatments to regulate activity of cells rather than to invoke thermal wound healing mechanisms [8,9]. This incurs far less risk for patients than other light modalities. The first written report on using photomodulation to improve facial wrinkles was in 2002 [10].

Photomodulation was first discovered from use of LED and low energy light therapy (LILT) in stimulating growth of plant cells [11]. The belief that cell activity can be upregulated or downregulated by low energy light had been discussed in the past, but consistent or impressive results had been lacking [12,13]. Some promise had been shown with wound healing for oral mucositis [13]. Wavelengths previously examined included a 670 nm LED array [13], a 660 nm array [14], and higher infrared wavelengths [15]. Fluence and duration of exposure were variable in these studies with high energy required for modest results [13].

To investigate LED light for rejuvenation purposes, a fibroblast culture model was utilized in conjunction with clinical testing. Particular packets of energy with specific wavelengths combined with using a very specific propriety pulse sequencing "code" were found to upregulate collagen I synthesis in fibroblast culture using reverse transcription polymerase chain reaction (RT-PCR) to measure collagen I [10]. The upregulation of fibroblast collagen synthesis correlated with the clinical observation of increased dermal collagen on treated human skin biopsies [16]. Curiously, both in the fibroblast and clinical model, collagen synthesis was accompanied by reduction of matrix metalloproteinases

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(MMP). In particular, MMP-1 (collagenase) was greatly reduced with exposure to 590–870 nm low energy light. Use of very low energy, narrow band light with specific pulse code sequences and durations was termed LED photomodulation by McDaniel *et al*. [10]. A device that utilizes pulsed code sequences of LED light to induce photomodulation was termed Gentlewaves® (Gentlewaves, Inc., Charlotte, NC, USA) and patented by McDaniel.

Clinical applications

LED photomodulation can be used both alone and in combination with a variety of common, non-ablative, rejuvenation procedures in an office setting. Several anti-inflammatory and wound healing applications are also possible. Treatments were delivered using the yellow/infrared light LED photomodulation unit with a full face panel. Energy density was set at 0.15 J/cm^2 and 100 pulses were delivered with a pulse duration of 250 ms and an off interval of 100 ms. Treatment time was approximately 35 seconds.

Photorejuvenation

This technique was evaluated on 6000+ patients over the last 6 years. Of these treatments, 10% were LED photomodulation alone and 90% were concomitant with a thermal-based photorejuvenation procedure. Using specific pulsing sequence parameters, which are the basis for the LED photomodulation "code," the original multicenter clinical trial was conducted with 90 patients receiving a series of eight LED treatments over 4 weeks [17–20]. This study showed positive results, with over 90% of patients improving by at least one Fitzpatrick photoaging category and 65% of the patients demonstrating global improvement in facial texture, fine lines, erythema, and pigmentation. Results peaked at 4–6 months following completion of a series of eight treatments [20]. Another retrospective study, using the same 590–870 nm LED array (Gentlewaves®), demonstrated similar results (Figure 55.1). These results were confirmed by digital microscopy [21].

Most recently, the 590 nm LED array was used in an independent clinical laboratory confirming the findings (data on file, L'Oréal Research, France). An additional clinical trial involving 65 subjects used silicone replica impressions of lateral canthal wrinkles (crow's feet). These replicas, illuminated by reproducible lighting both parallel and perpendicular to each wrinkle, were analyzed with image-analyzing software (Quantirides, Monaderm, Monaco). The analysis showed a significant reduction in the number of wrinkles 2–4 months after treatment accompanied by a significant reduction in the length of wrinkles at 5 months post-treatment. Subject self-assessment showed significant improvement in skin wrinkles, texture, softness, and radiance.

Others have confirmed that additional wavelengths of LED light, using red and infrared wavelengths, may be effective for skin texture improvement. Although these treatments were longer in duration, 36 patients receiving nine treatments over a 5-week period showed improvement in skin softness [22]. Each treatment was administered in continuous mode, without pulsing, with a treatment time of 20 minutes using 633 and 830 nm as an LED array (Omnilux™, Phototherapeutics, Altrincham, Cheshire, UK). Another

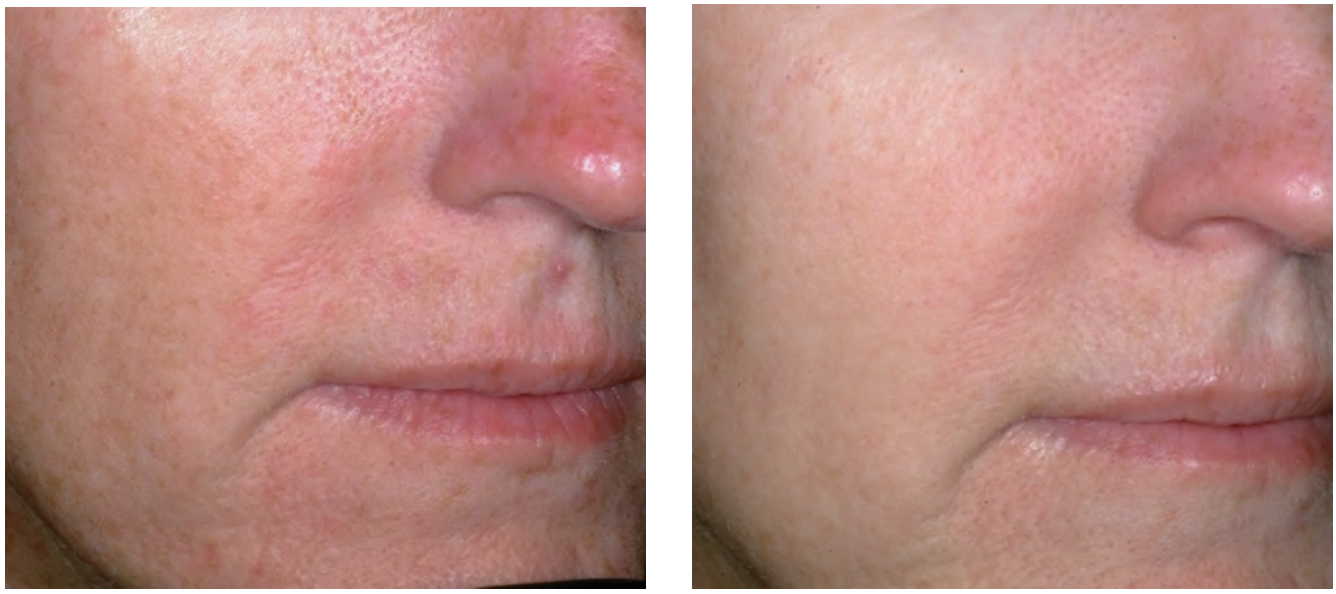


Figure 55.1 Smoothing of the skin seen after eight treatments over 4 weeks of Gentlewaves® photomodulation (Gentlewaves, Inc., Charlotte, NC, USA) (a) Before treatments. (b) Eight weeks after baseline. Reduction in wrinkles, pigmentation and improvement of texture are noted.

recent report using this system studied 31 subjects with facial rhytids who received nine light therapy treatments using combined wavelengths of 633 and 830 nm. Fluences were relatively high utilizing 126 J/cm^2 for 633 nm and 66 J/cm^2 for 830 nm. Improvements to the skin surface were reported at weeks 9 and 12 by profilometry performed on periorbital replicas. Results showed that 52% of subjects showed a 25–50% improvement in photoaging scores [23].

In the USA, the first Food and Drug Administration (FDA) cleared LED device to be used in the reduction of periocular wrinkles was in 2005 (Gentlewave; Figure 55.2). Other devices (Omnilux™, Photo Therapeutics Ltd., Altrincham, Cheshire, UK) then followed.

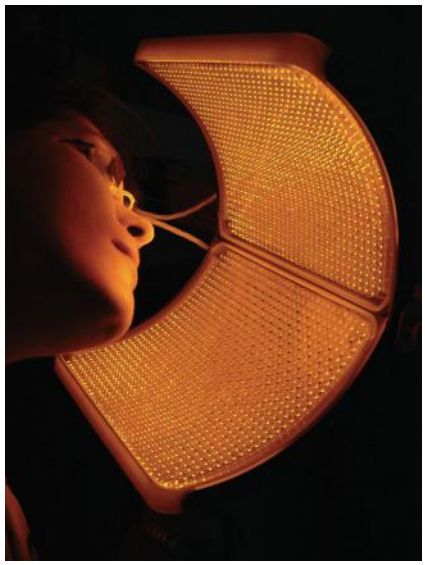


Figure 55.2 Gentlewaves LED photomodulation device. Array of LEDs.

Anti-inflammatory effects

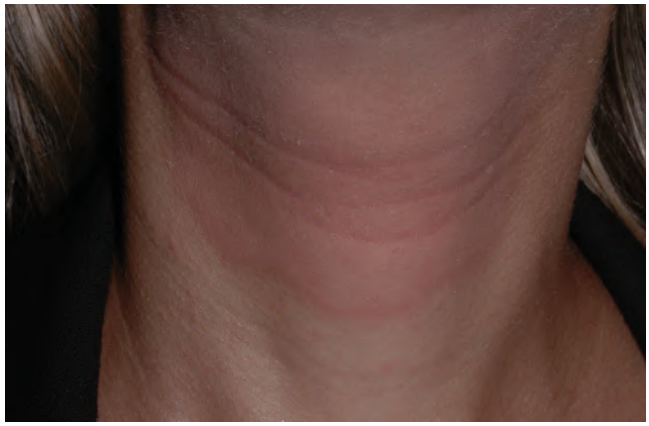
Photomodulation can also be used for the reduction of erythema from a variety of causes. Erythema may be induced from wide ranging skin injuries including but not limited to thermal laser treatments, UV burns, radiation therapy, blunt trauma, and skin disease. Treatment of atopic eczema in patients withdrawn from all topical medications led to resolution with 3–4 treatments over 1–2 weeks (Figure 55.3).

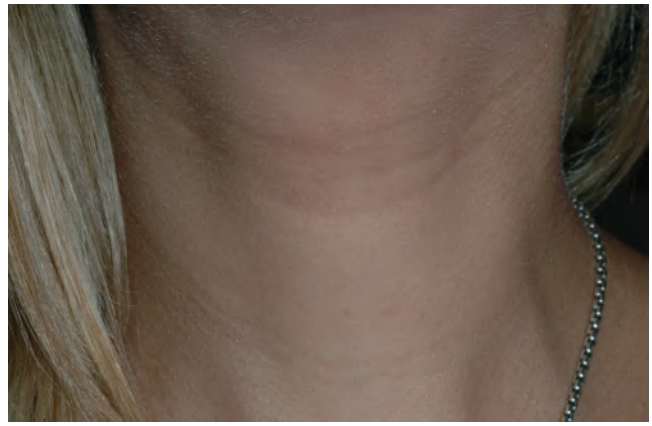
Use of LED photomodulation in combination with other laser modalities may results in faster erythema resolution. The enhanced erythema resolution may be a result of the anti-inflammatory effects of LED photomodulation. The mechanism has not yet been elucidated but downregulation of inflammatory mediators from lymphocytes or macrophages is possible. Studies on human skin fibroblasts treated with LED photomodulation have shown a reduction in interleukins IL-1B1 and IL-6 [24].

A recent study looked at whether LED photomodulation therapy could accelerate resolution of post-intense pulsed light (IPL) erythema [25]. Fifteen subjects were randomized to receive LED treatment to one side of the face immediately following a single IPL treatment for photodamage. Results showed mean erythema scores on the first visit were statistically significantly lower on the LED-treated side. This led the authors to conclude that LED photomodulation treatment may accelerate resolution of erythema following IPL treatment [25].

A study on radiation dermatitis examined whether LED photomodulation could alter and improve the outcome of intensity-modulated radiation treatments (IMRT) on overlying breast skin. Nineteen patients with breast cancer were

(a)





(b)

Figure 55.3 (a) Before shows flare of eczema following withdrawal of all therapy. (b) Atopic eczema after three treatments with Gentlewave LED photomodulation. The after image (b) shows effects of reduction of inflammation by LED photomodulation within 10 days.

treated with LED photomodulation immediately after every radiation session. Treatments were administered to post-lumpectomy patients receiving a full course of IMRT [26]. Skin reactions were monitored weekly using National Cancer Institute (NCI) criteria for grading. Age-matched controls (n = 28) received IMRT without LED photomodulation. The results of this study showed that LED treatment had a significantly positive effect. Of the LED treated patients, 94.7% (18) had grade 0 or 1 reaction and 5.3% (1) had a grade 2 reaction. Among controls, 4 (14.3%) had a grade 1 reaction and 24 (85.7%) had a grade 2 or 3 reaction. Of the non-LED treated group, 67.9% had to interrupt treatment because of side effects of skin breakdown with moist reactions but only 5% of the LED treated group had interrupted treatment. The authors concluded that not only did LED photomodulation treatments delivered immediately after each IMRT reduce the incidence of adverse NCI criteria skin reactions, but also allowed the full course of treatment and resulted in a final smoother skin texture with improved skin elasticity post-radiation treatment.

Additional data indicates an anti-inflammatory effect for LED photomodulation following UV-induced erythema. Using a solar simulator, findings indicate a photoprotective effect when delivered after UV radiation [24]. This concept is a rescue from UV damage even after inadvertant UV radiation has occurred. We have observed a reduction in UV erythema when LED photomodulation was supplied within hours after UV exposure. The use of 590–870 nm LED photomodulation produced significant downregulation of dermal matrix degrading enzymes, which were stimulated by the UV exposure [24]. Additionally, a pilot study with precise CO_2 laser epidermal destruction has shown promise with using this device for accelerated wound healing.

Parallel to wound healing, use of photomodulation has been extended to a protective or preventative effect following several types of toxic injury. Experiments using LED light to protect the retina against the toxic actions of methanol-derived formic acid in a rodent model of methanol toxicity have been successful. In a recent study, LED treatment protected the retina from the histopathologic changes induced by methanol on mitochondrial oxidative metabolism *in vitro* and retinal protection *in vivo* [27]. Photomodulation may enhance recovery from retinal injury and other ocular diseases in which mitochondrial dysfunction is postulated to have a role.

Human retinal pigment epithelial (RPE) cells were treated with LED photomodulation produced by acute injury from blue light wavelengths [28]. The results showed reduction of cell death at 24 hours from 94% to 10–20%. Another *in vitro* test on human RPE cells showed a sevenfold reduction in vascular endothelial growth factor (VEGF) expression at 24 hours post-LED exposure using LED photomodulation at 590–870 nm delivered at 0.1 J/cm^2 [29].

Photodynamic therapy

LED red light (630 nm) has been used in combination with a sensitizer (levulinic acid) for photodynamic therapy (PDT) [30]. When exposed to light with the proper wavelength, the sensitizer produces an activated oxygen species, singlet oxygen, that oxidizes the plasma membrane of targeted cells. As a result of a lower metabolic rate, there is less sensitizer in the adjacent normal tissue, thus less of a reaction. One of the absorption peaks of the metabolic product of levulinic acid, protoporphyrin, absorbs strongly at 630 nm red. A red LED panel emitting at 630 nm (Omnilux PDT™, Phototherapeutics, Altrincham, Cheshire, UK) has been used for this purpose in Europe and Asia [31]. A full panel 590 nm LED array has also been used for facilitating PDT. This therapy is delivered by application of levulinic acid (Levulan™, DUSA, Wilmington, MA, USA) for 45 minutes and exposure to continuous (non-pulsed) 590–870 nm LED for 15 minutes for a cumulative dose of over 70 J/cm^2. The results show reduction in actinic damage including improvement of skin texture and reduction of actinic keratoses [32].

The primary means for photomodulated upregulation of cell activity for collagen synthesis by LED is the activation of energy switching mechanisms in mitochrondria, the energy source for cellular activity. Cytochrome molecules are believed to be responsible for the light absorption in mitochrondria. Cytochromes are synthesized from protoporphyrin IX and absorb wavelengths of light from 562 to 600 nm. It is believed that LED light absorption causes conformational changes in antenna molecules within the mitochrondrial membrane. Proton translocation initiates a pump, which ultimately leads to energy for conversion of adenosine diphosphate (ADP) to adenosing triphosphate (ATP). This essentially recharges the "cell battery" and provides more energy for cellular activity.

Others have confirmed that mitochrondial ATP availability can influence cellular growth and reproduction, with lack of mitochrondrial ATP associated with oxidative stress [33]. Cellular aging may be associated with decreased mitochrondial DNA activity [34]. It has been concluded that LED light represents a novel, non-invasive, therapeutic intervention for the treatment of numerous diseases linked to mitochondrial dysfunction [35].

Previous work has also demonstrated rapid ATP production within mitochrondia of cultured fibroblasts exposed to 590–870 nm yellow/infrared LED light only with the proper pulsing sequence [9,36]. New ATP production occurs rapidly after LED photomodulation, triggering subsequent metabolic activity of fibroblasts [19]. There also appear to be receptor-like mechanisms, which result in modulation of the expression of gene activity producing upregulation or downregulation of gene activity as well as wide-ranging cell signaling pathway actions. The choice of photomodulation parameters has a vital role in determining the overall pattern

of gene upregulation and/or downregulation. In our experience, use of LED yellow/infrared light without the proper pulsing sequence leads to minimal or no consequences on mitochrondrial ATP production.

Conclusions

LED arrays for photomodulation are useful for collagen stimulation, textural smoothing, and reduction of inflammation. Pilot wound healing studies show slightly accelerated wound resolution. Cellular rescue from UV damage and other toxic insults has been shown in small studies. Thermal, non-ablative photorejuvenation and non-thermal LED photomodulation have a synergistic effect. LED photomodulation is delivered immediately subsequent to the thermal-based treatment for its anti-inflammatory effects, which may reduce the thermally induced erythema and edema of non-ablative treatments. Delivery of LED light immediately before and after thermal injury appears to increase anti-inflammatory and protective effects.

References

1 Weiss RA, Weiss MA, Beasley KL, Munavalli G. (2005) Our approach to non-ablative treatment of photoaging. *Lasers Surg Med* **37**, 2–8.

2 Munavalli GS, Weiss RA, Halder RM. (2005) Photoaging and nonablative photorejuvenation in ethnic skin. *Dermatol Surg* **31**, 1250–60.

3 Weiss RA, McDaniel DH, Geronemus RG. (2003) Review of nonablative photorejuvenation: reversal of the aging effects of the sun and environmental damage using laser and light sources. *Semin Cutan Med Surg* **22**, 93–106.

4 Weiss RA, Gold M, Bene N, Biron JA, Munavalli G, Weiss M, *et al*. (2006) Prospective clinical evaluation of 1440-nm laser delivered by microarray for treatment of photoaging and scars. *J Drugs Dermatol* **5**, 740–4.

5 Weiss RA, Goldman MP, Weiss MA. (2000) Treatment of poikiloderma of Civatte with an intense pulsed light source. *Dermatol Surg* **26**, 823–7.

6 Fatemi A, Weiss MA, Weiss RA. (2002) Short-term histologic effects of nonablative resurfacing: results with a dynamically cooled millisecond-domain 1320 nm Nd:YAG laser. *Dermatol Surg* **28**, 172–6.

7 Bogle MA. (2008) Fractionated mid-infrared resurfacing. *Semin Cutan Med Surg* **27**, 252–8.

8 Weiss RA, McDaniel DH, Geronemus RG. (2003) Review of nonablative photorejuvenation: reversal of the aging effects of the sun and environmental damage using laser and light sources. *Semin Cutan Med Surg* **22**, 93–106.

9 McDaniel DH, Weiss RA, Geronemus R, Ginn L, Newman J. (2002) Light-tissue interactions I: photothermolysis vs photomodulation laboratory findings. *Lasers Surg Med* **14**, 25.

10 McDaniel DH, Weiss RA, Geronemus R, Ginn L, Newman J. (2002) Light-tissue interactions II: photothermolysis vs photomodulation clinical applications. *Lasers Surg Med* **14**, 25.

11 Whelan HT, Smits RL Jr, Buchman EV, Whelan NT, Turner SG, Margolis DA, *et al*. (2001) Effect of NASA light-emitting diode irradiation on wound healing. *J Clin Laser Med Surg* **19**, 305–14.

12 Whelan HT, Buchmann EV, Dhokalia A, Kane MP, Whelan NT, Wong-Riley MT, *et al*. (2003) Effect of NASA light-emitting diode irradiation on molecular changes for wound healing in diabetic mice. *J Clin Laser Med Surg* **21**, 67–74.

13 Whelan HT, Connelly JF, Hodgson BD, Barbeau L, Post AC, Bullard G, *et al*. (2002) NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. *J Clin Laser Med Surg* **20**, 319–24.

14 Walker MD, Rumpf S, Baxter GD, Hirst DG, Lowe AS. (2000) Effect of low-intensity laser irradiation (660 nm) on a radiation-impaired wound-healing model in murine skin. *Lasers Surg Med* **26**, 41–7.

15 Lowe AS, Walker MD, O'Byrne M, Baxter GD, Hirst DG. (1998) Effect of low intensity monochromatic light therapy (890 nm) on a radiation-impaired, wound-healing model in murine skin. *Lasers Surg Med* **23**, 291–8.

16 Weiss RA, McDaniel DH, Geronemus RG, Weiss MA, Beasley KL, Munavalli GM, *et al*. (2005) Clinical experience with light-emitting diode (LED) photomodulation. *Dermatol Surg* **31**, 1199–205.

17 Weiss RA, McDaniel DH, Geronemus RG, Weiss MA. (2005) Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results. *Lasers Surg Med* **36**, 85–91.

18 McDaniel DH, Newman J, Geronemus R, Weiss RA, Weiss MA. (2003) Non-ablative non-thermal LED photomodulation: a multicenter clinical photoaging trial. *Lasers Surg Med* **15**, 22.

19 Geronemus R, Weiss RA, Weiss MA, McDaniel DH, Newman J. (2003) Non-ablative LED photomodulation: light activated fibroblast stimulation clinical trial. *Lasers Surg Med* **25**, 22.

20 Weiss RA, McDaniel DH, Geronemus R, Weiss MA, Newman J. (2004) Non-ablative, non-thermal light emitting diode (LED) phototherapy of photoaged skin. *Lasers Surg Med* **16**, 31.

21 Weiss RA, Weiss MA, Geronemus RG, McDaniel DH. (2004) A novel non-thermal non-ablative full panel led photomodulation device for reversal of photoaging: digital microscopic and clinical results in various skin types. *J Drugs Dermatol* **3**, 605–10.

22 Goldberg DJ, Amin S, Russell BA, Phelps R, Kellett N, Reilly LA. (2006) Combined 633-nm and 830-nm led treatment of photoaging skin. *J Drugs Dermatol* **5**, 748–53.

23 Russell BA, Kellett N, Reilly LR. (2005) A study to determine the efficacy of combination LED light therapy (633 nm and 830 nm) in facial skin rejuvenation. *J Cosmet Laser Ther* **7**, 196–200.

24 Weiss RA, McDaniel DH, Geronemus RG, Weiss MA. (2005) Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results. *Lasers Surg Med* **36**, 85–91.

25 Khoury JG, Goldman MP. (2008) Use of light-emitting diode photomodulation to reduce erythema and discomfort after intense pulsed light treatment of photodamage. *J Cosmet Dermatol* **7**, 30–4.

26 DeLand MM, Weiss RA, McDaniel DH, Geronemus RG. (2007) Treatment of radiation-induced dermatitis with light-emitting diode (LED) photomodulation. *Lasers Surg Med* **39**, 164–8.

27 Eells JT, Henry MM, Summerfelt P, Wong-Riley MT, Buchmann EV, Kane M, *et al.* (2003) Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci U S A* **100**, 3439–44.
28 Eells JT, Henry MM, Summerfelt P, Wong-Riley MT, Buchmann EV, Kane M, *et al.* (2003) Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci U S A* **100**, 3439–44.
29 McDaniel DH, Weiss RA, Geronemus R, Weiss MA. (2006) LED photomodulation 'reverses' acute retinal injury. Annual meeting of the American Society for Laser Medicine and Surgery, Boston, MA, April 6, 2006.
30 Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM. (2005) A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* **85**, 424–8.
31 Chen HM, Yu CH, Tu PC, Yeh CY, Tsai T, Chiang CP. (2005) Successful treatment of oral verrucous hyperplasia and oral leukoplakia with topical 5-aminolevulinic acid-mediated photodynamic therapy. *Lasers Surg Med* **37**, 114–22.
32 Weiss RA, McDaniel DH, Geronemus RG, Weiss MA, Beasley KL, Munavalli GM, *et al.* (2005) Clinical experience with light-emitting diode (LED) photomodulation. *Dermatol Surg* **31**, 1199–205.
33 Zhang X, Wu XQ, Lu S, Guo YL, Ma X. (2006) Deficit of mitochondria-derived ATP during oxidative stress impairs mouse MII oocyte spindles. *Cell Res* **16**, 841–50.
34 Sorensen M, Sanz A, Gomez J, Pamplona R, Portero-Otin M, Gredilla R, *et al.* (2006) Effects of fasting on oxidative stress in rat liver mitochondria. *Free Radic Res* **40**, 339–47.
35 Desmet KD, Paz DA, Corry JJ, Eells JT, Wong-Riley MT, Henry MM, *et al.* (2006) Clinical and experimental applications of NIR-LED photobiomodulation. *Photomed Laser Surg* **24**, 121–8.
36 Weiss RA, Weiss MA, McDaniel DH, Newman J, Geronemus R. (2003) Comparison of non-ablative fibroblast photoactivation with and without application of topical cosmeceutical agents. *Lasers Surg Med* **15**, 23.

Part 5: Skin Contouring Techniques

Chapter 56: Liposuction: Manual, mechanical, and laser assisted

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BASIC CONCEPTS

- The safety profile for liposuction is significantly improved when tumescent local anesthesia technique is employed.
- Tumescent local anesthesia utilizing lidocaine with epinephrine allows the removal of large volumes of fat with minimal associated blood loss and postoperative morbidity.
- Liposuction is a procedure for patients who are either at or approaching their goal weight, to achieve a more esthetic figure, contour, and shape in conjunction with a diet and exercise regimen.
- Preoperative consultation, setting realistic patient expectations for improvement, establishing patients' overall health status and past medical history and discussion of risks and benefits of the procedure are critical to the success of the procedure.
- Laser-assisted tumescent liposuction has been purported to result in mechanical cavitation of fat, resulting in greater ease of suction and greater skin retraction; however, additional studies are needed to confirm these results.

Introduction: history of liposuction with tumescent local anesthesia

The early history of liposuction begins with Fischer's description of hollow cannula liposuction in 1976 [1]. Shortly thereafter, Ilouz, a Frenchman trained in obstetrics and gynecology, and Fournier, a general surgeon, began practicing liposuction using the "wet technique," involving injection of hypotonic saline and hyaluronic acid into the fat prior to suction [2]. Fournier pioneered the "criss-cross" technique and syringe liposuction and became a teacher of the technique [3].

Shortly thereafter, in 1977, an American dermatologist, Lawrence Field, visited Paris and learned about liposuction and published his experience with the technique in 1984. Jeffrey Klein, an American dermatologist, was the first to publish a report of liposuction using exclusively tumescent local anesthesia (TLA) in 1987 [4]. Prior to this point, the pain associated with liposuction had necessitated the procedure be performed under general anesthesia.

In 1988, Hanke and Bernstein published a report on the safety of the TLA technique for liposuction, reporting the results of 9478 patients treated by dermatologists [5]. Shortly after attending Fournier's liposuction course in Paris, William Hanke, the editor-in-chief of the *Journal of Dermatologic Surgery and Oncology*, commissioned an issue of the dedicated to liposuction. Further innovations to the field evolved with the publication by Hanke and colleagues documenting the safety of TLA in 15 336 patients in 1995 [6]. Additionally, while initial reports by Klein established the safety of tumescent liposuction using a lidocaine dose of 35 mg/kg in 1990 [4], Ostad *et al.* [7] reported the safety at a total dose of 55 mg/kg. In 2000, Klein published a book entitled *Tumescent Technique* [8], highlighting many of his important contributions to the field including: TLA technique, the Klein microcannula, Klein infiltration pumps, multihole Klein Capistrano cannulas, and specific techniques for treating all body areas.

Since Klein's introduction of the technique of TLA for liposuction in 1987, it has revolutionized the technique among dermatologic surgeons and surgeons of all specialties performing the procedure. Liposuction with TLA facilitates the removal of large volumes of fat with minimal blood loss or postoperative morbidity, excellent esthetic results, and a remarkably superior safety profile to general anesthesia.

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

Table 56.1 Appropriate liposuction candidate selection.

Does the patient have realistic expectations of the procedure?
Is the patient at or near goal body weight?
Is the patient in good health in the absence of anticoagulant therapy?
Does the patient have localized fat deposits on the body that are diet and exercise resistant for which they are seeking treatment?
Does the patient have good or adequate skin tone?

Physiology: what skin contour problem does the procedure address and how does this procedure alter the contour problem?

Liposuction is a procedure that can assist patients to achieve a more idealized and balanced body contour (Table 56.1) [9–12]. It is designed for individuals at their ideal body weight who seek correction of a single or multiple anatomic sites with focal excess adiposity and laxity [9–12]. The ideal liposuction patient is a patient of ideal body weight with focal disproportionate adiposity, resulting in contour deformity [9–12].

Importantly, liposuction is not a weight loss procedure, and it should be emphasized that patients seeking the goal of weight loss are not good candidates for the procedure (Table 56.1) [9–12]. In initial patient consultations, it is important to set realistic patient expectations for the results of the procedure. The results of liposuction in all anatomic sites are limited by the existing bony structure, the texture and quality of the skin, the tone and build of muscle, and the pre-existing adiposity in areas not amenable to liposuction.

Liposuction can help to achieve a more idealized and balanced body contour, and patients will largely vary in seeking correction of a single area or multiple anatomic sites to achieve their own personal optimal correction.

Advantages and disadvantages

Liposuction with TLA allows the removal of large volumes of fat with minimal blood loss or postoperative morbidity, excellent cosmesis, and a remarkable safety profile. TLA techinique with the use of a dilute epinephrine and anesthetic achieves the aims of hemostasis and anesthesia at the surgical site [13–17]. The advantages of the technique include improved safety, precision, and patient convenience [13–17]. These advances have contributed to the enhanced safety profile and widespread growth in the popularity of the liposuction technique [13–17]. TLA can be utilized for any anatomic site treated with liposuction, from the neck to the ankles.

Figure 56.1 A 2-L liposuction cannula, filled with liposuction aspirate.

Advantages of the TLA technique include a significant reduction in blood loss attributed to the vasoconstrictive effects of epinephrine. This can be quantified by comparing the aspirate from TLA (containing 1–3% whole blood) with that from the procedure performed under general anesthesia (40% whole blood) [15]. Improved hemostasis results in both decreased blood loss as well as decreased bruising and discomfort for the patient in the postoperative phase [15]. In addition, the anesthetic and vasoconstrictive effects of the TLA are directed towards the sites being treated, resulting in prolonged anesthesia of several hours' duration as a result of the reservoir effect of TLA [12–15]. This results in decreased reliance upon postoperative narcotics.

The TLA solution also results in a hydrodissection effect, whereby the pressure of the solution allows easier and more uniform penetration and removal of adipose tissue by the cannula (Figures 56.1 and 56.2) [4–8, 12–15]. Tumescent fluid enlarges, magnifies, and lifts targeted fat, allowing for more precise removal of fat [4–8, 12–15].

With proper technique for infusion of the tumescent fluid, TLA can be performed without ancillary sedation and intravenous or general anesthesia [14,15]. With TLA, patient convenience is significantly enhanced during the perioperative recovery period where there is more rapid recovery [14–24]. In contrast, the recovery is much more prolonged after general anesthesia, both as a result of the after-effects of the anesthetic and from the increased bruising and discomfort associated with the procedure [14–24].

Complications with the TLA technique include discomfort, swelling, bruising, temporary loss of sensation, postinflammatory hyperpigmentation, and minimal scarring at the

incision sites but these are significantly less than those associated with the procedure performed under general anesthesia [14–24]. Potential risks of liposuction under general anesthesia are significantly greater and include deep venous thrombosis or pulmonary embolus, abdominal or other organ perforation, infection, and bleeding [21,23].

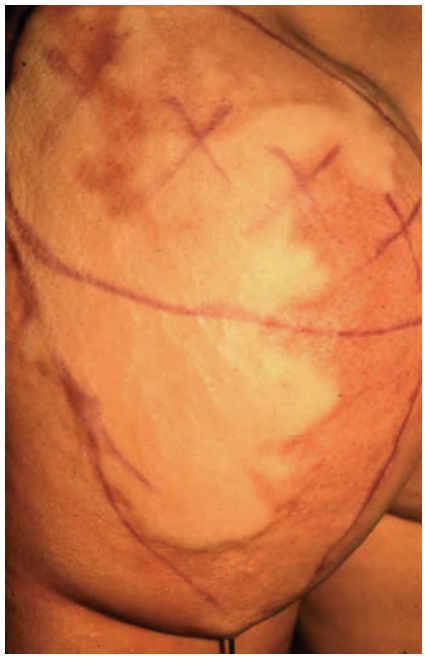


Figure 56.2 Blanching of skin visible after infusion of tumescent anesthesia with tumescent local anesthesia (TLA) technique.

Indications for tumescent liposuction, by anatomic site

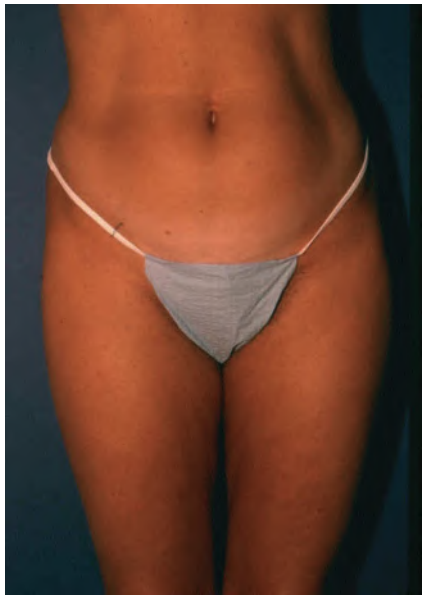
Abdomen

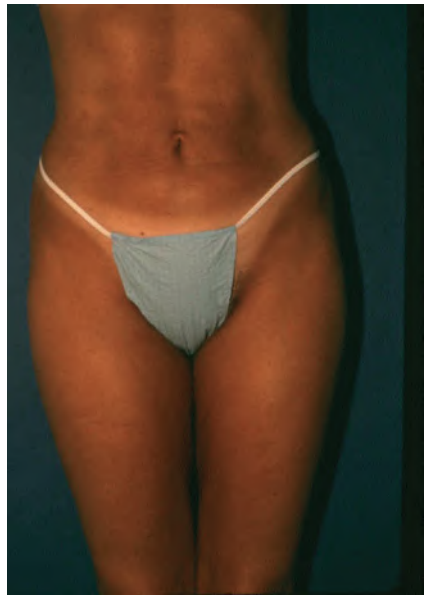
Patient selection has a significant role in liposuction surgery of the abdomen. Patients should be within 10–25 lb (5–12 kg) of their ideal body weight and should have good to excellent skin tone which will assist with skin contraction after the procedure [25].

The overall body shape of the patient should be examined during the preoperative physician examination [25]. The patient should be marked while standing to identify the larger areas of fatty deposition in the abdomen [25]. Incision sites are made in the following locations: two to three in the suprapubic region, one at the umbilicus, and two on the lateral portions of the umbilical fat depositions [25]. The patient should be lying on his or her back for the procedure; however, towards the end of the procedure, it is helpful if the patient lies in both lateral decubitus positions to identify pockets of fat as they fall away from the rectus muscle [25]. The goal of abdominal liposuction should be to reduce the deeper fatty layers while preserving a superficial, even layer of fat attached to the skin [25]. Oversuction can lead to dimpling of the skin, uneven fat deposits, and dermal necrosis [25].

Patients in group 1 (Table 56.2), lower abdomen only, are typically thin patients with a localized fatty deposition in the lower abdomen alone (Figure 56.3) [25]. These patients tend to respond very well to liposuction with high patient satisfaction.

(a)





(b)

Figure 56.3 Lower abdomen, anterior view: (a) pretreatment; (b) post-treatment.

Patients in group 2 (Table 56.2), requiring liposuction of both the upper and lower abdomen, must be carefully evaluated (Figure 56.4) [25]. This group may also be relatively thin; however, if suction of the lower abdomen alone is performed, they may have a protuberant overhanging upper abdomen [25]. Therefore, it is important to perform liposuction on both segments of the abdomen to ensure a proportionate appearance.

Patients requiring liposuction of the upper and lower abdomen in addition to the hips, waist, and back (group 3; Table 56.2; Figure 56.5) tend to be older postmenopausal women or those on hormone replacement therapy with a history of weight gain [25].

Men requesting liposuction of the abdomen may require more widespread liposuction to ensure a proportionate appearance as fat deposits in men in the abdomen are usually accompanied by excess fat on the chest, flanks, and back [25]. Many men are not good candidates for abdominal liposuction as much of the fat deposits are behind the rectus abdominus and thus are not accessible to suction during the liposuction procedure [25].

Table 56.2 Five groups of patients: abdominal liposuction.

1. Liposuction: lower abdomen
2. Liposuction: upper and lower abdomen
3. Liposuction: hourglass abdomen; upper and lower abdomen, hips, waist, and back
4. Liposuction and skin excision: mini-abdominoplasty with or without umbilical translocation
5. Complete abdominoplasty

The fourth group of patients (Table 56.2) demonstrate atrophic, stretched skin from pregnancy, advancing age, and rapid fluctuations changes in weight [25]. More extensive liposuction is needed in these patients and liposuction alone is often not satisfactory. Waiting 3–4 months after the procedure will allow the physician to assess if liposuction alone is sufficient or if the patient will require abdominoplasty procedure to address skin redundancy [25].

Hips, outer thighs, and buttocks

Evaluation of patients for liposuction in these anatomic sites requires a three-dimensional and universal approach to all anatomic site, otherwise a disproportionate appearance can result with more noticeable enlargement in the unsuctioned areas after suction of localized fat deposits. For the hips, outer thigh, and buttocks, it is important to observe review carefully with the patient all changes in underlying musculature, cellulite, and inelastic skin, none of which can be improved with liposuction. For the hips, the patient should be placed in the lateral decubitus position. For the thighs, the patient should also be in the lateral decubitus position with a pillow placed between the legs, which mimics the standing position and allows the femur to be directed anteriomedially [20].

The end result of suctioning should be that a region is flat, not concave [25]. Suctioning should also be equal on both sides and careful steps should be taken to monitor that relatively equivalent amounts of fat are removed from either side [25].

Liposuction of the buttocks must be performed carefully, with special consideration to the inferolateral gluteal crease, where a banana roll, comprised of a defined infragluteal fat

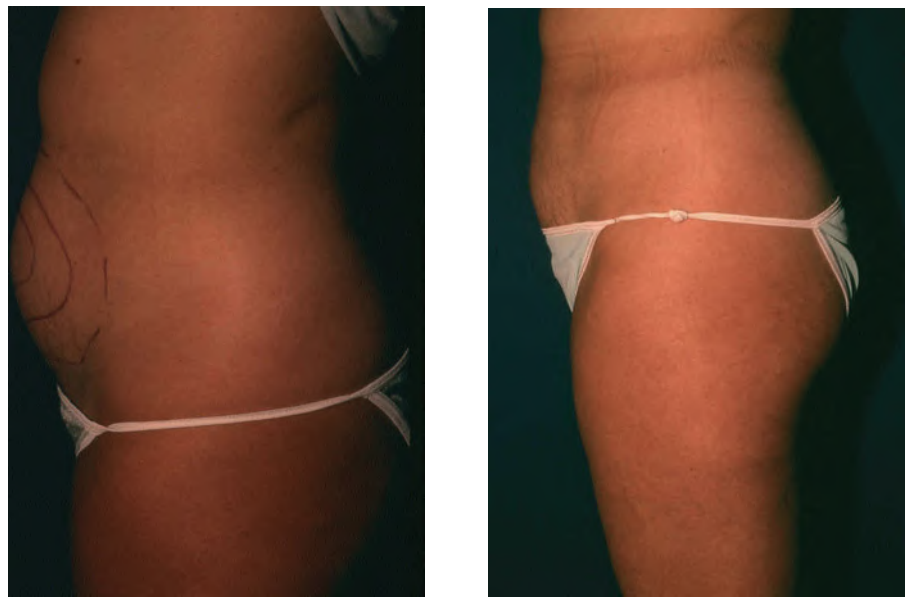


Figure 56.4 Lower abdomen and hips liposuction, lateral view: (a) pretreatment; (b) post-treatment.

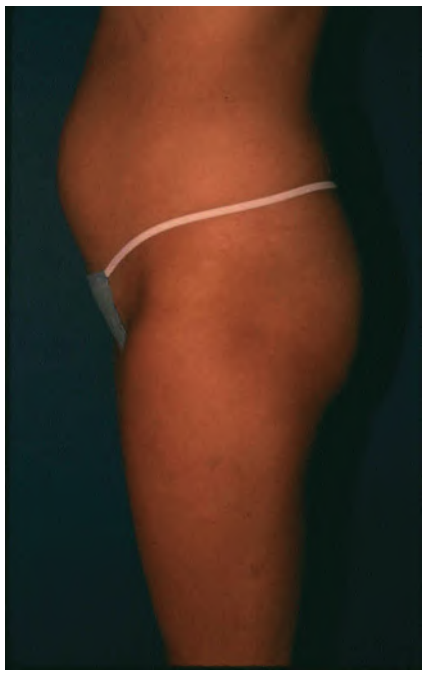
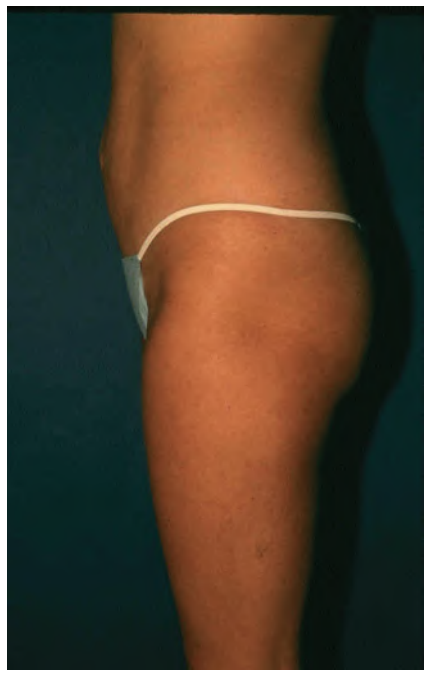
(a)   (b)

Figure 56.5 Lower abdomen, hips, and lateral thigh liposuction, lateral view: (a) pretreatment; (b) post-treatment.

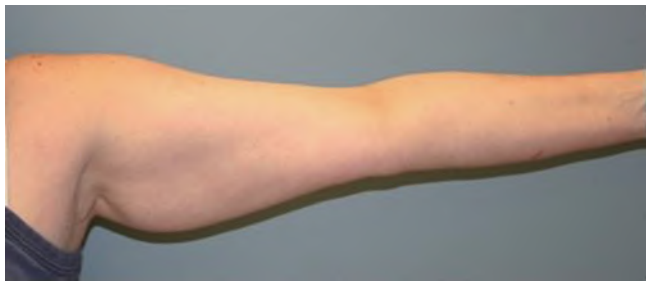
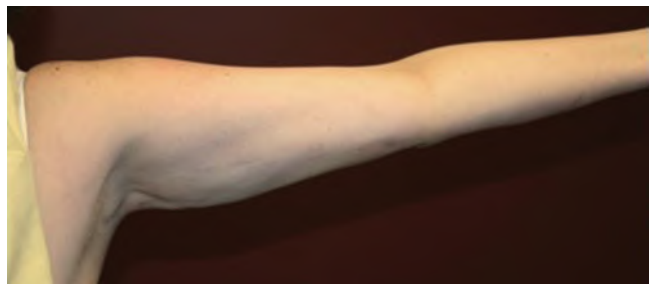
(a)   (b)

Figure 56.6 Arm, anterior view: (a) pretreatment; (b) post-treatment.

pocket, may worsen or lead to an atrophic buttock in the event of oversuction [25]. Physical examination must focus on bony and muscular prominences and asymmetry. Realistic expectations must be established with the patient as liposuction will not assist with underlying bony asymmetry, the presence of large or asymmetrical muscle masses, or skin laxity. Conservative buttock suction is recommended with removal of no more than 30–50% of fat from the middle and deep fat layers [25]. Superficial suctioning of the buttocks should be avoided as it is likely to result in undesirable dimpling.

Arms

Liposuction of the arms is performed in women with laxity of the proximal arm musculature and who have a pendulous fatty protuberance of the posterior, lateral, or anterior upper arm (Figure 56.6). The fat distribution in the arms is best visualized when the arms are extended at 90° from the body. Avoiding oversuctioning is critical for the arms and gentle liposuction should only be performed in the medial and posterior (extensor arms). As skin redundancy often contributes significantly to laxity of the arms, patients need to be advised that the goal is to decrease the convexity of the arms as opposed to complete removal of all redundancy of skin and soft tissue.

Excessive tumescent solution should be avoided in the upper arm region as there is a small risk for creation of "compartment syndrome" whereby a functional tourniquet develops distal to the infused region, brought about by fluid-induced compression of neural, vascular, and lymphatic structures in the area.

One position for the procedure is to lay the patient's arms entirely flat with palms facing down over the hips with the body in a lateral decubitus position, which will serve to maximally expose the posterior portion of the arm. The other position that is helpful is for the patient to be in a supine or lateral decubitus position with a hand brought behind the head, forearm flexed, and elbow pointing out,

which also exposes the posterior portion of the arm. Liposuction to the axilla should be avoided given the risks of damage to the branches of the brachial plexus in this area.

Neck and jowls

The goal of liposuction of the neck and jowls is to give improved definition of the cervicomental angle and jawline [26–30]. Aging in this region can be caused by a multitude of factors, including ptosis of fatty tissue and decreased elastic tissue. These changes in the subcutaneous tissue of the neck allow the anterior margins of the platysma to slide forward and result in protrusion of the submental and submandibular fat [26–30]. Patients with excess laxity in this area may benefit from a spectrum of procedures, including facelifts, chin implants, platysmal plication, and CO_2 laser resurfacing, and thus optimal selection of patients who will benefit from liposuction in this area is critical (Figure 56.7) [26–30].

Fullness in the neck and jowls can be attributed to a variety of factors, including redundant skin, muscle, or a low or anteriorly positioned hyoid bone (creating an obtuse cervicomental angle) [26–30]. Patients with low set or anteriorly placed hyoid bones are unlikely to benefit form liposuction alone. The ideal candidate should have a hyoid positioned at the level of the C3–C4 vertebrae, excellent skin elasticity, and a palpable submental fat pad [26–30].

In order to mark the neck liposuction patient, the anatomic boundaries must be distinguished, including the mandibular border, the jowls, the submental fat pad, the anterior borders of the sternocleidomastoid, platsyma band, and the thyroid cartilage (Figure 56.8) [26–30]. The patient should be seated with the head gently extended posteriorly and the chin raised with the small supportive pillow for neck support [26–30].

For liposuction of the neck and jowls, entry points should be along the submental crease, just below or lateral to the jowls [26–30]. If extensive lateral neck fat is present, additional insertion sites can be made in a neck fold behind the earlobes [26–30]. The suctioning plane should begin just above the platysma muscle, with subsequent suction with

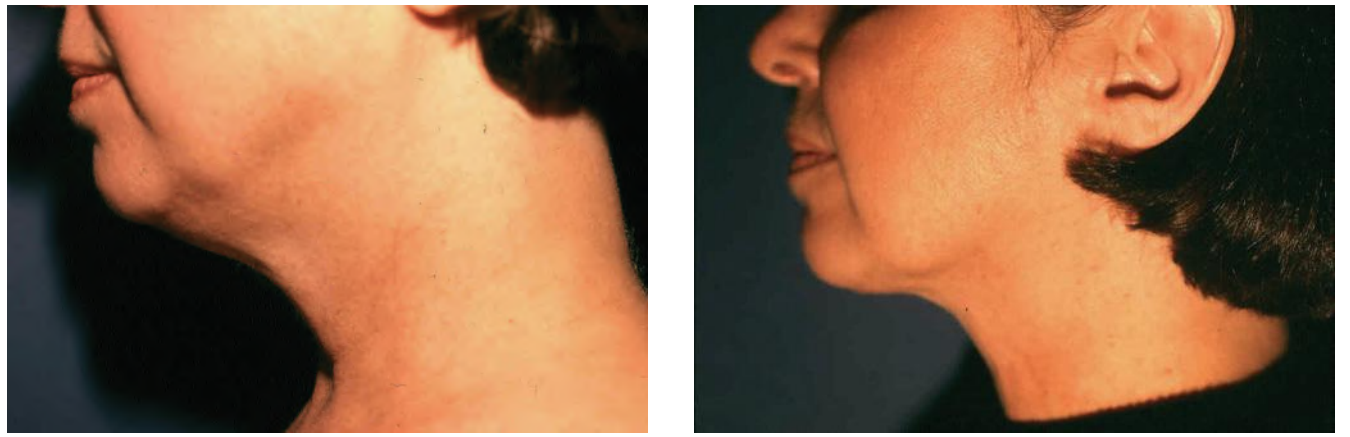


Figure 56.7 Neck, lateral view: (a) pretreatment; (b) post-treatment.

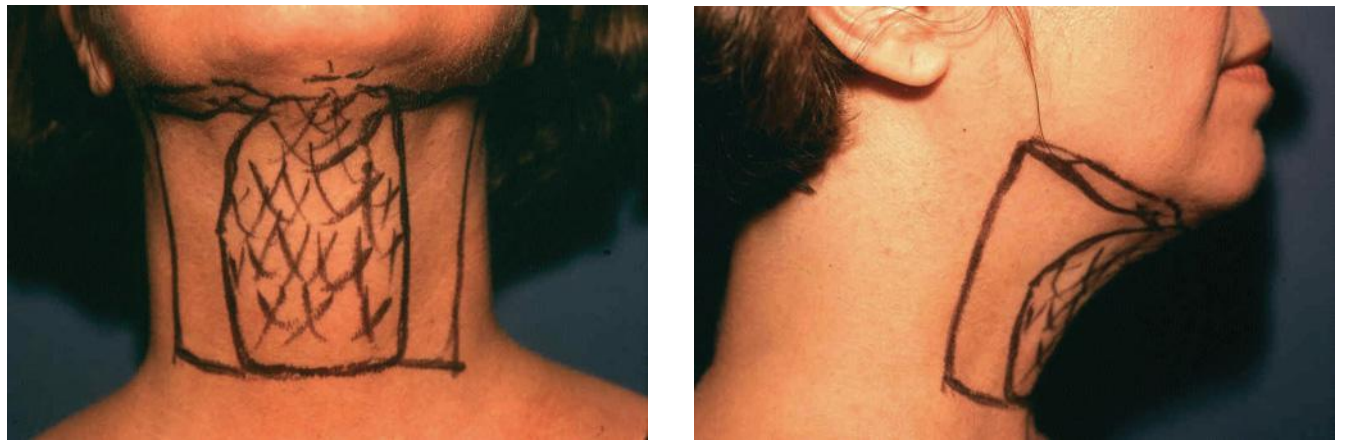


Figure 56.8 Neck liposuction markings: (a) anterior view; (b) lateral view.

small (1.5–2 mm) cannulae [26–30]. The cannula should be delicately applied in this area to suction above the platsyma in order to avoid placing the cannula through the platsyma [26–30]. In addition, the marginal mandibular branch of the facial nerve is located in this area (below the angle of the mandible at the anterior border of the masseter muscle), and care must be taken to avoid trauma to the nerve [26–30]. The nerve becomes increasingly superficial and more likely to be injured along or posterior (up to two fingerbreadths) to the posterior border of the sternocleidomastoid muscle [26–30]. The cannula can be used to elevate the subcutaneous fat away from the underlying structures in these areas to avoid injury to underlying structures [26–30]. Also, it is important to avoid oversuctioning cheeks and along the jowl–cheek margin, as an undesirable hollowed appearance results from oversuctioning in this area [26–30].

Female breast

Traditional breast reduction in women, reduction mammoplasty, requires general anesthesia with significant associated risks, including, seroma, hematoma, scarring, skin loss, and fat necrosis [31,32]. The procedure involves making a T-shaped incision extending from the areola to the inframammary folds, which in the majority of cases leaves an unattractive scar [31,32].

Liposuction as a means to decrease breast size is a relatively new procedure and when utilized alone to decrease breast size has only been described in the literature in a handful of cases [31,32]. For women with moderate to severe breast enlargement, liposuction may not be sufficient given that it may not address issues of excess skin and soft tissue [31,32]. A preoperative breast weight should be taken to establish the optimal amount of fat reduction and then calculate the percentage fat reduction after the procedure [31,32].

The patient should be positioned supine with the ipsilateral arm behind the head or with the arm posteriorly displaced in order to bring the breast flat against the chest wall [31,32]. Two incisions for suctioning should be made, one in the lateral axillary line and one in the mid-inframammary crease [31,32]. Suctioning should focus in the mid to deep plane of the lateral and inferior quadrants of the breast [31,32]. It is less desirable for suction in the superior quadrant to preserve the natural contour of the breast, as the upper quadrants typically flatten with age [31,32]. The surgeon determines the amount of fat removed, calculated as a percentage of total fat, based upon preoperative measurement [31,32]. It is currently recommended that less than one-third of the measured total breast volume be removed in one session [31,32]. Breast reduction in female breasts by liposuction alone represents a promising new application of this technology and presents significant advantages relative to traditional reduction mammoplasties, including less risk associated with general anesthesia, as well as benefits of decreased infection and scarring risks.

Male chest

A careful history and physician examination should be performed in men before attempting liposuction in the male chest, with specific attention to the palpation of the gynecomastia and regional lymph nodes [31–33]. Several authors also recommend palpation of the testes to evaluate for testicular tumors [31,32]. While rare, breast tumors do occur in men and thus all masses with suspicion for malignancy (asymmetry, firm, or fixed) should undergo mammogram, ultrasound, and/or biopsy [31,32]. Etiologies for male breast enlargement include fatty deposition, glandular deposition, medications (estrogen, spironolactone, digitalis, diazepam, phenytoin and clomiphene), alcoholism, hypogonadism, and hormone-secreting tumors of the pituitary, adrenal gland, and testis [31,32].

As the male breast is one of the most vascular sites for TLA, care must be taken to ensure the vasoconstrictive effect of epinephrine has taken effect prior to the procedure and that the pectoralis muscle is not traumatized during the anesthesia infusion or liposuction [31,32]. The male breast is also one of the most fibrous sites in which liposuction is performed, with significant variability in the content of glandular and fatty tissue present [31,32].

Incision sites for the liposuction cannula are placed along the periphery of the breast and in the inframammary crease to allow for complete infiltration and criss-cross suction of adipose tissue [31,32]. Suction is started with microcannulae, allowing for easier tissue penetration, such as the 16-gauge Capistrano cannula for initial tunneling with transition to a larger 14-gauge cannula [31,32]. The subareolar breast tissue can be gently suctioned with the use of a 16-gauge short (5 or 7 cm) Capistrano cannula [31,32].

Anesthesia technique

Tumescent solution should be prepared on the day of the procedure utilizing 0.9% sodium chloride solution (normal saline) [4–9]. The anesthetic is lidocaine, available in 1% or 2% solution. Epinephrine and sodium bicarbonate are added to aid in vasoconstriction and buffering, respectively [4–9]. The range of doses utilized for TLA range from conservative doses of 30–35 mg/kg to as high as 55 mg/kg [4–9]. Doses at the lower end of the range can be utilized when patients are taking medications that inhibit cytochrome P450, specifically the CYP3A4 isoenzyme, responsible for the clearance of lidocaine [4–9]. In particularly smaller individuals, lidocaine concentrations should be limited to 0.05–0.075% as the total dose is limited by weight [4–9]. Higher concentrations are generally advised on more sensitive areas, such as the chest, waist, and periumbilical area [4–9]. Epinephrine

is added to the solution at a concentration of 1 : 1 000 000 (1 mg 1 : 1000 epinephrine in 1 L solution of saline) [4–9]. Finally, bicarbonate is added in the amount of 10 mEq in 1 L [4–9]. Before mixing, the saline should be warmed to enhance the comfort of the patient during the infiltration process [4–9].

TLA should be administered once the patient has been comfortably positioned for the procedure. Insertion sites should be anesthetized with 1% lidocaine with epinephrine (usually at a dilution of 1 : 100 000) [4–9]. The incisions are created using a No. 11 blade through the dermis to allow entry of the blunt-tipped infiltration cannula into the subcutaneous tissue [4–9]. The infiltration cannula should be inserted and the infiltration rate should be appropriately adjusted for the anatomic site [4–9]. The infiltration rates should be less than 100 mL per minute to minimize patient discomfort [4–9]. Gentle advancement of the cannula should occur prior to infiltration of the tumescent solution [4–9]. Anesthesia should be performed using a fanned approach from the entry site with care taken not to put excessive strain on the entry site [4–9]. If the patient experiences excessive pain, slowing the rate of infiltration can improve patient comfort [4–9]. The infiltration endpoint is reached when the edges of the field become firm and indurated and the area of infiltration is blanched (secondary to vasoconstriction effect of epinephrine) [4–9].

Standard and advanced operating technique

After infiltration of the TLA is complete and after allowing 15–20 minutes for full epinephrine effect to occur, fat suction can begin [4–9]. Suction can be performed through the same sites of insertion of the TLA [4–9]. More aggressive thinner cannulas should be used first to break up the fibrous setae and to create tunnels for subsequent removal of fat with larger (3 mm), less aggressive cannulae [4–9]. Suction movement should proceed in a linear and vertical fashion with little horizontal movement in the creation of subcutaneous tunnels [4–9]. The cannula should be directed so that the aperture is facing downwards or opposite the dermis [4–9]. Both deep and superficial tunneling should be performed so that the physician's free or "smart hand" monitors the motion and position of the cannula tip [4–9].

Initially during the suctioning, the area is tense from the infiltration of TLA; however, as the suctioning proceeds, the area becomes more flaccid and techniques are needed to maintain the cannula in a uniform plane to ensure uniform suctioning [4–9]. One helpful technique is to have the assistant gently grasp the flaccid skin adjacent to the suction area and roll in such a way to flatten the suctioned area [4–9]. Another helpful technique is to have an assistant flatten the region by placing counter traction of the skin while the surgeon continues suction guided by their "smart hand" [4–9].

The endpoint of fat suction is determined by a number of factors, such as the observation that the aspirate has become increasingly bloody and devoid of suctionable fat and palpation of the area revealing minimal persistence of fat pockets and even distribution of the remaining fat [4–9]. When this occurs, suctioning should stop in this area and the cannula should be repositioned. Localized pockets of fat should be sought out and removed by lacing the cannula (with the suction apparatus off) into tunnels and gently pulling back and up against the dermis. Pockets of fat may become more pronounced with this maneuver and further suctioning of these well-defined areas helps create a more even result. The total volume of fat removed in a single procedure should not exceed 4500 mL. This equates to 6000–8000 mL of total aspirate, assuming 50–60% of the aspirate of fat. If the patient possesses areas of fat where the estimated loss is greater than 4500 mL, treatments should be planned over multiple visits [4–9].

Equipment

The fundamental equipment needed to perform liposuction includes an aspiration pump, liposuction cannulae, the infiltration pump, a sterile field, syringes with 1% lidocaine with or without epinephrine (to anesthetize the cannula insertion sites), a No. 11 blade, gauze, and clamps to secure tubing and drapes in place [34].

Various infiltration pumps for administration of the tumescent solution are available, the most optimal of which allow adjustment of the rate of administration of the TLA solution [34]. The infiltration pump is connected directly to the tumescent solution via intravenous tubing which is threaded through the power pump and connected directly to the tumescent solution through an infusion cannulae or needle [34].

The aspiration pump is an electrically powered device which is designed to create negative pressure and collect fatty tissue throughout the procedure [34]. There are a variety of machines available, the ideal of which are those with a closed collection system, overflow trap, and disposable air filter with efficient and uninterrupted suction [34].

The liposuction cannulae are comprised of stainless steel, aluminum, deldrin, or brass [34]. The shape, diameter, hole placement, and size determine the ease of fat removal as well as the relative injury to the tissue [34]. Easier fat removal is achieved with cannulae with several holes and a large-diameter tapered end (usually 3 mm), where the holes are located distally on the tip (e.g. Capistrano, Pinto, Cobra, Becker, and Eliminator cannulae; Wells Johnson Company,

Tucson, AZ, USA) [34]. Cannulae with smaller diameters (less than 3 mm), blunted ends, fewer holes, or holes placed more proximally relative to the tip are less aggressive and gentler to the tissue (e.g. Klein, Fournier, Standard cannulae; Wells Johnson Company, Tucson, AZ, USA) [34].

In fibrous tissue, it is best to begin with a cannula with an aggressive tip and a small diameter [34]. As the fibrous tissue is diminished, a less aggressive cannula with a larger diameter tip can be utilized [34]. In areas where the fat is soft, such as the inner thigh, smaller cannulae can be utilized to avoid oversuction. Per the guidelines of the American Academy of Dermatology regarding liposuction, the cannula diameter should be no greater than 4.5 mm in diameter [34]. As most liposuction cannula utilized are between 2 and 3 mm in size, they comply with this recommendation [34].

Complications

Long-term experience has shown that the complications associated with liposuction under the TLA technique are minor and significantly less than those associated with complications with liposuction performed under intravenous or general anesthesia [18–24]. The most common complications of liposuction using TLA include bruising, swelling, soreness, inflamed incision sites, and postoperative fatigue [18–24].

Preoperative phase

Obtaining informed consent from each patient prior to the procedure and reviewing the risks of the procedure, especially of skin contour abnormalities in areas of poor skin elasticity, will allow the patient to be more accepting of the final results [16]. It should be emphasized that there are limitations to the procedure. Safety dictates the amount of fat that can be removed [16]. Additionally, as a body contouring procedure, liposuction will not assist with pre-existing scars, pigmentary variation, cellulite, indentations, and skin textural changes [16]. Finally, it should be emphasized to the patient that his or she adopts and/or continues a regular exercise routine in order to assist with improved skin contraction and maintenance of results [16].

Preoperative assessment should also include assessment for possible abdominal wall hernias [16]. Blood tests should be performed to ensure the patient does not have an underlying bleeding tendency or liver transaminitis, which could also potentially affect clotting factor synthesis [16]. At a minimum, a full blood count with platelets, liver function tests, and a prothrombin time/partial thromboplastin time (PT/PTT) should be checked [16]. Additional studies to undergo with an underlying bleeding abnormality include: a bleeding time, von Willebrand's factor, factor V Leiden level, or hemophilia screen [16]. Detailed questions regarding bleeding complications with prior deliveries or surgeries may elicit a history of bleeding which gives an indication for further work-up [16].

A review of medication intake, both prescription and over-the-counter, is essential to the safety and success of the TLA procedure [16]. Intake of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is contraindicated before surgery, because of inhibition of platelet activity and subsequent increased perioperative bleeding [16]. Aspririn should be discontinued 7–10 days prior to surgery [16]. Ibuprofen and other NSAIDs should be discontinued 4–7 days prior to surgery [16]. The discontinuation of vitamins and herbal supplements, such as vitamin E, chondroitin, glucosamine, Ginkgo biloba, and ginseng is encouraged because of the anticoagulant effects of these agents [16].

Intraoperative phase

The key to achieving a smooth end result with liposuction involves performing the suction from multiple angles and directions in a criss-cross motion.

During the procedure, sterile technique must be emphasized, with the use of antiseptic washes to the area the night before and immediately prior to the surgery. Superficial infections, usually around incision sites, are typically culture positive for staphylococcus and streptococcus. However, deeper infections which occur in a delayed fashion several months after the procedure occur with atypical mycobacterial species (*Mycobacterium abscessus*, *M. chelonae*, *M. fortuitum*) and have been associated with improper cleaning and sterilization of surgical instruments.

During liposuction, the surgeon should always use the non-dominant hand or "smart hand" to assess the position of the liposuction cannula at all times. Elevating the skin with the "smart hand" and then passing the cannula along the adipose tissue horizontally will preserve the integrity of the abdominal wall. Superficial placement of the cannula in this area is recommended to maximize the amount of fat removed, induce skin contraction, and allow a safe layered approach to fat removal.

One of the significant advantages of liposuction using the TLA technique is that it minimizes blood loss. However, often surgeons will fail to wait long enough after infiltration of the TLA solution until the vasoconstrictive effects of epinephrine (15–20 minutes after infiltration of TLA solution) have taken effect. During the procedure, the surgeons should keep a close eye on the aspirate, directing the cannula away from areas where there are greater volumes of blood relative to fat in the aspirate. Selecting the appropriate cannula size (4 mm should be the largest utilized) and blunt tip style will have a significant role in the decreased tendency for bleeding and hematoma formation. To decrease the risk of bleeding and hematoma formation, larger procedures such as high volume abdominal liposuction, should be considered in two stages.

During TLA, the maximum dosage of lidocaine used should be 55 mg/kg [4]. The lowest dose of lidocaine that provides complete local anesthesia should be utilized. The normal saline utilized should contain lidocaine in concentrations of 0.05–0.1% [4]. The peak plasma concentration of lidocaine occurs 12–18 hours postoperatively, given the slow systemic absorption of lidocaine from the adipose tissue [4]. Patients, family, and staff taking care of the patient should be aware of the symptoms and signs of lidocaine toxicity.

Postoperative phase

Postoperative compression garments will both enhance skin contraction and assist with more rapid removal of local tumescent solution. The compression garment is also critical in order to minimize or eliminate bleeding, hematoma and seroma formation, and to speed wound healing. Patient comfort after the procedure is also greatly improved by wearing compression garments. In general, it is recommended that the garment be worn around the clock for the first week and be worn half-time for the subsequent 2–3 weeks.

Any signs of infection should be evaluated and cultured as soon as possible. With atypical mycobacterial infections, it is important to obtain the culture medium requirements of the laboratory and to notify the laboratory that special processing of the specimen is needed. A rare case of necrotizing fasciitis has been reported with liposuction and thus any patient presenting with severe pain out of proportion to examination, surface blistering, and tenderness should be promptly evaluated for possible débridement and started immediately on broad-spectrum antibiotics and supportive care.

Lidocaine, epinephrine, and bicarbonate utilized in the tumescent solution have all been proven to have antimicrobial effects on a diverse range of pathogens (bacteria, fungi, viruses) and thus the large dilute volume of anesthetic solution with the tumescent technique may further have a role in the low rates of infection associated with this procedure. In addition, using fine cannulas (4 mm or less) will assist with deep bruising and seroma formation and infection risk.

Leaving the cannula sites open to drain leads to decreased hematoma and seroma formation. If significant hematomas form, they will usually spontaneously resolve or can be evacuated once they have liquefied. Large hematomas can be very uncomfortable for the patient and can prevent him or her from returning quickly to usual routines. Seromas need to be drained, sometimes repeatedly with recurrence, with subsequent compression applied to the area (Figure 56.9).

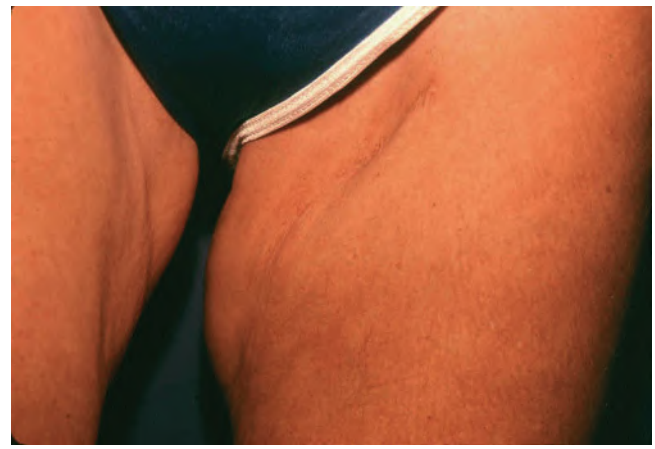


Figure 56.9 Adverse complication of liposuction: skin dimpling and scarring in medial thighs after overly aggressive liposuction procedure.

Conclusions and future directions

Liposuction with local TLA is a procedure that was designed and developed by dermatologic surgeons. It is a procedure with a documented safety record, longevity of results, and high levels of patient satisfaction. Liposuction using TLA only in the office setting has a documented superior safety profile which has been documented in a number of studies in the dermatologic surgery literature by Bernstein, Hanke, Coleman and Housman (Table 56.3).

Several of largest studies to date, the first by Hanke *et al.* in 1995 [6], reported data on 44 014 body areas treated with liposuction. There were no serious complications of death, emboli, hypovolemic shock, perforation of thorax or peritoneum, thrombophlebitis, seizures, or toxic reactions to drugs. Subsequently, in 2002, Housman *et al.* [24] reported data on 66 570 liposuction procedures. No deaths were reported and the serious adverse event ratio was low at 0.68 per 1000. In 2004, Hanke surveyed 39 tumescent liposuction centers and 688 patients treated with the tumescent technique to examine liposuction practice and safety [35]. The overall complication rate was 0.7%, with a minor complication rate of 0.57% and a major complication rate of 0.14% (1/688 patients). Patient satisfaction was very high among the surveyed population, where 91% of patients surveyed were positive about their decision to have liposuction.

In contrast, in the plastic surgery literature (Table 56.3) the case fatality and complication rates were significantly higher for liposuction. In the largest study to date among plastic surgeons by Grazer and de Jong in 2000 [36] evaluating data on 496 245 procedures, the fatality rate was 19.1/100 000; where the most common causes of death included thromboembolism (23.1%), abdomen/viscus perforation (14.6%), anesthesia/sedation/medication (10%), fat embolism (8.5%), cardiorespiratory failure (5.4%), massive infection (5.4%), and hemmorhage (4.6%).

Laser-assisted liposuction

Current studies are undergoing evaluating the ability to liquefy or rupture fat cells using various lasers [37–43]. The

Table 56.3 Liposuction safety studies.

Study/author	Year	Number of procedures	Specialty	Number of fatalities	Fatality rate
Newman, Dolsky [45]	1984	5458	Cosmetic surgeons (derm, ENT, etc.)	0	1/38426
Bernstein, Hanke [5]	1988	9478	Dermatologic surgeons	0	0
Temourian, Rogers [46]	1991	112756	Plastic surgeons	15	12.7/100000
Dillerud [47]	1991	3511	Plastic surgeons	0	0
Hanke *et al*. [6]	1995	15336	Dermatologic surgeons	0	0
ASPRS Task Force on Liposuction [48]	1998	24295	Plastic surgeons	5	20.6/100000
Jackson, Dolsky [49]	1997	200000	Cosmetic surgeons (derm, ENT, etc.)	1	2.4/100000
Grazer, De Jong [36]	2000	496245	Plastic surgeons	95	19.1/100000
Hughes [50]	2001	94159	Plastic surgeons	Not stated	1/47415 (lipo only) 17314 (lipo and other procedures) 1/3281 (lipo and abdominoplasty
Housman *et al*. [24]	2002	66570	Dermatologic surgeons	0	0
Hanke *et al*. [35]	2004	688	Dermatologic surgeons	0	0

laser devices most widely utilized to assist with liposuction include a helium-neon laser (635 nm), a diode laser (600–800 nm), and, most recently, a 1064 nm neodymium:yttrium aluminum garnet (Nd:YAG) laser [37–43]. The studies with a 635 nm diode laser utilized to release fat from adipocytes demonstrated changes in the adipose structure utilizing electron microscopy and magnetic resonance imaging (MRI) [37–44]. Six minutes of exposure to the 635 nm diode laser at 1.2 J/cm^2 resulted in a transitory pore in the cell membrane with resultant release of the fat into the interstitial space [37–44].

Recent studies have evaluated both the clinical and histopathologic effects of the 1064 nm Nd:YAG laser and 980 nm diode laser in laser-assisted lipolysis [37–44]. A recent study by Mordon *et al*. [37] demonstrated both enhanced lipolysis and skin contraction with the laser-assisted devices. Using an optimal thermal modeling approach, the authors demonstrated that increased heat generated by the laser in the deep reticular dermis may result in collagen and elastin synthesis and resultant skin tightening which they observed clinically after laser lipolysis. Goldman demonstrated skin contraction and enhanced lipolysis with the use of the 1064 nm Nd:YAG laser for submental liposuction [39]. Clinical results of tissue tightening were correlated with histologic analysis confirming laser-induced rupture of the adipocyte membrane. Kim *et al*. [38] reported the results of 29 patients treated with laser lipolysis with the 1064 nm Nd:YAG device and demonstrated clinical improvement (at 3 months, average of 37%) as well as decreased adiposity as measured by MRI (average of 17% reduction in volume). Greater improvement was noted in smaller volume areas, such as the submentum, in both clinical outcome and dermal tightening. However, several other recent comparative trials evaluating laser-assisted liposuction with the 1064 nm Nd:YAG laser have shown equivocal results with laser-assisted liposuction relative to liposuction alone [42–44].

Laser-assisted liposuction has been purported to result in both mechanical cavitation of fat resulting in greater ease of suction and greater skin retraction after the procedure resulting in enhanced tightening. However, further studies are highly needed to evaluate scientifically the benefits of pretreatment with lasers for ease of adipose removal and enhanced cosmesis [37–43].

References

1 Fischer G. (1990) Liposculpture: the correct history of liposuction, part I. *J Dermatol Surg Oncol* **16**, 1087–9.

2 Ilouz Z. (1983) Body contouring by lipolysis: a 5 year experience with over 3000 cases. *Plast Reconstr Surg* **72**, 591–7.

3 Fournier P. (1987) *Body Sculpting Through Syringe Liposuction and Autologous Fat Re-injection*. Corona del Mar: Samuel Rolf International.

4 Klein JA. (1990) Tumescent technique for regional anesthesia permits lidocaine doses of 35–55 mg/kg for liposuction. Peak plasma levels are diminished and delayed for 12 hours. *J Dermatol Surg Oncol* **16**, 248–63.

5 Bernstein G, Hanke CW. (1988) Safety of liposuction: a review of 9478 cases performed by dermatologists. *J Dermatol Surg Oncol* **14**(10), 1112–4.

6 Hanke CW, Bernstein G, Bullock S. (1995) Safety of tumescent liposuction in 15,336 patients: national survey results. *Dermatol Surg* **21**, 459–62.

7 Ostad A, Kageyama N, Moy R. (1995) Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction. *Dermatol Surg* **22**, 921–7.

8 Klein JA. (2000) *Tumescent Technique: TLA and Microcannular Liposuction*. St. Louis, MO: Mosby.

9 Hanke CW. (1999) State-of-the-art liposculpture in the new millennium. *J Cutan Med Surg* **3** (Suppl 4), S36–42.

10 Pasman WJ, Saris WH, Westerterp-Plantenga MS. (1999) Predictors of weight maintenance. *Obes Res* **7**, 43–50.

11 Brownell KD, Rodin J. (1994) Medical, metabolic and psychological effects of weight cycling. *Arch Intern Med* **154**, 1325–30.

12 Ozgur F, Tuncali D, Guker Gursu K. (1998) Life satisfaction, self-esteem and body image: a psychosocial evluation of aesthetic and reconstructive surgery candidates. *Aesthetic Plast Surg* **22**, 412–9.

13 Mann MW, Palm MD, Sengelmann RD. (2008) New advances in liposuction technology. *Semin Cutan Med Surg* **27**, 72–82.

14 Hanke CW. (1989) Liposuction under local anesthesia. *J Dermatol Surg Oncol* **15**, 12.

15 Lillis PJ. (1988) Liposuction surgery under local anesthesia. Limited blood loss and minimal lidocaine absorption. *J Dermatol Surg Oncol* **14**, 1145–8.

16 Butterwick J. (2003) Liposuction consultation and preoperative considerations. In: Narins RS, ed. *Safe Liposuction and Fat Transfer*. New York: Marcel Dekker.

17 Jacob CI, Kaminer MS. (2003) Tumescent anesthesia. In: Narins RS, ed. *Safe Liposuction and Fat Transfer*. New York: Marcel Dekker.

18 Hanke CW, Coleman WP. (1999) Morbidity and mortality related to liposuction: questions and answers. *Dermatol Clin* **17**, 899–902.

19 Coleman WP 3rd, Hanke CW, Lillis P, Bernstein G, Narins R. (1999) Does the location of the surgery or the specialty of the physician affect malpractice claims in liposuction? *Dermatol Surg* **25**, 343–7.

20 Landry GL, Gomez JE. (1991) Management of soft tissue injuries. *Adol Med* **2**, 125–40.

21 Klein JA. (2000) Miscellaneous complications. In: Klein JA, ed. *Tumescent Technique, Tumescent Anesthesia and Microcannular Liposuction*. St. Louis, MO: Mosby.

22 Narins RS, Coleman WP. (1997) Minimizing pain for liposuction anesthesia. *Dermatol Surg* **23**, 1137–40.

23 Klein JA. (2000) Thrombosis and embolism. In: Klein JA, ed. *Tumescent Technique, Tumescent Anesthesia and Microcannular Liposuction*. St. Louis, MO: Mosby.

24 Housman TS, Lawrence N, Mellen BG, George MN, Filippo JS, Cerveny KA, *et al*. (2002) The safety of liposuction, results of a national survey. *Dermatol Surg* **39**, 971–8.

25 Narins RS. (2003) Abdomen, hourglass abdomen, flanks and modified abdominoplasty. In: Narins RS, ed. *Safe Liposuction and Fat Transfer*. New York: Marcel Dekker.

26 Jacob CI, Kaminer MS. (2003) Surgical approaches to the aging neck. In: Narins RS, ed. *Safe Liposuction and Fat Transfer*. New York: Marcel Dekker.

27 Goddio AS. (1992) Suction lipectomy: the gold triangle at the neck. *Aesth Plast Surg* **16**, 27–32.

28 Kamer FM, Minoli JJ. (1993) Postoperative platysmal band deformity: a pitfall of submental liposuction. *Arch Otolaryngol Head Neck Surg* **119**, 193–6.

29 Key D. (2008) Efficacy of skin tightening and contour correction of the lower face and jowl using 1320 nm laser lipolysis: a comparison evaluation of lipolysis without aspiration, lipolysis with aspiration and aspiration without lipolysis. Abstract presented at American Society of Laser Medicine and Surgery Conference, Kissimmee, FL.

30 Goddio AS. (1992) Suction lipectomy. The gold triangle at the neck. *Aesth Plast Surg* **16** 27–32.

31 Samdal F, Kleppe G, Amland PR, Abyholm F. (1994) Surgical treatment of gynecomastia. *Scan J Plast Recontstru Hand Surg* **28** 123–30.

32 Matarasso A, Courtiss EH. (1991) Suction mammoplasty, the use of suction lipectomy to reduce large breasts. *Plast Reconstr Surg* **87**, 709–10.

33 Gray LN. (1988) Liposuction breast reduction. *Aesthetic Plast Surg* **22**, 159–62.

34 Bernstein G. (1999) Instrumentation for liposuction. *Dermatol Clin* **14**, 735–49.

35 Hanke W, Cox SE, Kuznets N, Coleman WP 3rd. (2004) Tumescent liposuction report performance measurement initiative: national survey results. *Dermatol Surg* **30**, 967–77.

36 Grazer FM, de Jong RH. (2000) Fatal outcomes from liposuction: census survey of cosmetic surgeons. *Plast Reconstr Surg* **105**(1), 436–46.

37 Mordon SR, Wassmer B, Reynaud JP, Zemmouri J. (2008) Mathematical modeling of laser lipolysis. *Biomed Eng Online* **7**, 10.

38 Kim KH, Geronemus RG. (2006) Laser lipolysis using a novel 1,064 nm Nd:YAG Laser. *Dermatol Surg* **32**, 241–8.

39 Goldman A. (2006) Submental Nd:YAG laser-assisted liposuction. *Lasers Surg Med* **38**, 181–4.

40 Ichikawa K, Miyasaka M, Tanaka R, Tanino R, Mizukami K, Wakaki M. (2005) Histologic evaluation of the pulsed Nd:YAG laser for laser lipolysis. *Lasers Surg Med* **36**, 43–6.

41 Morton S, Wassmer B, Reynaud P, Zemmouri J. (2008) Mathematical modeling of laser lipolysis. Abstract presented at American Society of Laser Medicine and Surgery Conference, Kissimmee, FL.

42 Dressel T, Zelickson B. (2008) Laser liposuction a work in progress. Abstract presented at American Society of Laser Medicine and Surgery Conference, Kissimmee, FL.

43 Weiss R, Weiss M, Beasley K. (2008) Laser lipolysis: skin contraction effect of 1320 nm. Abstract presented at American Society of Laser Medicine and Surgery Conference, Kissimmee, FL.

44 DiBernardo B, Goldman M, Saluja R, Woodhall K, Reyes J. (2008) Mulicenter study evaluation of sequential emission of lasers for the treatment of fat with laser assisted lipolysis.

Abstract presented at American Society of Laser Medicine and Surgery Conference, Kissimmee, FL.

45 Dolsky RL, Newman J, Fetzek JR, Anderson RW. (1987) Liposuction. History, techniques, and complications. *Dermatol Clin* **5**(2), 313–33.

46 Teimourian B, Rogers WB 3rd. (1989) A national survey of complications associated with suction lipectomy: a comparative study. *Plast Reconstr Surg* **84**(4), 628–31.

47 Dillerud E, Håheim LL. (1993) Long-term results of blunt suction lipectomy assessed by a patient questionnaire survey. *Plast Reconstr Surg* **92**(1), 35–42.

48 ASPRS Task Force on Liposuction, available at http://www.plasticsurgery.org/Medical_Professionals/Publications/PSN_News_Bulletins/ASPS_urges_members_to_exercise_caution_in_lipoplasty_procedures_Task_Force_report_calls_for_scrutiny_of_training_large_volume_removals.html, accessed August 2, 2009.

49 Dolsky RL. (1997) State of the art in liposuction. *Dermatol Surg* **23**(12), 1192–3.

50 Hughes CE 3rd. (1999) Patient selection, planning, and marking in ultrasound-assisted lipoplasty. *Clin Plast Surg* **26**(2), 279–82; ix.

Chapter 57: Liposuction of the neck

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BASIC CONCEPTS

- Neck liposuction is used to remove excess fat from the neck area and minimize skin sagging.
- Small cannulas and multiple entry sites are necessary to achieve even fat removal without ridging or deformity.
- Tumescent anesthesia is key to reducing pain and bruising while facilitating fat removal.
- Proper selection of patients with fat in front of the platysma muscle can ensure a successful outcome.
- Overremoval of fat on the lower neck should be avoided.

Introduction

One of the first signs of aging that prompts patients to seek cosmetic treatment is the sagging neck. Tumescent liposuction of this area often dramatically rejuvenates the neckline and is one of the most common body areas treated with this modality. Although this area may seem complicated to the novice surgeon, liposuction of the neck is relatively quick, safe, and readily learned. It is also well tolerated by patients with rapid healing in 3–4 days. With careful selection of patients and good technique, this is a very rewarding area for patients and surgeon alike.

Anatomy

The primary goal of liposuction of the neck is restoration of the cervicomental angle (CMA). This is the angle formed by the horizontal plane of the submental region and the vertical plane of the neck (Figure 57.1) [1]. The ideal angle is generally considered to be 90–100° or more, up to 135° [1–3]. Other anatomic features of a youthful neck include definition of the inferior mandibular border, subthyroid depression, a thyroid notch visible as a gentle indentation, and a visible anterior border of the sternocleidomastoid muscle [1]. The face should be distinct from the neck such that a shadow should be cast on to the upper neck by the mandible. With aging and/or genetics, there may be accumulation of submental fat leading to blunting of the CMA or a "double chin." Other anatomic factors may also contribute to an obtuse CMA such as a low-lying hyoid bone, microgenia, or retrognathia. Ideally, the hyoid bone should be positioned at the C3–C4 level [4]. Lateral to the submental region, there may be loss of definition of the submandibular region leading to an unattractive continuum between the face and the neck. Further contributing to fullness in this area may be ptotic submandibular glands located along the inferior midportion of the mandibular ramus. Other stigmata of aging in the lower third of the face may need to be addressed such as the presence of jowls and the development of a depression just medial to the jowl called the prejowl sulcus [5].

The platysma muscle is the thin layer of muscle just deep to the submental fat pad arising from the cervicopectoral fascia inferiorly and attaching to the depressor anguli oris, risorius, and mentalis muscles superiorly with a varying degree of decussation at the midline [6]. Approximately 75% of the time, the fibers interlace 1–2 cm below the chin but separate in the suprahyoid region. Less often, the fibers decussate all the way down to the thyroid cartilage or not at all [7]. With aging, the medial fibers of the platysma muscle may hypertrophy into thick visible bands. Deep to the platysma, there may be a collection of fat that is midline and submental. While the preplatysmal fat pad is accessible to tumescent liposuction, the retroplatysmal fat pad is not and requires direct excision for removal. Having the patient clench his or her teeth tightens the platysma and aides in distinguishing pre- or retroplatysmal fat [3]. The amount of submental retroplatysmal fat has been estimated to vary between 30% and 57% of the total amount [8].

Also deep to the platysma is the marginal mandibular branch of the facial nerve, which is vulnerable to trauma during liposuction of this area. This motor nerve runs along the mandible, parallel to the ramus and is typically most superficial at the anterior border of the masseter muscle (Figure 57.2). However, the position of this nerve is variable, and it can be found 3–4 cm inferior to the ramus. Caution

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

must be exercised when suctioning this region because repeated pressure and rubbing from the cannula may result in temporary neuropraxis. While this typically lasts only 4–6 weeks, the distorted appearance is very distressing to the patient. To minimize injury to this nerve, patients should be asked to clench their teeth and the anterior edge of the massester should be marked where the nerve is likely to be found, at or just below the level of the ramus. Other techniques to minimize potential injury to this nerve are described below. Another structure less vulnerable to injury is the external jugular vein which passes over the sternocleidomastoid muscle. The vessel could be injured from inadvertent deep penetration by the cannula from a lateral position.

Esthetic considerations

To the novice surgeon, liposuction of the neck entails simply removing fat in the submental area. However, there are some esthetic principles and proportions that should be considered for optimal esthetic results (Figure 57.1) [9,10]. When evaluating the cervicomental angle, one should evaluate the entire profile of the head and neck. The ideal profile should be viewed with the head held in the Frankfurt horizontal plane. This is the horizontal plane, parallel to the floor, in which a horizontal line can be drawn through the highest point of the ear canal meatus and the lowest point of the orbital rim [10]. In this position, the chin is at the proper level for assessing the CMA and for uniformity of preoperative and postoperative photographs. It is said that in this position, the glabella, nasal root, lip projection, and mentum should ideally align in a vertical facial plane. Utilizing this proportion enables the surgeon to assess the relative strength of the chin and the adequacy of volume in the face. The face should be divisible by thirds from the midline frontal scalp to glabella, the glabella to the infranasal area, and the infranasal area to the mentum. Often, the lower third of the face is reduced in volume because of bone loss, aging, genetics, or other factors.

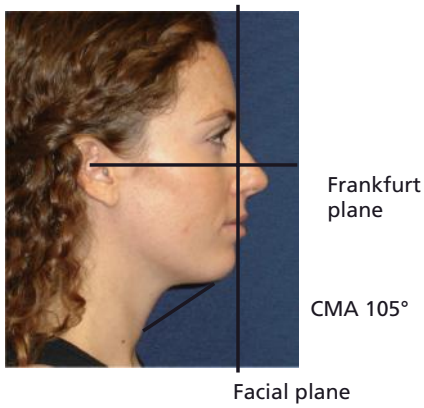


Figure 57.1 The youthful neck with a cervicomental angle of 100°. The facial and Frankfurt plane are shown with glabella, subnasale, and chin in alignment.

Patient selection

Potential candidates for submental liposuction fall into three groups: correction of genetic traits, rejuvenation for mild to moderate aging, and restoration of more advanced aging. The latter two groups may also have some pre-existing hereditary factors. All groups should be assessed systematically and all determinates to the aging neck evaluated (Table 57.1).

The first group of patients tends to be relatively young, typically less than 30 years, and usually of normal weight, although this deposit makes them look heavier or older than they are. Although the skin quality is excellent, the profile is obscured by submental fat. There are often contributing factors to the obtuse CMA, such as microgenia or a low-lying

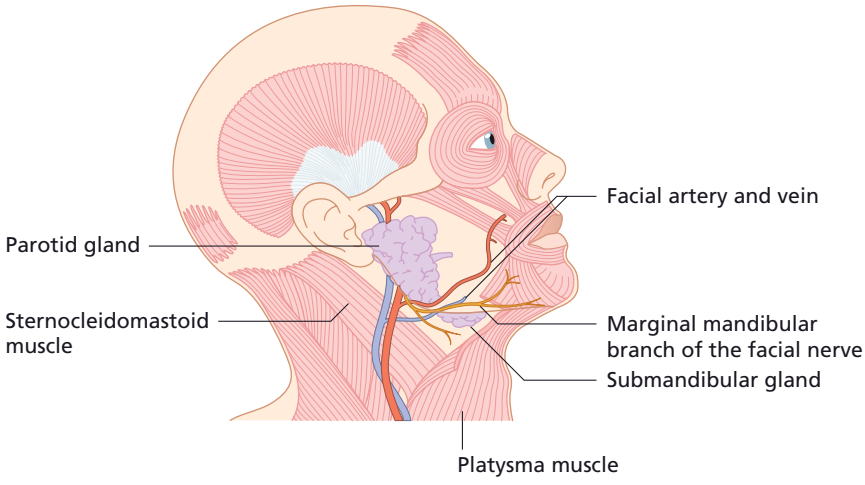


Figure 57.2 Marginal mandibular branch of the facial nerve and other relevant anatomy.

Table 57.1 Preoperative assessment.

1	Cervicomental angle
2	Degree of submental fat
3	Platysma banding
4	Degree of subplatysma fat
5	Hyoid position
6	Presence of jowls
7	Position of submandibular glands
8	Adequacy of chin profile
9	Skin thickness
10	Skin laxity

hyoid bone. These limitations should be addressed at the time of the consultation. Patients in this age group may also have quite full cheeks, but with age cheek hollows often become more marked. Removal of fat may then retrospectively be seen as inappropriate.

The next group of patients is typically 35–50 years old with some skin laxity brought about by photoaging, facial volume loss, and a genetic tendency towards submental fat accumulation. They are often mildly overweight, but even at ideal weight, the problem persists.

The last group is over 55 years old and has submental fat but in addition significant skin redundancy, bone and volume loss, platysma banding, and photoaging. Many in this group would fare better with reconstructive surgery, but at times the risk:benefit ratio – that is, the improvement offered by liposuction alone – will satisfy those wishing to avoid the risks of a more invasive surgical procedure. These patients should be carefully assessed, as liposuction alone could significantly worsen the appearance of the skin, platysma bands, or expose ptotic submandibular glands.

In all three groups, males may show relatively less improvement than females. Their thickened, bearded skin retracts less readily than that of females. Even thinner females with little submental fat often show good benefit because of marked skin retraction after liposuction.

Consultation and physical examination

The consultation is a key step in communicating expected risks and benefits. In our practice, patients initially voice their concerns to a practice consultant. The consultant reviews treatment options and helps patients develop and prioritize their beauty wish list. Patients often pull back the neck tightly and, in the same breath, state they would never want a facelift. If liposuction alone is being considered, it is helpful to grasp the submental fat and tuck it up under the chin. This maneuver essentially "removes" the fat from view without pulling up on the jowls (Figure 57.3). If the patient has lax, photoaged skin, the surgeon should bunch it up a little and show the patient that it could look more wrinkled after the procedure. The surgeon should pull the skin back and demonstrate the probable result of a rhytidectomy to help the patient visualize the different results of different procedures. Any contributing factors to the blunted neck angle are reviewed with the patient at this point and additional corrective measures and alternative treatments are discussed. Platysma bands can be identified by having the patient grimace. An overview of the risks is also part of the consultation.

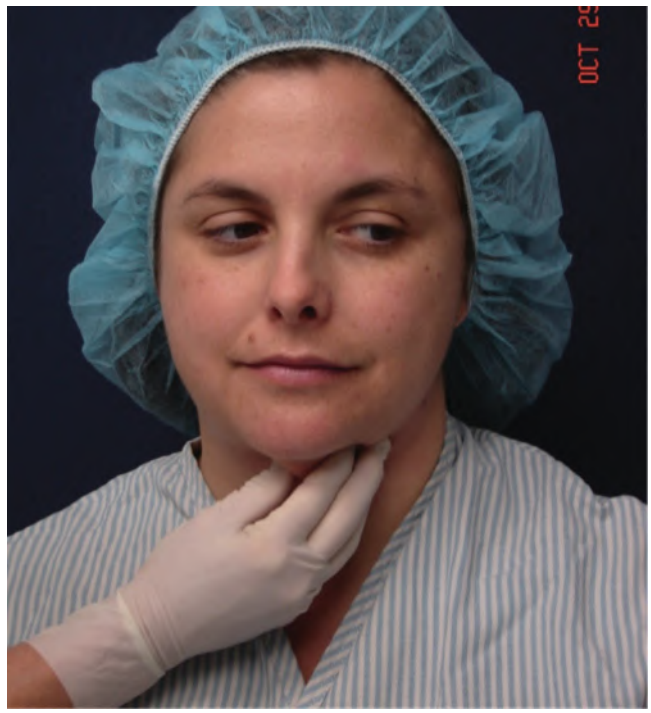


Figure 57.3 Grasping and tucking the submental fat to demonstrate expected results of submental liposuction without upward posterior retraction seen in rhytidectomy.

At this point, the surgeon typically leaves the room, and the consultant answers additional questions, reviews the fee quote, and offers to schedule the procedure. Should the patient decide to proceed, he or she returns for a second visit for a preoperative examination. At this visit, the patient has a modified physical examination, reads and signs consents forms, and is given written preoperative and postoperative instructions. Preoperative laboratory studies and photographs are completed. Typical preoperative laboratory studies include: full blood count, chemistry panel, prothrombin time/partial thromboplastin time (PT/PTT), international normalized ratio, and viral titers. A prescription for preoperative antibiotics is given to start the night before surgery for a total of 10 days.

Procedure

Markings

The preoperative markings are summarized in Table 57.2. With the patient in an upright position, the edge of the mandible is outlined and a circle is drawn around the perimeter of the main accumulation of fat in the submental area (Figure 57.4). An "X" is then marked on the most visible mound within that circle. An additional circle may be drawn just inferior to the submental area if indicated, or concentric circles may be drawn around the main deposit of fat. The jowls are outlined as they extend both superior and inferior to the mandibular border. Again, the fullest aspects of the jowl are marked with an "X." Laterally, fullness superior to the mandible is outlined. Inferior to the mandible, small "X's" or a line should be drawn where maximum definition is desired. This is the area where a linear shadow should be cast.

The patient is then instructed to clamp down on the back teeth. The edge of the masseter is then palpated and an "X" is placed at the probable location of the marginal mandibular nerve, preferably in a different color. The platysma is assessed during this maneuver and the bands may be outlined in another color. Other landmarks that may be highlighted include the anterior border of the sternocleidomastoid muscle, the hyoid bone, and the inferior border of the neck.

Table 57.2 Preoperative marking.

1	Mark border of mandible
2	Encircle submental fat and place "X" on apex
3	If present, outline jowl and excess fat in lower lateral cheek
4	Make a line or "X's" where submandibular concavity desired
5	Mark likely position of marginal mandibular nerve
6	Dot in platysma bands if indicated
7	Draw parallel vertical lines to base of neck

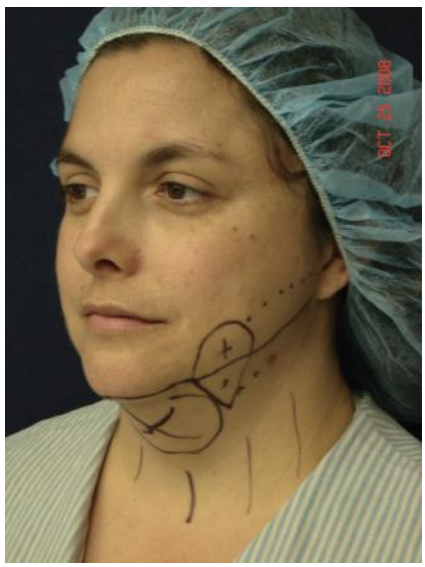


Figure 57.4 Preoperative markings.

Parallel vertical lines are drawn from the immediate submental area down the remainder of the neck to the base of the neck. Fat is rarely removed from the lower two-thirds of the neck because the skin here is often so thin that it will look more aged and wrinkled if underlying fat is removed. The long vertical lines remind the surgeon not to remove fat but rather to tunnel through, without suction. Tunneling is thought to create tissue injury that will then stimulate some neocollagenesis and perhaps thicken or tighten the skin to some degree. On rare occasion if the patient has horizontal rhytids of the lower two-thirds of the neck and excessive fat, very conservative liposuction of the lower neck will significantly improve fat bulges and horizontal furrows.

Anesthesia and infiltration

Patients undergoing liposuction of the neck do not require general anesthesia and many of them could undergo the procedure without any sedation at all. However, most patients prefer to have some anxiolysis and are typically given 1 mg lorazepam p.o. prior to the procedure. Alternatively, if a surgicenter is utilized, an intravenous line may be started and the patient given 1.0 mg midazolam IV along with 25 µg fentanyl IV as a one-time dose. Intravenous medications are often preferred because the patient will feel instantly relaxed and will be nearly fully awake when the procedure is over. One must be careful with intravenous medicationss to avoid excessive sedation and apnea; however, the low doses utilized above result in mild sedation with appropriate responsiveness.

The patient is then positioned in a supine position with a neck roll partially under the shoulders so that the head rolls back comfortably in an extended position. After prepping with benzalkonium chloride antiseptic (Zephiran™, Sanofi-Aventis, Bridgewater, NJ, USA), the patient is draped with sterile towels, including a sterile turban (Figure 57.5). A lap sponge is placed over the patient's eyes for comfort and protection.

Tumescent anesthesia of the neck is the next step. Superficial blebs of tumescent lidocaine are first made in five sites, corresponding to the entry sites for the cannula. Dilute lidocaine consisting of Klein's standard formula with lidocaine 0.1% is infiltrated into the subcutaneous space with the aid of an infusion pump [11]. A 25-gauge spinal needle is used initially in a fan-like motion, introduced through five blebs, until the entire surgical field has been partially infused. The tumescent fluid is warmed, the infusion rate is low, and the needle gauge is small, assuring that there is minimal

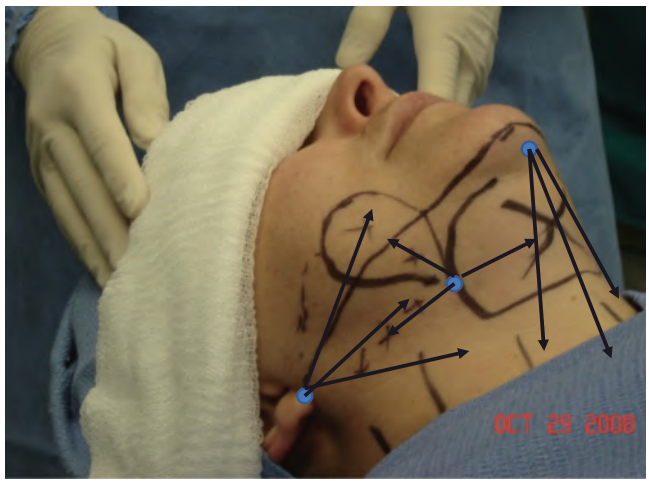


Figure 57.5 Operative position with chin extended. Three of the five entry sites are denoted with circles and typical fanning pattern shown.

Table 57.3 Standard technique.

1	Debulk in midline submental region from three entry sites
2	Turn head laterally, suction lateral cheek/submandibular region
3	Avoid rasping mandible
4	Conservative suction of the jowl
5	Repeat steps 2 and 3 on contralateral side
6	Return head to central position. Tunnel inferiorly
7	Palpate all areas for smoothness
8	Apply French tape

discomfort for the patient. Approximately 50–100 mL is utilized at this point. The spinal needle is then changed to 20-gauge, at a faster infusion rate, so that very quickly, within 5–15 minutes, the entire surgical field is tumesced. The patient may feel a bit anxious at this point because the neck will feel taut. Reassure patients that they can still breathe and swallow and that the tightness will loosen within a few minutes of starting the liposuction. It should be noted that it is not necessary to infiltrate the lower half of the neck. While the procedure is underway, the solution will drift inferiorly to the sternal notch, so that at the end of the procedure, when tunneling the lower neck may be desired, the lower neck will have adequate anesthesia. Typical volumes of infiltrated solution are 400–500 mL.

Liposuction: standard operative techniques

The standard liposuction procedure utilizes five entry sites and a thorough suction with small cannulae (Table 57.3). The submental area is approached through three small stab incisions with an 11 blade. Although it may be tempting to perform the entire procedure through one site, the most thorough and smooth result requires criss-crossing through multiple sites. In addition, one avoids a depression which is commonly seen under a single incision site. Only small cannulae are utilized, such as the Klein 14 and 16 gauge Finesse, to avoid ridges or troughs in thin-skinned patients. In patients with thicker skin, a slightly more aggressive cannula is sometimes needed such as a 12-gauge Klein Finesse or the multi-holed Klein Capistrano, gauge 14. These smaller cannulas also preserve connective tissue strands throughout the fat and are thought to maximize retraction of the skin.

A thorough fanning technique is utilized through all three incisions with the cannula attached to the suction device. An assistant may anchor the skin at the entry site and elsewhere to minimize skin buckling, thereby facilitating long smooth strokes of the cannula. This is the area to be aggressive, from the submental crease to the superior edge of the thyroid cartilage, approximately 8–9 cm caudal to the submental crease. The end point in this area is a thin pinch of the skin. When lifting up a cannula under the skin, the overlying skin should be palpated and free of lumps. A thin layer of fat, approximately 3–5 mm in thickness should be left to prevent surface irregularities [12]. The cannula may be visible beneath the skin.

The patient's head is then turned to the side and a fourth incision site is made. If indicated by the preoperative examination, very conservative liposuction of the lower cheek is performed. Usually, less than 10 strokes of the cannula are needed in order to taper the face. One must be careful not to overressect this area and to feather (tunnel without suction) into the cheek immediately superior to the treated area in order to avoid a shelf or step-off. It is also important that fat is left behind. A strong, smooth, mandibular border is a youthful feature so it is rarely necessary to remove fat immediately overlying the mandible. The cannula is then directed approximately 3–4 cm below the ramus. This is a key area for removing fat to optimize definition between the head and the neck. Thorough removal is performed along this region. The surgeon must be mindful not to rasp against the ramus while performing liposuction with the head turned because of the proximity of the marginal mandibular nerve. In this position, the nerve may be located 3–4 cm below the mandible and become more superficial. Although it is deep to the platysma, this muscle is very thin and could be punctured by a small cannula [13]. If liposuction is needed near the ramus, one should pinch up the skin off the ramus and avoid deep fat.

Special attention is then directed toward the jowl. If the jowl is large, a separate stab incision is made with an 18-gauge No-Kor needle, at the most caudal extension of the jowl (Figure 57.6). A 16-gauge Klein Finesse cannula is then utilized to very conservatively remove less than 30% of the fat. Excessive removal in this area is not necessary as the skin will redrape nicely and overresection will result in deepening of the adjacent marionette fold. These same steps are then repeated on the contralateral side.

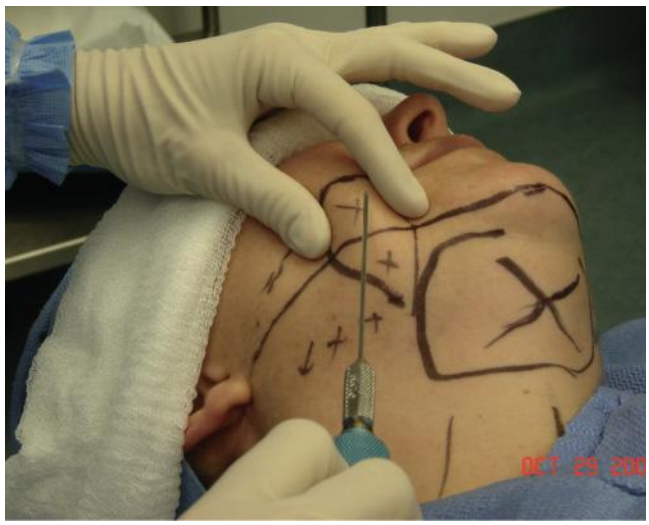


Figure 57.6 Liposuction of the jowl with a 16-gauge Klein Finesse cannula. The skin is pinched up by the non-dominant hand to avoid rasping the cannula against the mandible.

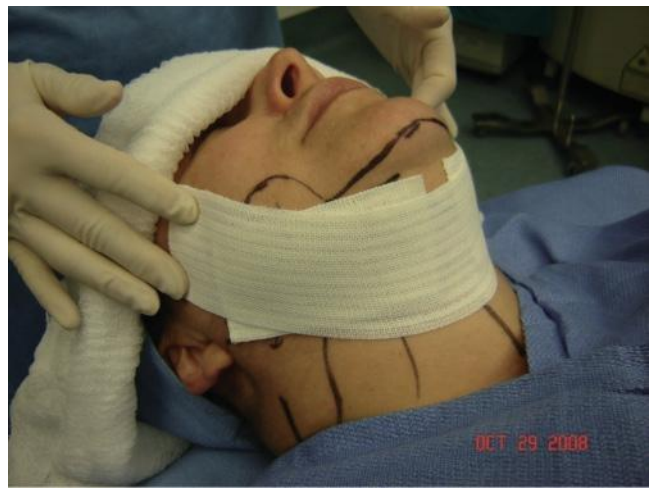


Figure 57.7 French tape with two shorter pieces applied with traction to the midline and a third piece across entire area. This helps to decrease central pooling.

After liposuction of both sides, the head is then returned to a central position. A 14-gauge Klein Finesse cannula is passed through the three central incisions sites to check for remaining fat deposits.

Sometimes there are stubborn deposits inferior to the lowermost extension of the jowls and this area is specifically checked. Tunneling or feathering without suction is then performed with the cannula passing through the entire surgical field, down to the sternal notch without suction. Some surgeons recommend "windshield wiping" at this point in order to gain maximal skin retraction. In the author's opinion this is not necessary and may have a negative effect in the development of delayed and unattractive adherence of the skin to underlying fascia. If platysma bands were visible at the preoperative examination, it may be helpful to take a spatula-tipped cannula and tunnel underneath them to reduce cutaneous attachments. Others prefer a closed neck V-shaped neck dissector to release tethering fibrous bands [14].

At the end of the procedure, three pieces of French tape are applied as shown in Figure 57.7. This helps to minimize pooling of tumescent fluid and free floating adipocytes in the submental area and minimizes postoperative bruising. It is removed 23–48 hours after the procedure.

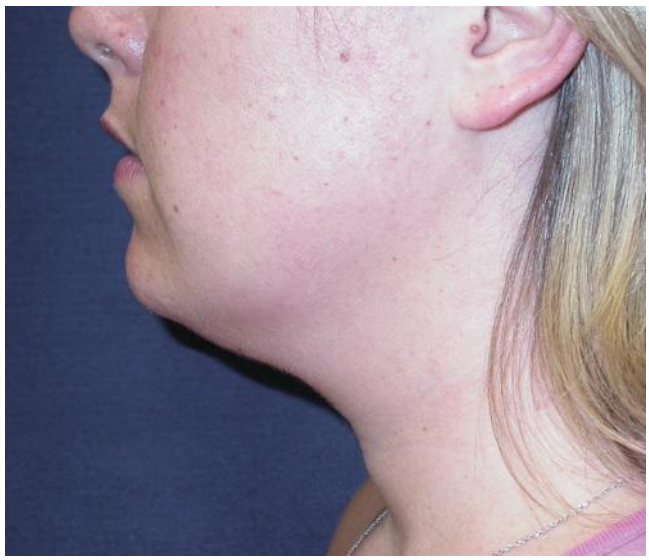
Postoperative course

In addition to French tape, patients wear a chin strap 24 hours a day for 3–4 days. The strap is then worn 2–4 hours per day for another 3 weeks. Immediately after the procedure, patients experience minimal to no discomfort. Mild discomfort may last 2–4 days. Patients may return to work after the initial few days at home. Purpura is typically minimal. If it develops, it tends to drift below the collar line and can be covered with clothing or scarves. During the first 2 weeks postoperatively, the submental area swells and patients will note increasing induration. There may be small focal areas of induration appearing as lumps or areas of stiff skin that crease unnaturally with movement. Patients should be advised ahead of time because induration always develops as an expected, temporary condition that resolves over a period of 4–8 weeks. Lymphatic massage may be helpful as the induration most likely represents a localized interstitial edema. Rarely, a larger nodule develops that is unsightly. Low doses of 2.5 mg/mL Kenalog (Bristol-Myers Squibb Princeton, NJ, USA) may be injected to reduce the edema more quickly.

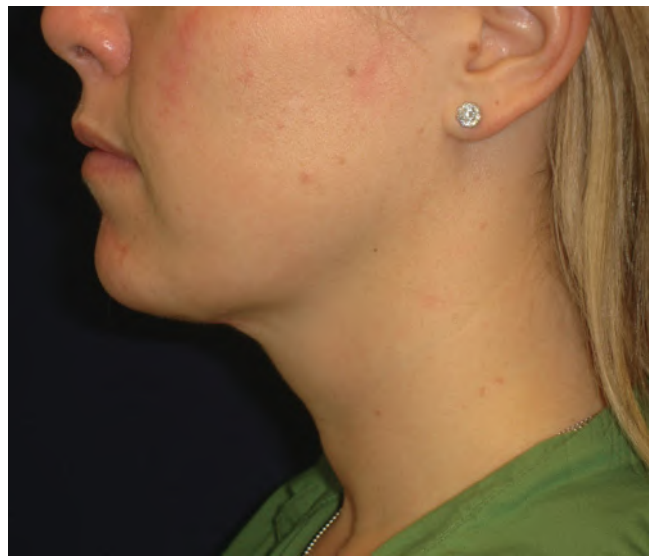
After the healing process, expected benefits of liposuction of the neck and jowls include reduction of adipocities, and skin retraction leading to elevation of the submental area, flattening of the jowls, and a reduced cervicomental angle (Figures 57.8 and 57.9). The capacity of the skin of the neck to retract and redrape in this area is outstanding and remarkable even compared to liposuction in other areas [15]. The very small incision sites (3 mm or less) heal readily and essentially ensure a scarless procedure. Avoiding both surgical scars and general anesthesia are key aspects of this procedure that factor into the patient's choice over more invasive options.

Complications

Submental liposuction has a very low rate of complications with proper careful technique. Immediate potential complications include bleeding or hematoma. With tumescent liposuction and blunt-tipped cannulas the risk of significant

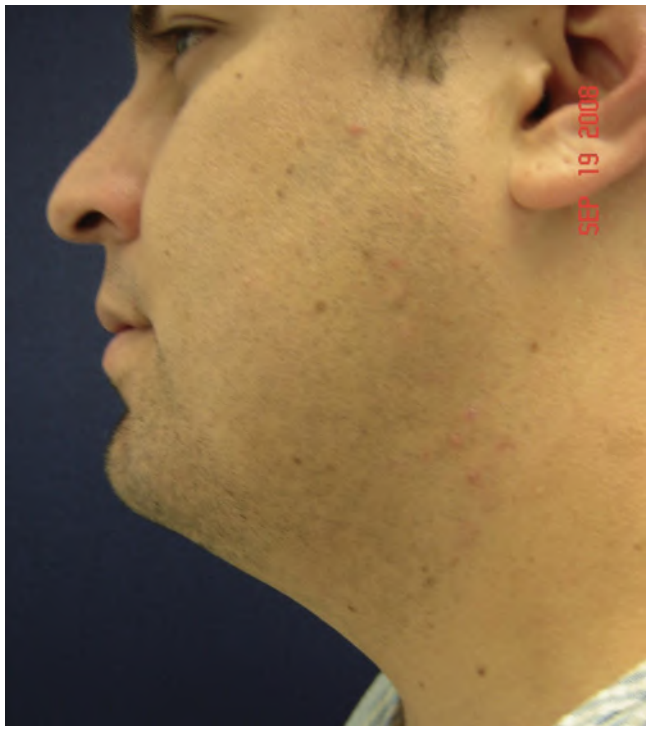


(a)

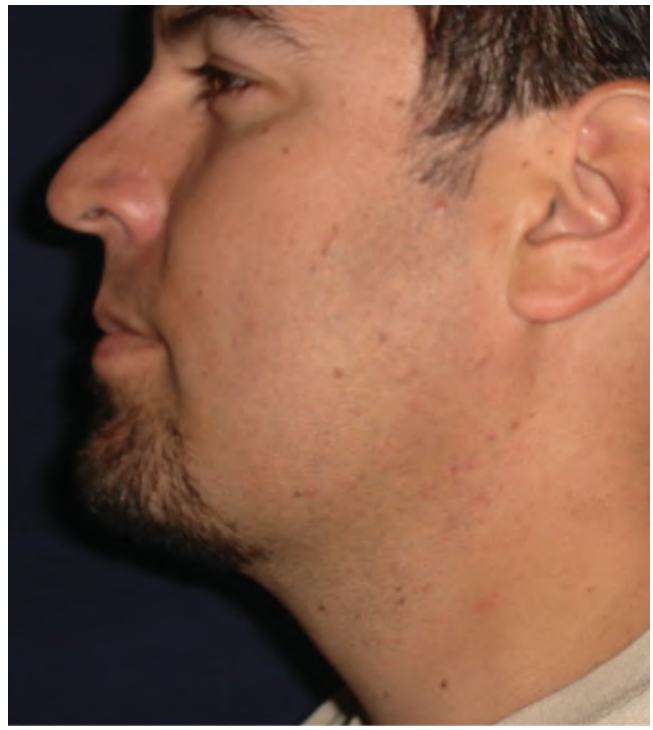


(b)

Figure 57.8 Before (a) and 3 years after (b) removal of 50 mL of supranatant fat.



(a)

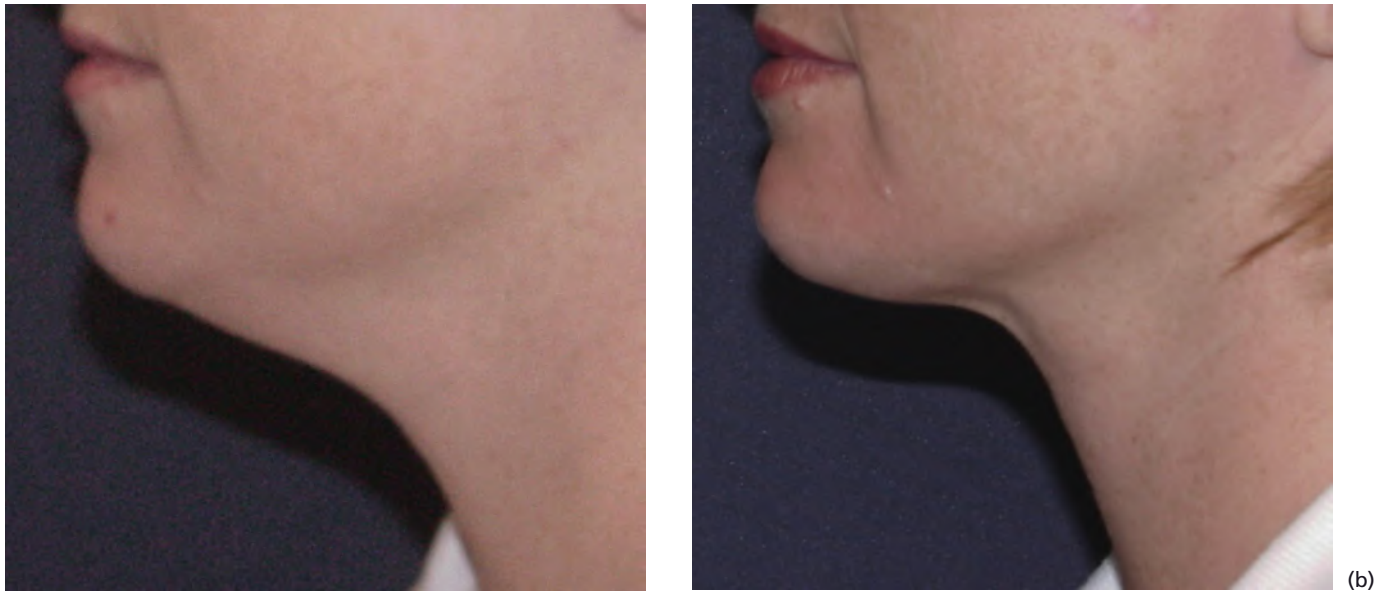


(b)

Figure 57.9 Before (a) and 1 month after (b) removal of 100 mL of supranatant fat. CoolLipo laser applied at 15 W, 40 Hz for 625 pulses with simultaneous suction. After suction, skin tightening was performed at 5 W, 50 Hz for 93 pulses.

bleeding is very low. Postoperative compression further minimizes this risk.

Temporary injury to the marginal mandibular nerve is probably the most common complication. It is important to be aware of the likely position of this nerve, anterior to the masseter muscle and at the level of the ramus or 3–4 cm inferior to the border. The nerve is most vulnerable when the head is turned to the side. It is also prone to injury if one attempts to treat the jowl from a medial, submental incision site. Avoidance of brushing against the mandible in any position and avoidance of penetrating the thin platysma muscle is essential. In addition, approaching the jowl from the previously described inferior position should nearly eliminate this potential risk. If paresis develops, it presents



(a) (b)

Figure 57.10 Small platysma bands unmasked after submental liposuction (b).

not as ipsilateral weakness, but rather hyperkinesis of the contralateral side.

This side effect is temporary, rarely lasting beyond a few weeks, but it may last for 2–3 months. If troublesome to the patient, a few units of botulinum toxin may be placed in the contralateral, hyperkinetic, depressor labii inferioris. Permanent injury to the marginal mandibular nerve has not been reported after tumescent liposuction because there is no sharp instrumentation. Sensory nerves may also be temporarily affected. Reassurance that the numb feeling will resolve within 4–6 weeks generally consoles the patient. Postoperative edema has been mentioned previously.

One more troubling aspect of this is the development of a submental fold. This is most likely caused by the compression garment loosening in this area. Patients with larger necks, low hyoid bones, and who frequently flex their neck for work or hobbies (i.e. needlepoint) seem to be at risk for this complication, which presents as a ridge, just posterior to the submental crease. Careful taping with French tape and admonition to elevate the chin regularly will mitigate this risk.

Overresection is an avoidable complication. Overressection in the submental area leads to a "cobra" neck in which there is an actual depression under the chin with flaring of the sides because of the relative overabundance of adjacent fat [16]. The jowls are another danger zone in which the surgeon may be overly aggressive and cause a depressed, aged appearance. If patients are thin-skinned and/or elderly, overresection will lead to increased wrinkling of the skin. Conservative liposuction, leaving a thin blanket of fat, is best in these patients.

Although it may not be a result of overresection, performing liposuction of the neck may unmask platysma bands and ptotic submandibular glands (Figure 57.10). A thorough preoperative examination should help to detect these patients. In one study of 301 patients, submental obesity and the anatomic pattern non-decussating platysma fibers were found to be significant correlates in the development of the postoperative platysmal banding [17]. The bands may be treated with botulinum toxin A (Allergan, Inc., Irvine, CA, USA) after surgery or adjuvant procedures such as platysmaplasty at the time of surgery.

Excessive defatting in a patient with a round face, without tapering the lower face, can result in a "lollipop" appearance. Tapering of the lower face will prevent this appearance; however, care must be given to feather superiorly to avoid a shelf or step off. Infection is very rare with tumescent liposuction of any area. Patients are advised of this low risk, which is further reduced by preoperative antibiotics, and sterile procedures during surgery.

Advanced and ancillary operating techniques

Submental liposuction is an excellent stand-alone procedure but it also lends itself to the addition of other procedures. At times, these procedures are essential for an acceptable outcome. Examples include platysmaplasty for thick, pronounced platysma bands that are present at rest or with mild animation [14,18]. A mini or full rhytidectomy may be added for excessively lax skin and jowls [11]. The use of

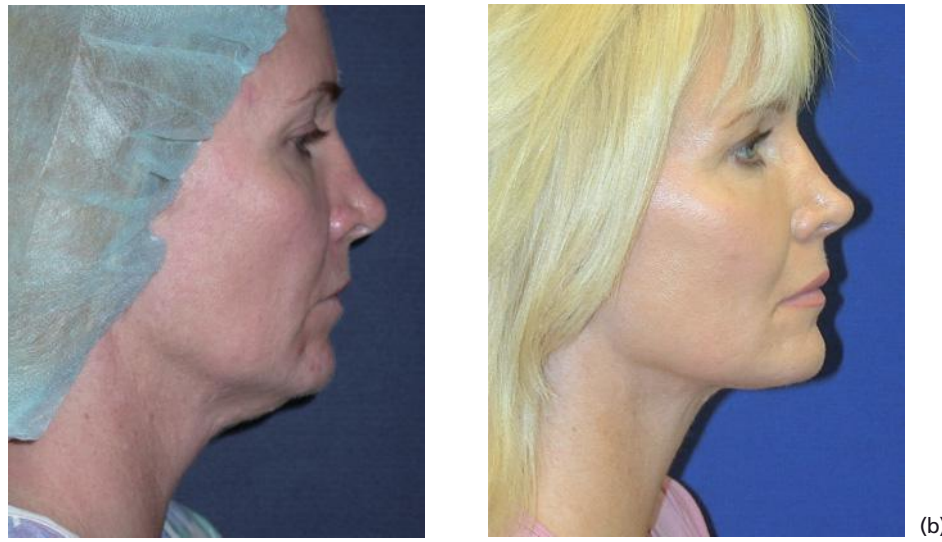


Figure 57.11 Before (a) and 6 months after (b) submental liposuction (25 mL) combined with fat augmentation to cheeks and chin (21 mL).

various lasers and devices to melt fat and/or tighten skin has been touted by some, but at this point, clinical data are lacking. At other times, procedures may be added to enhance an otherwise good outcome. With photoaged skin, for example, one may perform a resurfacing procedure to the face and neck immediately following the liposuction procedure. A typical procedure would add a fractionated laser versus a more invasive laser to avoid the oozing and discomfort from more aggressive laser procedures while wearing the chin strap. If the chin is recessed and/or the chin height short, chin implants may be inserted through a submental incision [19]. Alternatively, autologous fat transfer may be easily added to the procedure (Figure 57.11) [20]. Fat may be utilized from the neck, but it is usually difficult to obtain enough fat through a hand-held syringe, particularly if the fat is to be centrifuged as well. Another donor site may be necessary. Other areas of the face in which volume restoration will enhance the neckline include the prejowl sulcus, marionette fold, or mandibular border. Full-face volume restoration if indicated will elevate the cheeks and jowls and often lift the submental area.

Conclusions

Liposuction of the neck is a procedure that is straightforward, takes 1 hour or less, and is rapidly healing with few complications. It is often a stand-alone procedure or it can be combined with other procedures that may be indicated in the aging patient or those with pre-existing anatomic factors. Proper patient selection and good technique that avoids overresection are key elements for achieving optimal results. Because aging of the neckline and drooping jowls are often the first major complaint of the aging patient, it is incumbent of the dermasurgeon to achieve mastery of this technique as it is likely to become one of his or her favorite procedures to perform.

References

1 Prendiville S, Kohoska MS, Hollenbeak CS, *et al*. (2002) A comparative study of surgical techniques on the cervicomental angle in human cadavers. *Arch Facial Plast Surg* **4**, 236–42.
2 Ellenbogen R, Karlin J. (1980) Visual criteria for success in restoring the youthful neck. *Plast Reconstr Surg* **66**, 826.
3 Jacob CI, Berkes BJ, Kaminer MS. (2000) Liposuction and surgical recontouring of the neck: a retrospective analysis. *Dermatol Surg* **26**, 635–2.
4 Moreno A, Bell WH, Zhi-Hao Y. (1994) Esthetic contour analysis of the submental cervical region. *J Oral Maxillofac Surg* **52**, 704–13.
5 Mittelman H. (1994) The anatomy of the aging mandible and its importance to facelift surgery. *Facial Plast Surg Clin N Am* **2**, 301–10.
6 de Castro CC. (1980) The anatomy of the platysma muscle. *Plast Reconstr Surg* **66**, 680–3.
7 Hoefflin SM. (1998) Anatomy of the platysma and lip depressor muscles: a simplified mnemonic approach. *Dermatol Surg* **24**, 1225–31.
8 Lambros V. (1992) Fat contouring in the face and neck. *Clin Plast Surg* **19**, 401–14.
9 Powell N, Humphreys B. (1984) *Proportions of the Aesthetic Face*. New York: Thieme-Stratton.
10 Farkas LG, Sohm P, Kolar JC, Katic MJ, Munro IR. (1985) Inclination of the facial profile: art versus reality. *Plast Reconstr Surg* **75**, 509–19.
11 Klein JA. (1990) Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. *J Dermatol Surg Oncol* **16**, 248–63.

12 Watson D. (2005) Submentoplasty. *Facial Plast Surg Clin N Am* **13**, 459–67.
13 Langdon RC. (2000) Liposuction of neck and jowls: five-incision method combining machine-assisted and syringe aspiration. *Dermatol Surg* **26**, 388–91.
14 Jacob CI, Kaminer MS. (2002) The corset platysma repair: a technique revisited. *Dermatol Surg* **28**, 257–62.
15 Goddio AS. (1992) Suction lipectomy: the gold triangle at the neck. *Aesth Plast Surg* **16**, 27–32.
16 Fattahi TT. (2004) Management of isolated neck deformity. *Atlas Oral Maxillofacial Surg Clin N Am* **12**, 261–70.
17 Kamer FM, Minoli JJ. (1993) Postoperative platysmal band deformity. *Arch Otolaryngol Head Neck Surg* **119**, 193–6.
18 Knipper P, Mitz V, Maladry D, Saad G. (1997) Is it necessary to suture the platysma muscles on the midline to improve the cervical profile? An anatomic study using 20 cadavers. *Ann Plast Surg* **39**, 566–71.
19 Newman J, Dolsky RL, Mai ST. (1984) Submental liposuction extraction with hard chin augmentation. *Arch Otolaryngol* **110**, 445–57.
20 Butterwick KJ. (2003) Enhancement of the results of neck liposuction with the FAMI technique. *J Drug Dermatol* **2**, 487–93.

Chapter 58: Hand recontouring with calcium hydroxylapatite

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BASIC CONCEPTS

- The aging hand is a common area of concern for patients.
- Adequate treatment solutions were hampered by injection pain and the absence of treatment longevity.
- The soft tissue filler calcium hydroxylapatite is effective for rejuvenating aging hands.
- Calcium hydroxylapatite combined with lidocaine reduces pain of injection, improves product rheology of the procedure, and deposits the product in the correct metacarpal spaces.
- The volume of injected calcium hydroxylapatite varies with physician preference.

Introduction

This chapter begins with a description of the aging hand, then identifies various cosmetic hand treatment products used by physicians for the past 20 years. Calcium hydroxylapatite is then introduced as an alternative to past dermal fillers. A discussion of how to add anesthesia to the calcium hydroxylapatite follows. The author then leads the reader through a step-by-step instruction of injection of the product into the aging hand. The chapter closes with a summary and a discussion of the various volumes of product and possible durability effects that have been used by various physicians.

Physiology of the hand

The great Irish playwright Oscar Wilde once said that "a woman who tells you her age will tell you anything." Well, in his day she did not have to; one could just examine her hands. Today, with the technology of hand recontouring, her secret is safe.

The hands have always been problem areas for physicians to rejuvenate and a myriad of applications and techniques have been used, both surgical and non-surgical with limited success. Until recently, no gratifying procedure has been successful in producing the effect of Botox on wrinkles or intense pulsed light (IPL) and lasers on vessels.

Signs of the aging hand include: a textural, crepe-like appearance, dryness, dyscromia, increased skin laxity, and volume loss giving the sunken appearance highlighting bones, tendons, and veins. A combination of both fractional non-ablative, or ablative laser resurfacing to address the epidermal defects, and the ideal subdermal filling agent to correct the loss of skin elasticity, volume, and wrinkling, is needed to address the aging hand. Both men and women can benefit from volume restoration and can attain a plumper, more youthful hand appearance with the proper technique and product.

A panoply of dermal fillers exists in the esthetic marketplace. These have been well described in the 2008 American Society for Dermatologic Surgery (ASDS) guidelines publication [1]. Zyderm® collagen (Collagen Corp., Palo Alto, CA, USA), the original filler since 1982 and the gold standard for more than two decades, and Zyplast® (Collagen Corp., Palo Alto, CA, USA), followed by Cosmoderm® and Cosmoplast® (Allergan, Irvine, CA, USA) did not produce optimal results because of its consistency and flow characteristics, as well as lack of longevity. The filler was injected into the atrophic area, but did not cover objectionable structures. Collagen and hyaluronic acid fillers also did not flow well, yielding lumps and bumps.

Harvested fat has also been used by some physicians. However, the large-bore needles required for injection often leave unsightly puncture marks. More importantly, the results were modest at best, and short-lived, requiring a second surgical procedure to harvest the fat.

Cosmetic Dermatology: Products and Procedures. Edited by Z.D. Draelos.

Advantages of calcium hydroxylapatite for treatment of the aging hand

In 2007, Florida dermatologists Mariano Busso (Coconut Grove) and David Applebaum (Boca Raton) reported off-label clinical experiences using calcium hydroxylapatite (CaHA; Radiesse, BioForm Medical, San Mateo, CA, USA) for hand recontouring [2]. Their idea involved addition of lidocaine to the existing Radiesse compound. (Radiesse was approved in later 2006 for treatment of severe lines and wrinkles of the face such as nasolabial folds as well as treatment for HIV-associated facial lipoatrophy.) As a result, pain of treatment was reduced to nearly none, with immediately pleasing results to patients in one treatment session.

Radiesse consists of CaHA microspheres, 25 µm to 45 µm in diameter, in a carboxymethyl cellulose carrier gel. The CaHA is identical to the component found in human bone. The carrier gel disperses within weeks, leaving behind the calcium microspheres. It does not induce osteogenesis when placed in tissue but laboratory studies show neocollagenesis extending out to 72 weeks [3]. Hand recontouring required a substance that could not only fill atrophic areas of the dorsal hand, but could also conceal the vein and tendon color. Radiesse is white, opaque, possesses the proper viscosity, and flows smoothly with a low extrusion force (Table 58.1).

Technique of injection of CaHA into the hand

Contrary to the technique developed for collagen injection in 1982, CaHA hand recontouring requires a different injection technique: bolus injection, followed by vigorous massage, allowing the CaHA to fill where needed. It is a new technique, not predicated on line filling, but rather on steady vigorous massage to deliver the material to required atrophic areas (Table 58.2).

Preparing the Radiesse-lidocaine mixture

Prior to injecting CaHA into the hands, it is homogenized with 0.5 mL of 2% plain lidocaine. The 1.5 mL CaHA Luer-Lok syringe is attached via a Rapid Fill Luer-Lok to Luer-Lok connector (Baxa, Englewood, CO, USA) to a 3-mL Luer-Lok syringe containing 0.5 mL lidocaine (Figure 58.1) The use of a 3-mL Luer-Lok syringe is ideal for the homogenization process, because a high extrusion pressure is generated to mix the two liquids. The Baxa connector should be filled with lidocaine prior to making the connection, otherwise the CaHA will not flow. Instead, the plunger will move down without product emerging from the needle tip, the result of air in the mixture. The CaHA is first injected into the syringe containing the lidocaine and mixed back and forth for 10 passes until the filler–lidocaine mixture is

Table 58.1 Representative treatment products for the aging hand.

Product category	Duration of effect*†	Advantages	Disadvantages
Autologous fat	Widely variable, from 4 months to more than 12 months	Biocompatibility, potential neovascularization	Harvesting required, not amenable to patients with lipodystrophy, does not conceal structures
Calcium hydroxylapatite (Radiesse®)	Approximately 12–15 months	Biocompatibility, collagen proliferation, immediate correction, no overcorrection needed, minimal pain	Time required for mixing with lidocaine
Collagen [bovine] (Zyderm®, Zyplast®) CosmoDerm®, CosmoPlast® (human)	Approximately 2–3 months	Long history of use in US esthetics No testing required	Skin testing for hypersensitivity reactions, does not conceal structures
Hyaluronic acids (Juvederm™, Restylane®, Perlane®)	Approximately 6–9 months	Wide variety of products available	Visibility of papules, color not easily blended into skin of dorsum, tindall effect, does not conceal structures
Poly-L-lactic acid (Sculptra®)	Approximately 18–24 months	Sustained collagenesis after a few weeks post-injection	Multiple treatments often necessary, does not conceal structures

* Facial areas (scant literature on longevity in hand).
† ASDS Guidelines.

Table 58.2 Steps of in-office procedure for treatment of the aging hand. (Adapted from Busso M, Applebaum D. (2007) Hand augmentation with Radiesse® (calcium hydroxylapatite. *Dermatol Ther* **20**, 315–17.)

1	Combine Radiesse with lidocaine, using a Luer-Lok connector for the Radiesse syringe and a 3-mL syringe containing 0.5 mL of 2% plain lidocaine
2	Identify the areas of treatment, usually between the second and fifth metacarpals, from the dorsal crease of the wrist to the metacarpophalangeal joints
3	Isolate the area of treatment with skin tenting between thumb and forenger of non-injecting hand, or forceps
4	Using a 27-gauge, 0.5-inch needle, inject the boluses of CaHA-lidocaine mixture into the areolar plane between the subcutaneous layer and superficial fascia of the hand as needed
5	Have the patient make a fist of the injected hand, then firmly massage mixture to disperse
6	Schedule follow-up with patient in 2–4 weeks; repeat treatment for any areas missed during initial visit

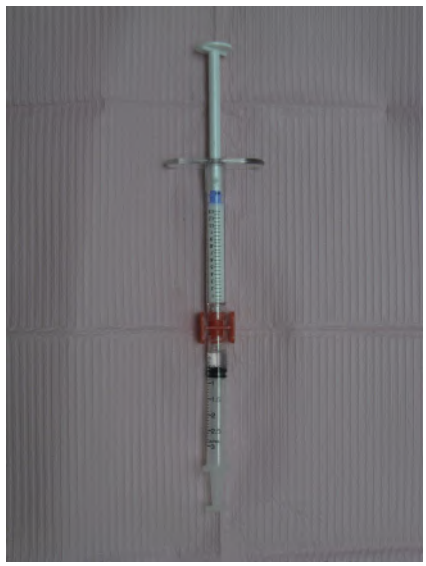

Figure 58.1 Radiesse with lidocaine using the Baxa connector.

smooth and without bubbles (Figure 58.2) [4]. The addition of the anesthetic changes the viscosity and filler extrusion force, delivering a more malleable mixture which is less viscous and therefore requires a smaller extrusion force.

Where to inject

Careful injection site selection can considerably limit the amount of bruising. Before injecting, carefully examine the hand to ensure selection of an area devoid of veins or tendons. The imaginary line of bolus injection(s) is midway between the dorsal crease of the wrist and the metacarpophalangeal joints, bound laterally by the fifth metacarpal and medially by the second metacarpal. This boundary can

Figure 58.2 Radiesse–lidocaine mixture with 1.5 mL Radiesse and 0.5 mL 2% plain lidocaine.

be modified depending on the injector's judgment regarding the location of the defects to be filled.

How to inject

The patient should be comfortably seated on an examination table with the hands extended in front of them, preferably resting on a Mayo stand covered with a soft pillow, adjusted to the height of the patient's knees, allowing gravity to have the desired effect on the defects to be corrected. The skin must be tented in order to separate it from the underlying veins and tendons (Figure 58.2). Entry is into the areolar plane, which is located between the superficial fascia and the subcutaneous fat. The thumb and forefinger of the non-injecting hand are used to lift the skin and create the entry point in the center of the tent (Figure 58.3). With a 27-gauge by 0.5 inch needle (or the new 28-gauge with 27-gauge inner lumen) attached to the prefilled CaHA syringe, inject 2–4 boluses of product across the previously described area of the dorsum of the hand, refilling the syringe when necessary. The average bolus amount is about 0.2–0.5 mL CaHA emulsion (Figures 58.4–58.6).

Post-injection hand massage

At this point, massaging – the quintessential element of relocating the CaHA – is begun (Figure 58.7). Have the patient make a tight fist. To relieve friction and enhance the process, apply a liberal amount of Aquaphor (Beiersdorf Inc., Wilton, CT, USA) or white petrolatum to the dorsum. Begin pushing the boluses, one at a time, distally, laterally and medially, so that the bolus is flattened and spread as far as possible. Care should be taken not to encroach upon the metacarpophalangeal joints or the medial and lateral dorsopalmar junctions; product is not intended for these areas.

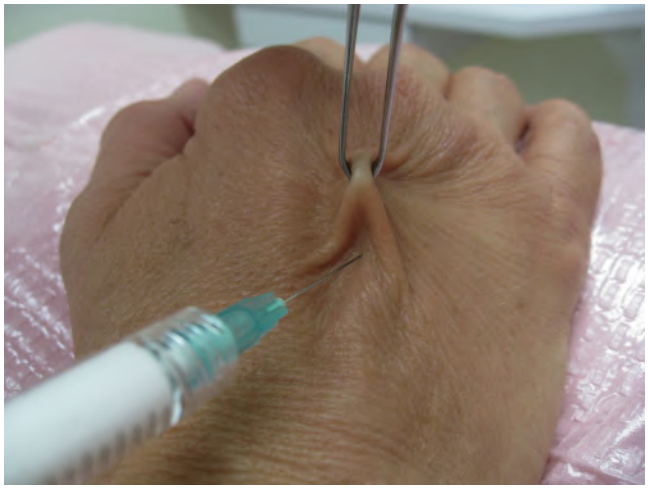

Figure 58.3 Tenting of the skin technique.

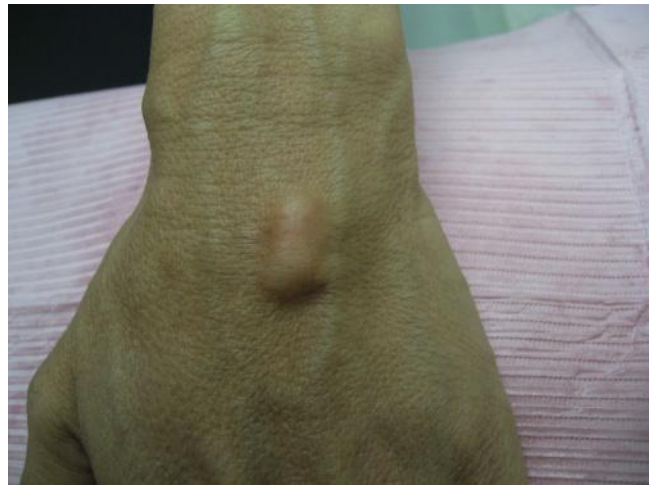

Figure 58.6 Injected bolus prior to closed-fist massage.

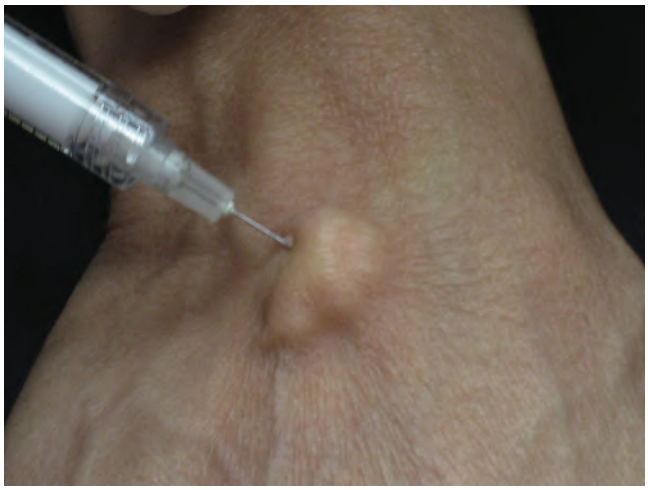

Figure 58.4 Injecting and forming bolus of Radiesse mixture (0.5 mL bolus) in the areolar plane.

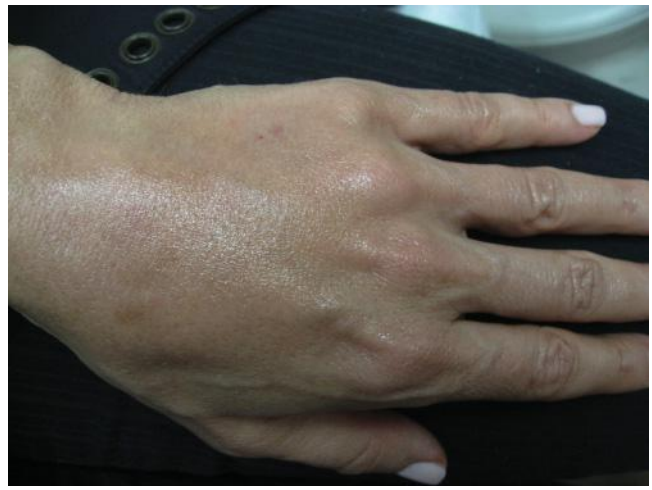

Figure 58.7 Partial massage of bolus into the dorsum.

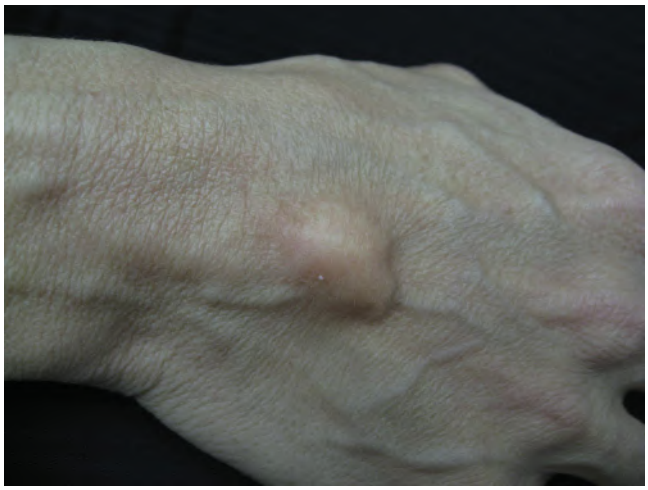

Figure 58.5 Injected bolus prior to closed-fist massage.

After completing treatment of the first hand, have the patient sit on that hand while you treat the other hand. It will help in the smoothing out process as well as add to hemostasis if needed. In the event of a hematoma, have the patient hold pressure firmly for 5–10 minutes, and proceed to begin treating the contralateral hand. When the other hand is completed, go back and complete the "bruised" hand. Each hand usually requires between one and two 1.5-mL syringes. CaHA is also available in 0.3 mL and 0.8 mL syringes, should a full 1.5-mL syringe not be needed for the second syringe.

Post-treatment care

After treatment is completed apply ice packs to the hands. The patient leaves the office with the disposable pack, using it for as long as it stays cool. Use of the ice pack will help reduce some of the possible swelling. The patient should be told to carry on with normal activities beginning the follow-

ing day. Schedule the patient for follow-up in 2 weeks, and if at this time there are skip areas noticed, fill them in using the 0.3-mL CaHA syringe mixed with 0.12 mL of 2% lidocaine.

Adverse events

Because it is a compound identical to that found in bone, CaHA has high biocompatibility and low adverse event risks. Adverse events in published studies have been few and of short duration [5–8]. They include ecchymosis, erythema, and occasional edema, when used in facial applications other than the lips. In general, the diluted product described for off-label use in the hands is even more forgiving. Clinical experiences with treatment of the aging hand suggest that adverse events in this area are infrequent and not severe. Anecdotal reports, however, have noted hand edema persist for 5–7 days post injection.

Results

Figures 58.8–58.11 represent a 45-year-old female patient who received 1.5 mL CaHA mixture per hand during the initial visit, and did not have a touch-up performed. Figures 58.12–58.16 represent a 58-year-old female patient who also received 1.5 mL of CaHA mixture in each hand, and returned for a touch-up of the left hand only with 0.3 mL CaHA at week 8.

Discussion

As with every new technique in surgery, refinements and modifications are the rule as time goes on. New approaches

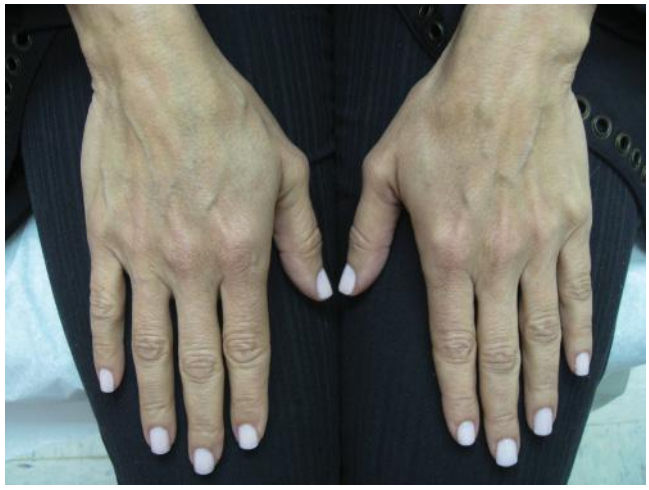

Figure 58.8 45-year-old female patient prior to treatment.

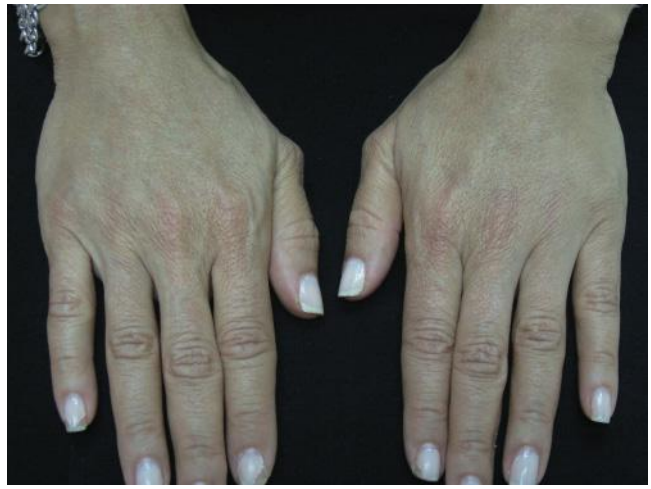

Figure 58.9 Same patient 2 weeks post-treatment with 1.5 mL mixture in each hand.

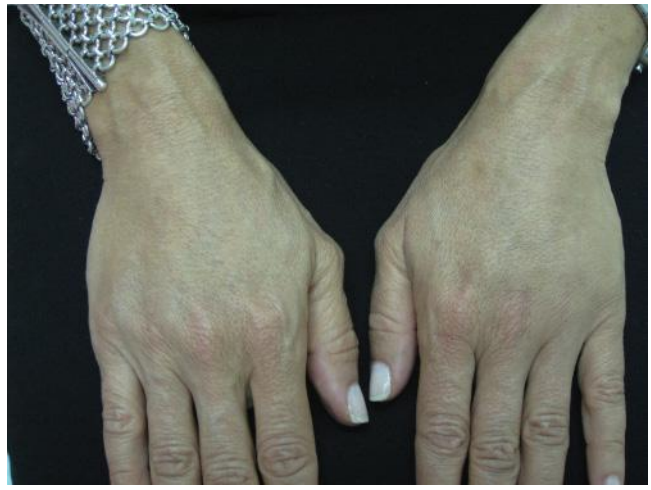

Figure 58.10 Same patient 8 weeks post-treatment.

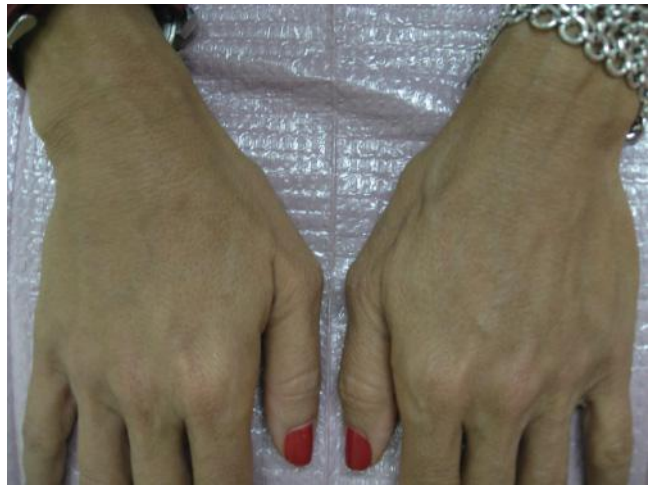

Figure 58.11 Same patient 12 weeks post-treatment.

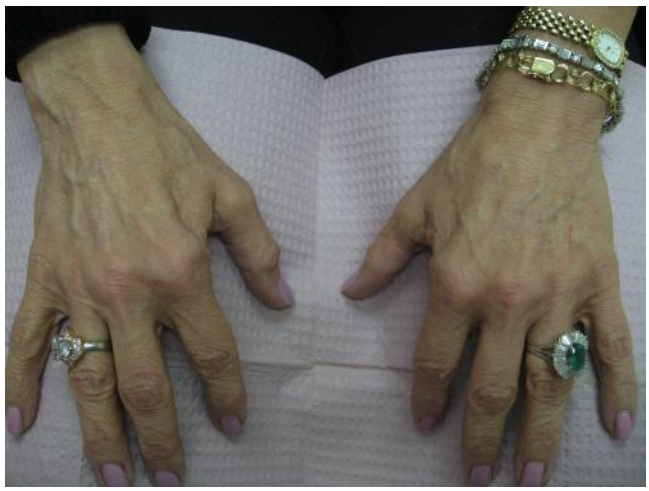

Figure 58.12 58-year-old female patient pretreatment (pianist).

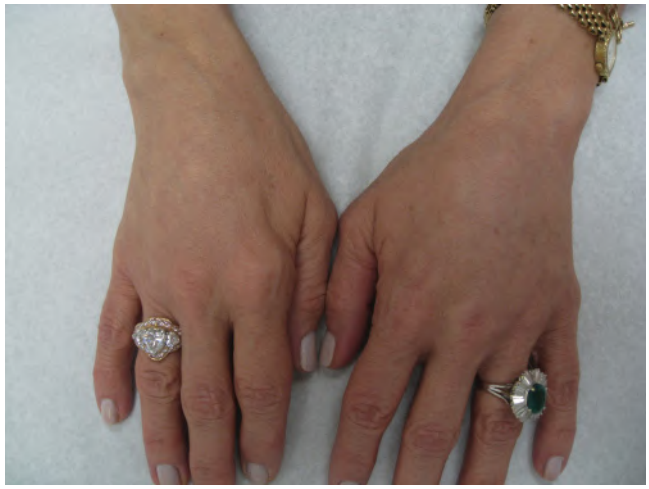

Figure 58.13 Same patient 2 weeks post-treatment with 1.5 mL Radiesse mixture for each hand.

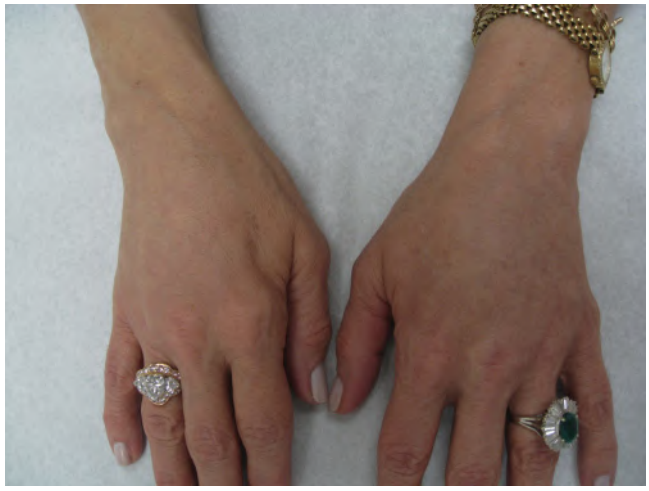

Figure 58.14 Same patient 8 weeks post-treatment with a touch-up using 0.3 mL Radiesse mixture for only left hand performed at 4 weeks after initial treatment.

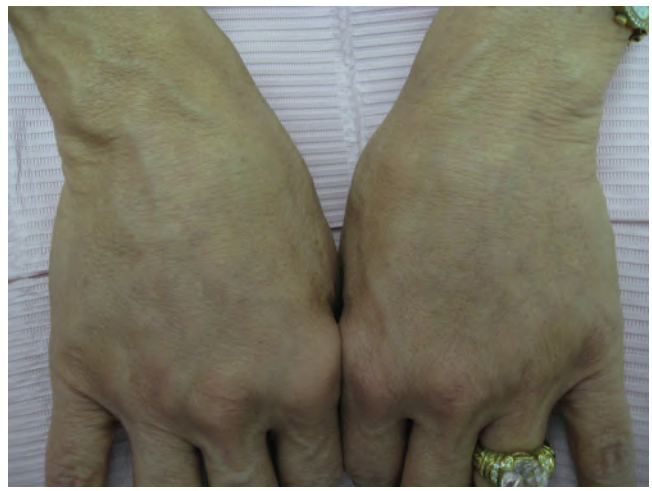

Figure 58.15 Same patient at 20 weeks after initial treatment.

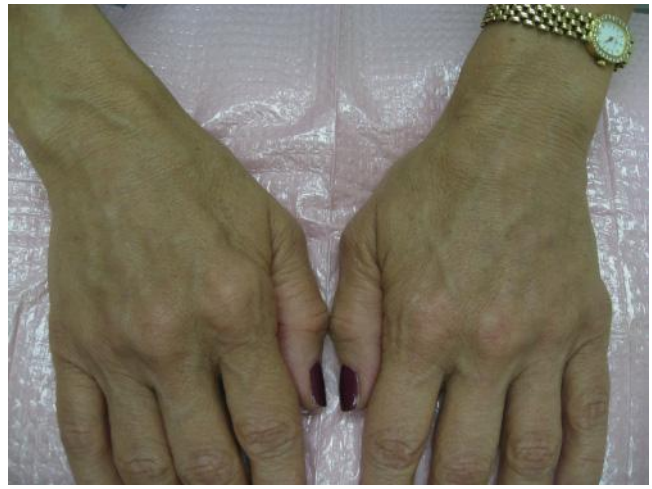

Figure 58.16 Same patient at 28 weeks after initial treatment.

to the same technique give rise to slight revisions and adjustments leading to a better outcome. The original technique described by Busso was a single, voluminous bolus of an entire syringe of Radiesse and lidocaine, which was then spread out over the hand. Some physicians prefer the large-volume bolus approach; others believe it is less advantageous than the multiple, smaller-volume bolus approach.

The volume of lidocaine remains an open question. The original volumes of lidocaine with the single bolus injection were much smaller (0.10 mL per 1.5 mL CaHA) than the volumes found in many clinical settings today (0.23–2.0 mL per syringe). In many personal communications, the author has determined that a larger volume of lidocaine is preferred for optimum results. These volumes have ranged 0.12–2.0 mL lidocaine per 1.5-mL syringe of CaHA. A mixture of 0.5 mL of 2% lidocaine per 1.5-mL CaHA syringe and 0.12 mL for the 0.3-mL CaHA syringe appear optimal. There are several reasons why these two volumes are the volumes

of choice. In the first place, considerably less hand swelling occurs when 0.5 mL lidocaine is used than using 2.0 mL. In addition, this volume enhances product flow and makes massage of injected mixture relatively easy. However, the most important reason is longevity and the convenience issue for the patient. Much less product is used with higher dilutions, and therefore the correction may not endure as long as with smaller dilutions. Busso's recent paper states "physicians have reported that they see no significant decrease in durability for media diluted with lidocaine" [4]. At this point, controlled clinical trials are needed to determine that dilution with lidocaine does not negatively affect longevity of CaHA correction, not only in the hands, but for all applications.

This issue of higher dilutions and possible decreased durability can easily be addressed, but it means more procedures at the 2-week follow-up than necessary. Follow-up sessions should address the missed areas that are inevitable, not retreating areas where the "excess" lidocaine has been absorbed. Another refinement that is helpful is the use of a smooth forceps to create the subsequent tents that might be needed. Once the emollient has been applied to the skin, a gloved hand on greasy skin will not be able to create the tent.

Conclusions

Past experiences with products for treating the aging hand have met with limited success. These products – harvested fat, collagen, and hyaluronic acids – have disadvantages for placement in the hands for contouring enhancements. Foremost among these is the short duration, usually less than 3 months, and the inability of all of the other fillers to conceal the objectionable structures of the aging hand. CaHA appears well-suited for consideration as a product for recontouring of the hand, with a duration of effect of 6 months or longer. Unlike other areas, where there is not a lot of muscle activity, the hand's muscles and tendons are constantly moving, creating the friction that accelerates product breakdown. This is in contrast to more static treatment areas where there is greater longevity of correction. Perhaps the single most important and unique characteristic of CaHA that makes it ideal for hand recontouring is its opacity, the trait that enables the concealment of the undesirable structures of the aging hand. CaHA is also clinically unchanged by the addition of lidocaine, enabling painless treatment.

References

1 Alam M, Gladstone H, Kramer EM, Murphy JP, Nouri K, Neuhaus I, *et al*. Guidelines Task Force. (2008) American Society for Dermatologic Surgery (ASDS) Guidelines of Care: Injectable Fillers. *Dermatol Surg* **34**, 115–48.

2 Busso M, Applebaum D. (2007) Hand augmentation with Radiesse® (calcium hydroxylapatite). *Dermatol Ther* **20**, 315–7.

3 Berlin AL, Hussain M, Goldberg DJ. (2008) Calcium hydroxylapatite for facial filler rejuvenation: a histologic and immunohistochemical analysis. *Dermatol Surg* **34**, 64–S67.

4 Busso M, Voigts R. (2008) An investigation of changes in physical properties of injectable calcium hydroxylapatite in a carrier gel when mixed with lidocaine and with lidocaine/epinephrine. *Dermatol Surg* **34**, 16–24.

5 Tzikas TL. (2008) A 52-month summary of results using calcium hydroxylapatite for facial soft tissue augmentation. *Dermatol Surg* **34**, 9–15.

6 Carruthers A, Liebeskind M, Carruthers J, Forster BB. (2008) Radiographic and computed tomographic studies of calcium hydroxylapatite for treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds. *Dermatol Surg* **34**, 78–84.

7 Moers-Carpi M, Vogt S, Martinez Santos B, Planas J, Rovira Vallve S, Howell DJ. (2007) A multicenter, randomized trial comparing calcium hydroxyalaptite to two hyaluronic acids for treatment of nasolabial folds. *Dermatol Surg* **33**, 144–51.

8 Sadick NS, Katz BE, Roy D. (2007) A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. *Dermatol Surg* **33**, 122–7.

Part 6: Implementation of Cosmetic Dermatology into Therapeutics

Chapter 59: Antiaging regimens

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BASIC CONCEPTS

- The appearance of aging skin can indeed be reversed without invasive treatments by daily skin care using scientifically proven techniques and products.
- Proper cleansing and exfoliation smooth the skin's surface to decrease pore size and wrinkles within days.
- Sun protection by application of ample amounts of high-SPF, UVA-protective, highly water-resistant sunscreen is essential to protect from photoaging and to enhance natural repair.
- Topical retinoids as well as topical antioxidants such as vitamins C and E, selenium, genestein, and coenzyme Q10 not only protect from but also reverse photoaging if the correct molecular forms and concentrations are applied.

Introduction

In her book, *Survival of the Prettiest*, Etcoff [1] synthesizes literature and research from anthropology, biology, psychology, and archeology to show that indeed appreciation of one's own and others' beauty is hard-wired in human brains. Etcoff concludes, "Flawless skin is the most universally desired feature of beauty." This chapter presents a basic skin regimen to protect from photodamage and reverse the appearance of aging. The four necessary steps are cleansing, exfoliation, protection, and treatment. Helpful techniques and scientific research proving efficacy of specific ingredients are presented.

Cleansing

Proper cleansing is an essential component of skincare. The face accumulates endogenous and exogenous soils. Sebaceous gland size and density are greatest on the face, upper back, and chest. The natural oils, sweat, and sebum secretions create a hydrolipid film on the skin surface that, in addition to applied cosmetics, traps and accumulates environmental pollutants such as dust, airborne irritants, and compounds from cigarette smoke. Care must be taken to accomplish thorough cleansing without irritation or drying.

Therefore, a gentle, effective cleanser is of utmost importance. Surfactants are the ingredients that bind to dirt and oil for removal. These surfactants are classified by their charge on the surface-active moiety as anionic (negatively charged, for good foaming and lathering), cationic (positively charged), amphoteric (both positive and negative, considered to "condition" skin while helping to foam), and non-ionic (which are used in baby products to suppress foam) [2]. Components of surfactants can bind to the stratum corneum proteins, decreasing the skin's ability to bind and hold water. With continued, frequent use, surfactants can damage the skin barrier. New synthetic surfactants improve cleansing with less irritation.

Other components of cleansers include polypeptides and synthetic polymers to make the product smooth and to soften skin, polymers to moisturize, preservatives, opacify-

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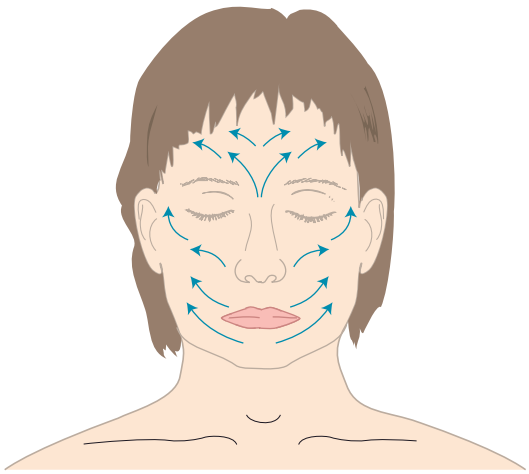


Figure 59.1 To treat wrinkles while washing, gently rub upward horizontally across the upper lip and "up and out" on the rest of the face – perpendicular to the direction of wrinkles.

ing agents, and fragrance. With frequent washing, these ingredients can cause sensitivities or contact allergy in certain individuals. Because cleansers are rinsed off, their contact time with the skin is reduced causing less contact allergy. Newer cleansers are less alkaline than older formulations, so they are less drying.

In recent years, antibacterial agents (e.g. triclosan and triclocarban) have been added to hand cleansers. Surprisingly, these agents are rarely skin irritants. However, some physicians voice concern, fearing development of bacterial resistance to these antibiotics with frequent use. Originally, triclosan was thought to kill bacteria by a "broad-based" mechanism, similar to alcohol and peroxide. However, recent research demonstrated that triclosan acts at a specific gene site in *Escherichia coli* to inhibit replication, so resistant strains could evolve [3]. Thorough washing with gentle cleansers removes dirt and has been shown to be as effective as using these antibacterial compounds.

Cleansing the face should be accomplished with lukewarm water and the fingertips. The face and neck should be washed with upward, outward motions. On the face, one should always rub perpendicular to the direction of those wrinkles that could develop later. On the forehead, cheeks, chin and neck, rub up and out; above the upper lip and under the eyes, the strokes should be first horizontal, then upward at the edges, as illustrated in Figure 59.1. Sunscreen, moisturizer, or other treatments should be applied immediately after gently towel-drying.

Exfoliation

Exfoliation is the rejuvenation treatment providing the most immediate improvement in appearance. Exfoliation removes the outer layers of stratum corenum, and thus treats the hyperkeratosis of dry skin. Exfoliative rubbing perpendicular to the direction of wrinkles minimizes small wrinkles because the surface is smoothed (Figure 59.1).

Exfoliation can be chemical or mechanical. Chemical exfoliants such as hydroxyacids and retinoic acid remove dead surface cells by keratolysis. Mechanical exfoliants include cleansing grains, waxy creams that adhere to the surface cells, as well as slightly abrasive terry washcloths, non-woven polyester polishing pads, brushes, or loofas which physically "sand" the skin surface by rubbing. Grainy exfoliants with aluminum oxide crystals can be effective, but the user must be careful not to get the grains into the eyes. Exfoliants to be avoided are those with apricot or almond kernels, walnut shells, and pumice – all of which have irregularly shaped particles with sharp edges which can be too rough on delicate skin and dangerous if they get into the eyes. The immediate improvement in small wrinkles by gentle exfoliation can be appreciated in Figure 59.2.

Masks are among the oldest face mechanical exfoliants. Masks can "wash off" or "peel off." Some "wash off" masks are made of clay, which harden and are removed with water rinsing. "Peel-off" masks contain synthetic polymers that are quite safe and effective. Some masks may irritate the skin; it is advisable to test on the inner wrist before treating the face.

Protection

The single most effective therapy for aging skin is sun protection [4]. Avoid sun exposure between 10AM and 4PM, and beware of "hidden sun": UVA is not filtered by glass and neither UVA or UVB are filtered by clouds. People get their worst burns on cloudy days, especially when skiing or when on the beach or in the water. Sunscreen should be applied often and generously.

Sunscreens are classified as organic filters (which absorb photons of UV light) or inorganic filters (which reflect or scatter UV radiation) [5]. As shown in Figure 59.3, some organic sunscreen agents block only UVB (*p*-aminobenzoic acid [PABA] and its esters padamate A and O, the cinnamates, and salicylates); others absorb primarily UVB and some low wavelength UVA (octocrylene, benzophenones, anthranalides). Mexoryl XL or SL blocks UVB as well as most UVA. The UVA absorbing sunscreen avobenzone (Parsol 1789) can degrade with exposure to UV [6], but stabilizing compounds (benzylidene camphor and diphenyl cyanoecrylate derivatives, both UVB filters) can be effectively added [7]. The inorganic filters with microfine titanium dioxide and zinc oxide are total UVB blocks, blocking low wavelength UVA and almost all UVA, respectively. Thus, zinc oxide provides better protection than titanium dioxide [8]. The new technology with microfine particles makes them

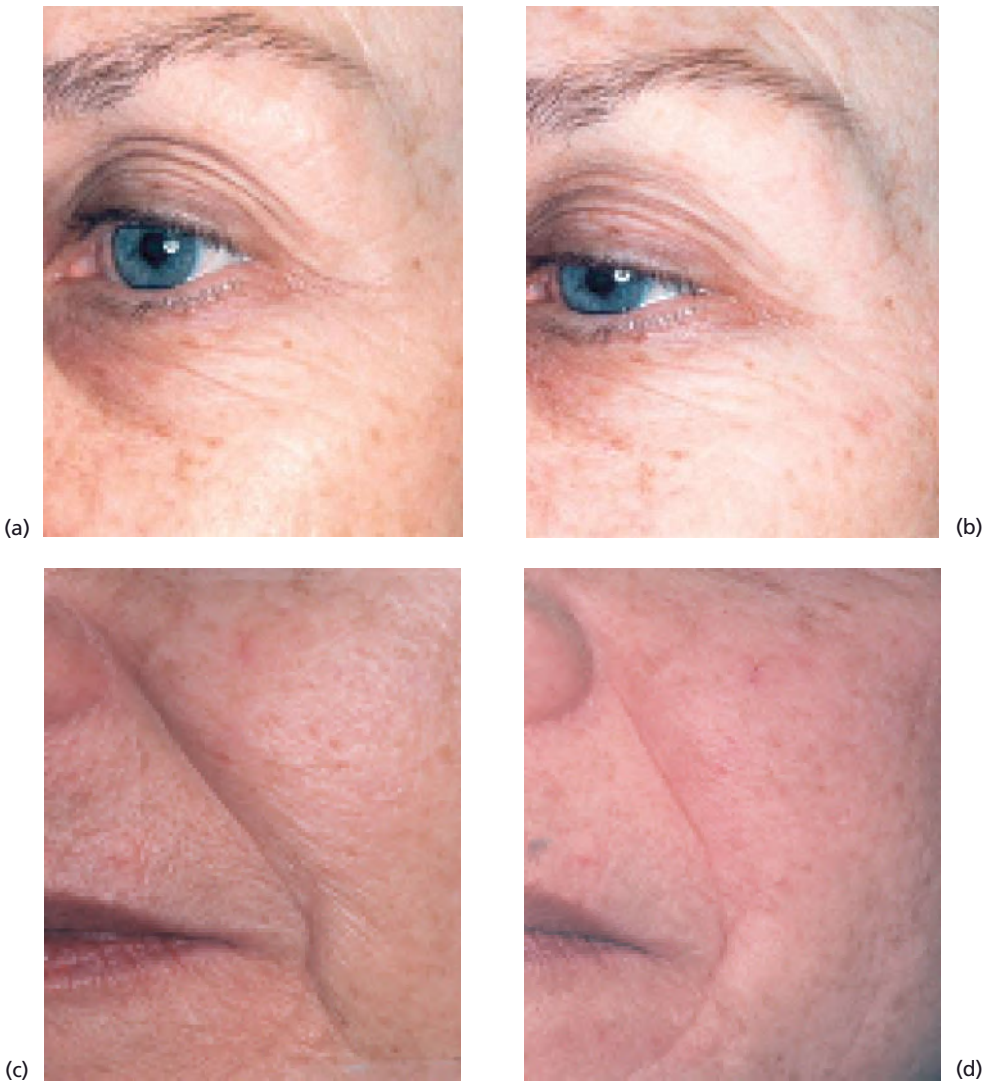


Figure 59.2 Tiny wrinkles and crepy skin can be treated immediately at home by exfoliation. Improvement is seen in this 60-year-old woman's face after she simply washed with a non-woven polyester polishing pad and used a waxy exfoliant that mechanically "sticks" and removes surface cells. (a) and (c), pre-exfolitaion; (b) and (d), post-exfoliation.

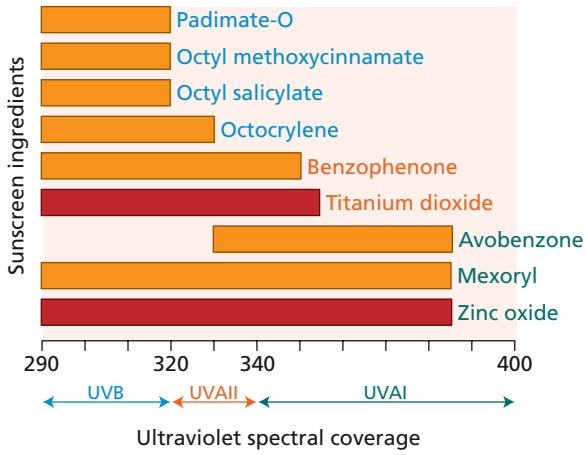


Figure 59.3 Ultraviolet spectral coverage of sunscreen ingredients.

non-opaque and cosmetically appealing. The concentration and the size of the microparticles determine SPF efficacy [5].

The ability of a sunscreen to prevent UVB-mediated erythema is measured by the internationally accepted standard sun protection factor (SPF), the ratio of equivalent exposure by UVB in sunscreen-protected compared with unprotected skin. (An SPF of 30 means that the amount of UB exposure in 10 minutes without sunscreen is equivalent to 10 minutes × 30 = 5 hours of exposure with sunscreen.) The SPF should be at least 25–30. After SPF, the second important criterion for a sunscreen is that it be "highly water resistant," meaning it is effective for about 90 minutes. Many prefer a different sunscreen for the face than for the body. These criteria are summarized in Table 59.1.

Further protection with topical antioxidants and sun protective clothing, hats, and sunglasses are indicated. Sun pro-

Table 59.1 Criteria of a good sunscreen.

1. High SPF (SPF 25 or higher)
2. Protection against UVA and UVB
3. Highly water resistant
4. Non-comedogenic
5. Excellent esthetics

SPF, sun protection factor.

tective clothing is rated using UV protective factor (UPF), measured by the amount of UV radiation transmitted through the fabric. A fabric with a UPF of 40–50 transmits only 2.6% of biologically effective radiation, in contrast with normal summer clothing that typically has a UPF of only 4–10, providing a maximum SPF of 30% but often only an SPF of about 2 if wet [9]. New products (such as SunGuard (2,2′-(1,2-ethenediyl)bis[5-[[4-(methylamino)-6[[4-(methylamino)catonyl]-phenyl]amino]-1,3,5-triazin-2-yl] amino]-, disodium salt)) have recently become available to be added when washing clothes to give a UPF of 30 that lasts 20 washes.

Treatment

There are several medical treatments for antiaging purposes. These include retinoic acid, hydroxy acids, and topical antioxidants. Many products are advertised, but their efficacy may not have been demonstrated by rigorous placebo-controlled, double-blind clinical trials.

Hydroxyacids

Hydroxyacids (HAs) have been used for centuries. Cleopatra routinely applied HAs and Marie Antoinette washed with red wine, benefitting from tartaric acid.

Hydroxyacids were reintroduced to dermatology in 1974 when Van Scott and Yu [10] reported improvement of severe hyperkeratosis and icthyosis. Hydroxyacids are classified by the position of the hydroxyl group attached to the acid moiety: α-hydroxyacids (AHAs) (glycolic acid, lactic acid, and citric acid), β-hydroxyacids (BHAs) (tropic acid, salicylic acid [SA] – called a BHA but actually an α-hydroxybenzoic acid), and the "new generation" polyhydroxy acids (PHAs) (gluconolactone or lactobionic acid – a naturally occurring component of skin). AHAs act rapidly (within 2 weeks) to smooth the surface skin by reducing epidermal cornecyte adhesion, first at the innermost level of the stratum corneum (just above the stratum granulosum) [11]. Epidermal damage of photoaging is corrected in 14–16 weeks, resulting in a thinned stratum corneum, epidermal acanthosis, and decreased melanogenesis [12]. An increase in epidermal intercellular hyaluronic acid improves surface moisturization by water retention.

An elegant study demonstrated that epidermal keratolysis is followed by dermal penetration which increases synthesis of glycosaminoglycans and increases fibroblast proliferation and production of collagen and elastin [13]. A 25% increase in skin thickness was measured after 6 months' treatment with 25% AHAs with no inflammation.

SA is unique among the hydroxyacids in that it is lipophilic and is particularly attracted to sebaceous orifices, thereby exhibiting its keratolytic properties not only to smooth surface wrinkles, but also to decrease pore size and prevent acne. As an excellent keratolytic agent, SA solubilizes intercellular cement by disrupting corneocyte adhesion layer by layer, from the surface downward. SA may also be directly bacteriostatic.

The PHAs have several advantages. They have larger molecules, so they penetrate the skin gradually and are therefore less irritating than AHAs or SA. PHAs are recommended for patients with sensitive skin, rosacea, or atopic dermatitis [12]. They can even be used in conjunction with retinoic acid without irritation. PHAs also give improved moisturization of the stratum corneum when compared with AHAs. PHAs have anti-inflammatory and antioxidant activity, further enhancing repair of cutaneous photoaging [14].

Three key factors determine HA efficacy:

1 *Type of hydroxyacid* (described above).

2 *Concentration*: the higher the concentration, the more effective but the more possible irritation. Concentrations of 8–12% glycolic and lactic acids are available by prescription, as are concentrations of SA greater than 3%. High concentrations are used for medical chemical peels.

3 *pH (acidity)*: the amount of biologically free acid determines the clinical strength [15]. To be effective, the hydroxyacid must be acidic.

There is a delicate balance in attaining efficacy without irritation. For each type of hydroxyacid or mixture thereof, the concentration and pH determines the strength and the clinical benefits [15].

Retinoids

Retinoids are the "gold standard" for reversing photoaging of the skin. Retinoic acid (tretinoin) has been used for more than 35 years for the treatment of acne. In the late 1980s, the remarkable clinical improvement of wrinkles and solar lentigos after treatment with topical tretinoin was documented [15–17]. UV exposure leads to decreased expression of retinoic acid receptors (RAR) and retinoic X receptors (RXR) (in particular, RAR-α and RXR-γ, the two major nuclear receptors in keratinocytes) with subsequent activation of transcription factors (AP-1 and NF-IF) which increase proliferation and inflammation and activate the matrix metaloproteinases (MMPs) which break down extracellular

matrix proteins [18]. By binding to these receptors, topical retinoids restore expression, thereby reversing UV-induced damage at all levels of the epidermis and dermis [19,20].

Retinoids increase epidermal proliferation causing epidermal thickening with compaction of the stratum corneum and deposition of glycosaminoglycans intercellularly; with epidermal proliferation, inhibition of excess melanogenesis and shedding of melanin-laden keratinocytes resolves mottled hyperpigmentation; and retinoids directly induce collagen synthesis and reduce collagen breakdown by inhibiting the UV-induced MMPs [21,22], thereby correcting wrinkles.

Topical tretinoin also reverses intrinsic aging, perhaps even more significantly in non-sun-exposed than in photoaged skin. A marked increase in epidermal thickness (with a more undulating dermoepidermal junction), in anchoring fibrils, and in dermal angiogenesis with new elastic fibers and glycosaminoglycans was observed [23].

Previously, topical tretinoin was postulated to make the skin more sensitive to UV exposure. Indeed, resolution of unattractive hyperkeratosis may allow more UV to penetrate deeper, but the inhibition of the UV-induced MMPs that break down collagen results in less UV damage with tretinoin treatment. Occasionally, irritation (retinoid dermatitis) can occur, especially when beginning treatment. This can usually be avoided by starting with lower concentrations (0.025% cream instead of 0.05% cream or 0.01% gel), other formulations (microsphere gels, new generic formulations, or different retinoids as described below), and less frequent application. Patients with sensitive skin should begin with a mild formulation, applying initially each 3 days and increasing to daily over several weeks or months. Most of the improvement occurs within the first year, improvement is maintained with continued use, as proven by up to 4-year histologic studies [22].

Other "second generation" retinoids have been proven effective in treating photodamage [22]. Retinaldehyde cream (0.05%) and retinol cream (up to 1.6%) are comparable to tretinoin in efficacy, but are more irritating. Tazarotene (0.5% and 0.1%) may give faster improvement but is also more irritating. Adapalene (0.1% cream and gel) is less irritating but probably less effective than tretinoin.

Antioxidants

The skin naturally uses nutritional antioxidants to protect itself from photodamage and topical application has been investigated. The challenge is to make topical antioxidant formulations that are stable and that give percutaneous absorption to deliver high concentrations of the active forms to the dermis as well as the epidermis.

Vitamin C

If the retinoids are the "gold standard," topical vitamin C is the "silver standard" for reversing photoaging of the skin. Vitamin C (L-ascorbic acid) is the body's major aqueous-phase antioxidant. Dietary vitamin C is absolutely required for life.

Environmental free-radical stress depletes vitamin C levels in the skin. UV exposure of 1.6 minimal erythema dose (MED) decreases vitamin C to 70% normal, and 10 MED to 54% [20]. Although vitamin C is itself not a sunscreen, topical vitamin C protects against solar damage. As an antioxidant, vitamin C deactivates the UV-induced free radicals, decreasing erythema and sunburn. This protection has been confirmed by histologically: treatment with topical 10% vitamin C decreases the number of abnormal "sunburn cells" by 40–60% and reduces the UV damage to DNA by 62% [24].

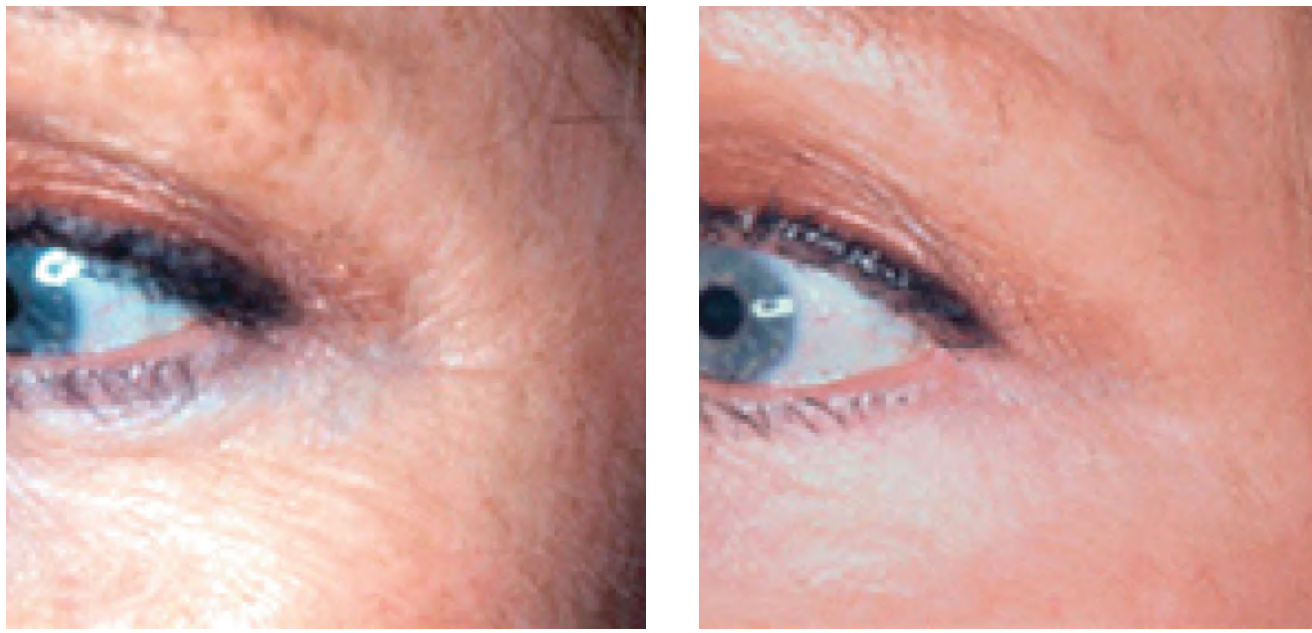
The main function of vitamin C is as the essential co-factor for collagen synthesis. When 10% vitamin C was added to *in vitro* elderly fibroblasts, collagen proliferation and synthesis increased by factors of 6 and 2, respectively [25]. Vitamin C also inhibits tyrosinase, thereby lightening solar lentigos.

Formulation is key to optimizing percutaneous absorption of vitamin C. Because L-ascorbic acid is inherently unstable – making it an excellent antioxidant – an effective topical delivery system is crucial. Many products contain stable derivatives, which are not metabolized by the skin (such as ascorbyl-6-palmitate or magnesium ascorbyl phosphate) and therefore have no appreciable cutaneous activity [26]. Other formulations do not result in measurable absorption of vitamin C because they are not at the correct pH. Topical absorption of 10% vitamin C cream was proven by radioactive labeling studies in pigs. After treatment, 8.2% was found in the dermis, and 0.7% was in the blood [27]. The most effective concentration for topical delivery is 20%, giving maximal skin levels after 3 days.

Vitamin E (d-α-tocopherol)

Natural vitamin E is the most important lipid-soluble, membrane-bound antioxidant in the body. Natural dietary vitamin E can exist in four methylated forms (α, β, χ, δ); synthetic vitamin E is a mixture of eight (d,l) stereoisomers. The d-α-tocopherol isomer has the greatest biologic efficacy. In order to attain activity through cutaneous application, the natural non-esterified form must be applied in concentrations greater than 2% (5% is optimal) [28]. Most commercial products containing "vitamin E" contain a mixture of 32 synthetic isomers, esterified, and in quite low concentrations. Allergic contact dermatitis has been reported from such formulations, although no adverse reaction has ever been reported with the natural d-α-tocopherol.

In a mouse model, topical d-α-tocopherol has been shown to be impressively effective in protecting against all acute and chronic UV-induced damage, and far more effective than the esterified topical d-α-tocopherol succinate [29]. Vitamin E has also been demonstrated to reverse photoaging dramatically. Figure 59.4 shows the dramatic decrease in periorbital rhytides after 4 months of daily application of



(a) (b)

Figure 59.4 Correction of periorbital wrinkles after 4 months of once-daily treatment with 0.05% d-α-tocopherol cream. (a) Before. (b) After.

d-α-tocopherol (5%). Histology confirmed this improvement in a mouse model. The UV-induced epidermal hypertrophy and hyperkeratosis, the increased incidence of damaged "sunburn cells" in the basal layer, and the disruption of dermal collagen and elastin were all corrected after 8 weeks of topical treatment (KE Burke, L Riciotti, EG Gross, unpublished observations).

Vitamin C with vitamin E

In cells, vitamins C and E interact synergistically to provide antioxidant protection. In membranes, vitamin E is oxidized as it quenches peroxyl free radicals and intracellular vitamin C regenerates the vitamin E activity [30]. Oral vitamin C with E in high doses protects against UV-induced erythema in humans, whereas either vitamin alone is ineffective [27]. Compared to twofold protection for either vitamin alone, topical L-ascorbic acid (15%) with α-tocoperol (1%) gives fourfold protection against UV-induced erythema, decreasing the number of damaged "sunburn cells" seen histologically and decreasing thiamine dimer formation in porcine skin [29]. Fortunately, mixing these hydrophilic and lipophilic antioxidants in a topical formulation stabilizes each.

Vitamin C with vitamin E and ferulic acid

Ferulic acid is a potent antioxidant present in the cell walls of grains, fruits, and vegetables. Ferulic acid alone absorbs some UV and therefore is itself a weak sunscreen. When mixed with vitamins C and E, it further stabilizes the formulation and acts synergistically to double the photoprotection from fourfold to eightfold [31]. This triple antioxidant combination has been made into the SkinCeuticals product C E Ferulic (15% vitamin C, 1% vitamin E, and 0.5% ferulic acid).

Other antioxidants

Coenzyme Q10

Coenzyme Q10 (ubiquinone or CoQ10) is a component of the mitochondrial electron transport chain in all plant and animal cells, including human cells, especially in organs with high rates of metabolism such as the heart, liver, and kidney. In the skin, CoQ10 acts as an antioxidant, although the level is naturally relatively low, with 10 times more in the epidermis than the dermis [32]. CoQ10 has been shown to reverse natural intrinsic aging by increasing rates of cell division and increasing natural hyaluronic acid [33]. Decreased wrinkle depth was documented by optical profilometry using 0.3% ubiquinol cream for 6 months [34]. CoQ10 also suppresses UVA destruction of collagen [33].

α-Lipoic acid

α-Lipoic acid (αLA), made in cells of all plants and animals, has many impressive antioxidant properties and has been shown to retard aging in heart and brain cells in laboratory studies. However, the evidence for reversal of photoaging in the skin is scant: 33 women applied 5% αLA to half of their faces for 12 weeks and noted some decrease in wrinkles, skin roughness, and fading of dark spots [35]. αLA provides little or no protection against sun damage [33].

Selenium

Selenium is a trace mineral essential to human life because it is the required co-factor for the intracellular antioxidant

Table 59.2 Photoprotection and reversal of photoaging.

Treatment agent	Source	Photoprotection	Treatment of wrinkles	Treatment of solar lentigos
α-Hydroxy acids	Sugar cane, milk, fruits*	–	++	++
β-Hydroxy acids	Willow or sweet birch bark, wintergreen leaves*	–	++	++
Retinoic acid	Vitamin A*	Dermis only	++++	++++
Vitamin C	Citrus fruits, red peppers	+++	++++	++++
Vitamin E (d-α)	Sunflower oil	+++	++++	+++
Ferulic acid	Cell wall of fruits, grains, vegetables	++++	?	?
Coenzyme Q10 (ubiquinone)	Fish, shellfish, spinach, nuts	Dermis only	++	?
α-Lipoic acid	All plant and animal cells (including humans)*	–	+	+
L-selenomethionine	Grains, saltwater fish	++++	++++	++
Genistein	Soy	+++	?	?

+, Minimal effect noted in good studies; ++++, maximal effect (a "gold standard") ?, not studied.
* Produced synthetically for cosmetic products.

enzymes glutathione peroxidase and thiodoxin reductase. Topical L-selenomethionine (0.02–0.05%) has been shown to protect the skin from both acute and chronic UV damage (erythema, pigmentation, and skin cancer) [36]. Application increases MED [37] and delays the onset and decreases the incidence of skin cancer [38]. Furthermore, when applied to sun-damaged skin, topical L-selenomethionine was shown clinically and histologically to reverse photoaging as effectively as retinoic acid – with a decrease in hyperkeratosis and regeneration of collagen and repair of elastic tissue.

Genistein

Genistein is a potent antioxidant isolated from soy, which has been proven to protect against UV-induced erythema and skin cancer [38]. As a phytoestrogen, genistein confers the additional benefit of stimulating collagen synthesis, and thus may prove to be an excellent treatment for wrinkles.

In Table 59.2, this author has summarized her personal impressions of the clinical efficacy of well-researched topicals for photoprotection and reversal of photoaging. Others include niacinamide (smoothing texture, improving red blotchiness, and dark spots, decreasing yellowing, and improving fine lines, wrinkles, and elasticity – but is only about one-third to one-fifth as effective as retinoic acid), and kinetin (a synthetic plant growth hormone that retards senescence in plants, shown to reverse aging of skin cells in the laboratory, but in the author's experience only minimally helpful in correcting wrinkles).

Conclusions

The appearance of aging skin can be treated non-invasively. Strategies include primary prevention (with changes in lifestyle by not smoking, avoiding excessive sun exposure, and assiduous protection when in the sun) and treatment. Some treatments improve the appearance immediately and others act physiologically to inhibit further photodamage and to reverse previous damage at a molecular level. New therapies for photoaging are promoted, but many have not been subjected to large, placebo-controlled, double-blind, clinical trials.

References

1 Etcoff N. (1999) *Survival of the Prettiest: The Science of Beauty*. New York: Anchor Books, Random House.
2 Rieger MM. (2000) Skin cleansing products. In: Rieger MM, ed. *Harry's Cosmeticology*. New York: Chemical Publishing Company, Inc., pp. 485–500.
3 Levy CW, Roujeinikova A, Sedelnikova S, Baker PJ, Stuitje AR, Slabas AR, *et al.* (1999) Molecular basis of triclosan activity. *Nature* **308**, 383–4.
4 Glaser DA. (2003) Anti-aging products and cosmeceuticals. *Facial Plast Surg Clin North Am* **11**, 219–27.

5 Forestier S. (2008) Rationale for sunscreen development. *J Am Acad Dermatol* **58**, S133–8.

6 Roscher NM, Lindeman MKO, Kong SB, *et al.* (1994) Photodecomposition of several compounds commonly used as sunscreen agents. *J Photochm Photobiol A* **80**, 417–21.

7 Deflandre A, Forestier S, Lang G, *et al.*, inventors; L'Oreal, assignee. (1997) Photostable cosmetic composition containing a UV-A screen and a UV-B screen and a process for stabilizing the UV-A screen with the UV-B screen. US patent US 5605680. February 25.

8 Pinnell SR, Fairhurst D, Gillies R, Mitchnick MA, Kollias N. (2000) Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. *Dermatol Surg* **26**, 309–14.

9 Diffey BL. (2001) Sun protection with clothing. *Br J Dermatol* **144**, 449–51.

10 Van Scott EJ, Yu RJ. (1974) Control of keratinization with the alpha hydroxy acids and related compounds. *Arch Dermatol* **110**, 586–90.

11 Van Scott EJ, Ditre CM, Yu RJ. (1996) Alpha-hydroxyacids in the treatment of signs of photoaging. *Clin Dermatol* **14**, 217–26.

12 Grimes PE, Green BA, Wildnauer RH, Edison BL. (2004) The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* **73**, 3–13.

13 Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WC, *et al.* (1996) Effects of AHAs on photoaged skin: a pilot clinical, histological and ultra-structural study. *J Am Acad Dermatol* **34**, 187–95.

14 Green B, Briden ME. (2009) *PHAs and bionic acids: next generation hydroxy acids*. In: Draelos ZD, Dover JS, Alan M, eds. Philadelphia, PA: Elsevier Saunders, In press.

15 Weiss JS, Ellis CN, Headington JT, Tincoff T, Hamilton TA, Voorhees JJ. (1988) Topical tretinoin improves photodamaged skin: a double-blind, vehicle-controlled study. *JAMA* **259**, 527–32.

16 Kligman AM, Grove GL, Hirose R, Leyden JJ. (1986) Topical tretinoin for photoaged skin. *J Am Acad Dermatol* **15**, 836–59.

17 Burke KE, Graham GF. (1988) Tretinoin for photoaging skin: North Carolina vs. New York. *JAMA* **260**, 3130.

18 Fisher GJ, Wang ZQ, Datta SE. (1997) Pathophysiology of premature skin aging induced by ultraviolet radiation. *N Engl J Med* **337**, 1419–28.

19 Stratigos AJ, Katsambas AD. (2005) The role of topical retinoids in the treatment of photoaging. *Drugs* **65**, 1061–72.

20 Shindo Y, Wit E, Han D, Packer L. (1994) Dose–response effects of acute ultraviolet irradiation on antioxidants and molecular markers of oxidation in murine epidermis and dermis. *J Invest Dermatol* **23**, 470–5.

21 Wang Z, Boudjelal M, Kang S, Voorhees JJ, Fisher GJ. (1999) Ultraviolet irradiation of human skin causes functional vitamin A deficiency, preventable by all-*trans* retinoic acid pretreatment. *Nat Med* **5**, 418–22.

22 Bhawan J, Olsen E, Lufrano L, Thorne EG, Schwab B, Gilchrest BA. (1996) Histologic evaluation of the long-term effects of tretinoin on photoaged skin. *J Dermatol Sci* **11**, 177–82.

23 Kligman AM, Dogadkina D, Lauker RM. (1993) Effects of topical tretinoin on non-sun-exposed protected skin of the elderly. *J Am Acad Dermatol* **39**, 25–33.

24 Darr D, Combs S, Dunston S, Manning T, Pinnell S. (1992) Topical vitamin C protects porcine skin from ultraviolet radiation-induced damage. *Br J Dermatol* **127**, 247–53.

25 Phillips CL, Combs SB, Pinnell SR. (1994) Effects of ascorbic acid on proliferation and collagen synthesis in relation to donor age of human dermal fibroblasts. *J Invest Derm* **103**, 228–32.

26 Pinnell SR, Yang HS, Omar M, Monteiro-Riviere N, DeBuys HV, Walker LC, *et al.* (2001) Topical L-ascorbic acid: percutaneous absorption studies. *Dermatol Surg* **27**, 137–42.

27 Fuchs J, Kern H. (1998) Modulation of UV-light-induced skin inflammation by d-α-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. *Free Radic Biol Med* **25**, 1006–12.

28 Burke KE, Clive J, Combs GF Jr, Commisso J, Keen CL, Nakamura RM. (2001) The effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. *J Nutr Cancer* **38**, 87–97.

29 Lin JY, Selim MA, Shea CR, Grichnik JM, Omar MM, Monteiro-Riviere NA, *et al.* (2003) UV photoprotection by combination topical antioxidants vitamin C and E. *J Am Acad Dermatol* **48**, 866–74.

30 Chan AC. (1993) Partners in defense, vitamin E and vitamin C. *Can J Physiol Pharmacol* **71**, 725–31.

31 Lin FH, Lin JY, Gupta RD, Tournas JA, Burch JA, Selim MA, *et al.* (2005) Ferulic acid dstabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *J Invest Dermatol* **125**, 826–32.

32 Hoppe U, Bergemann J, Diembeck W, Ennen J, Gohla S, Harris I, *et al.* (1999) Coenzyme Q10, a cutaneous antioxidant and energizer. *BioFactors* **9**, 371–8.

33 Pinnell SR, Lin J-Y, Lin F-H, *et al.* (2004) Alpha lipoic acid is ineffective as a topical photoprotectant of skin. Poster presentation, 62nd Annual Meeting of the American Academy of Dermatology, Washington, DC.

34 Eucerin Q10 Anti-Wrinkle Sensitive Skin Crème. (2003) From Wrinkle Reduction Study 2003. In: *Eucerin Q10 Product Compendium*. Wilton, CT: Beiersdorf Inc., p. 11.

35 Beitner H. (2003) Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoaging of facial skin. *Br J Dermatol* **149**, 841–9.

36 Burke KE, Combs GF, Gross EG, Bhuyan KC, Abu-Libdeh H. (1992) The effects of topical and oral L-selenomethionine on pigmentation and skin cancer induced by ultraviolet irradiation. *Nutr Cancer* **17**, 123–37.

37 Burke KE, Burford RG, Combs GR Jr, French IW, Skeffington GR. (1992) The effect of topical L-selenomethionine on minimal erythema dose of ultraviolet irradiation in humans. *Photodermatol Photoimmun Photomed* **9**, 52–7.

38 Wei H, Saladi R, Lu Y, Wang Y, Palep SR, Moore J, *et al.* (2003) Isoflavone genistein: photoprotection and clinical implications in dermatology. *J Nutrition* **133**, 3811S–9S.

Chapter 60: Over-the-counter acne treatments

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BASIC CONCEPTS

- Over-the-counter cosmeceutical products are frequently used in the treatment of acne.
- Topical benzoyl peroxide is one of the most effective over-the-counter acne treatments.
- Other active agents in acne products include hydroxy acids, salicylic acid, sulfur, and retinol.
- Leave-on products have a more profound effect on acne than cleansers.
- Cleansing cloths and scrubs may be used for their sebum removal and keratolytic activity.

Introduction

Although acne is one of the most common conditions that a general dermatologist treats [1], most people with acne will first try to self-treat before seeking the assistance of a healthcare professional. A survey carried out in 2000 demonstrated that 75% of acne sufferers waited about 1 year prior to seeking the help of a healthcare professional [2]. Another study estimated that one-third of those battling acne will ever consult a physician regarding their condition [3]. Without the assistance of a physician, patients will often turn to the drugstore shelves to treat their acne.

A plethora of over-the-counter (OTC) modalities exists for treating acne. These modalities include topical cleansers, creams, lotions, gels, and masks as well as mechanical treatments, essential oils, and oral vitamins. The non-prescription acne market is one of the fastest growing segments of the dermatologic industry. This OTC market worldwide is estimated to be 2–4 times the size of the prescription market [4]. Estimates from 2001 revealed that consumers spend approximately $100 million per year on OTC antiacne products [5].

The Food and Drug Administration (FDA) is the regulatory agency that presides over the marketing of non-prescription acne products. In the Final Acne Monograph, the FDA states that any product labeled as an "acne drug product" is defined as: "A drug product used to reduce the number of acne blemishes, acne pimples, blackheads and whiteheads." The FDA defines OTC products that fit this description to include: salicylic acid, sulfur, sulfur combined with resorcinol, and benzoyl peroxide [6]. Although products cannot be sold bearing an antiacne label unless they contain one of the above approved ingredients, many other products are marketed towards the acne-prone consumer claiming to "heal," "purify," or "cleanse," the skin and pores.

In this chapter we address OTC products that are marketed for the treatment of acne, not just those products that the FDA defines as an "acne drug product." There are a multitude of OTC products with labeling that implies an acne efficacy. Some of these washes and leave-on products contain benzoyl peroxide, salicylic acid, alfa-hydroxy acids, polyhydroxy acids, retinol, or sulfur. Mechanical treatments exist as well and come in the form of cleansing brushs, adhesive pads, heating devices, and scrubs. Some patients may turn to homeopathic remedies such as tea tree oil or chamomile. Oral vitamins, such as vitamin A, zinc, or nicotinamide are also tried as an OTC acne fix.

Soaps and syndets

Studies show that over half of those with acne believe that their condition is caused by poor hygiene and dirt on the skin [7]. This belief often leads patients to alter both how they wash their face and their face washing frequency. While washing the face twice daily is more optimal then washing once or four times daily, the quantity of cleansings probably does not matter as much as the substance that is used to wash the face [8]. A multitude of cleansers exist and can be categorized as either soaps or syndets. Traditional soaps are made of fats and an alkali and have a basic pH of 9–10. This pH, which is higher than the skin's pH, disrupts the intercellular lipids that hold the stratum corneum together. The disintegration of the intercellular "cement" causes skin irritation. Syndets are made of synthetic deter-

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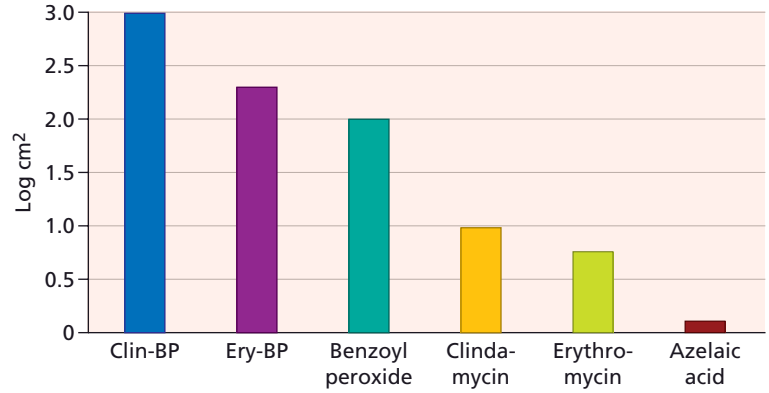

Figure 60.1 Reduction in *Propionibacterium acnes* with topical therapy. Clin-BP, clindamycin and benzoyl peroxide; Ery-BP, erythromycin and benzoyl peroxide. (From Leden JJ. (2001) The evolving role of *Propionibacterium acnes* in acne. *Semin Cutan Med Surg* **20**, 139–43.)

gents and have a pH of 5.5–7, similar to the skin's natural pH. Because syndets only contain less than 10% soap, they are much less damaging to the stratum corneum [9]. The benefit of syndet cleansers specifically for acne patients has been demonstrated in studies.

One study, looking at 25 patients undergoing acne treatment, were randomized to cleanse with either a soap or a syndet. After 4 weeks, those using the syndet cleanser reported having significantly less acne and less oil. Both patients and dermatologists reported less irritation in those using the syndet cleanser [10]. Although not all-inclusive, some brands of syndet cleansers include Cetaphil, Aveeno, Purpose, Basis, Oil of Olay, and Dove. There are additional cleansers that are marketed specifically for acne use that contain an active antiacne ingredient (e.g. benzoyl peroxide or salicylic acid).

Benzoyl peroxide

Benzoyl peroxide is commonly found in OTC antiacne washes, creams, and lotions. In fact, 23% of people aged 13–27 have used an OTC benzoyl peroxide product [11]. Benzoyl peroxide was first utilized in 1917 to bleach flour. In the 1960s, benzoyl peroxide began to have medical applications for treating leg and decubitus ulcers. Several years later, in 1979, it was first used for treating acne. Benzoyl peroxide has antibacterial, anti-inflammatory, and comedolytic properties, which makes it effective in acne treatment. It has antimicrobial properties against *Propionibacterium acnes* and *Staphylococcal aureus*. One study demonstrated an almost 2-$\log_{10}$ decrease in *P. acnes* concentration just after 2 days of 5% benzoyl peroxide use [12]. Another study confirmed this fast-acting effect showing that *P. acnes* counts reduced by a mean of 2-$\log_{10}$ after applying 10% benzoyl peroxide cream for 3 days. After 7 days, there was no further decline in *P. acnes* levels [13]. Benzoyl peroxide has greater antimicrobial properties against *P. acnes* than any of the topical antibiotics alone. However, unlike the antibiotics, benzoyl peroxide will not induce bacterial resistance. Using a topical antibiotic with the addition of benzoyl peroxide will increase the bactericidal effect of the antibiotic (Figure 60.1) [14]. Furthermore, it will also prevent the development of *P. acnes* resistance when used in combination with a topical or oral antibiotic [15].

Benzoyl peroxide also acts as an anti-inflammatory agent by reducing oxygen free radicals and also by lessening *P. acnes* density. The reduction of *P. acnes* has a profound anti-inflammatory effect because the bacteria induce monocytes to produce tumor necrosis factor α (TNF-α), interleukin-1β, and interleukin-8 [16,17]. The strong anti-inflammatory and antibacterial effects of benzoyl peroxide can be parlayed into good clinical results, as shown in a large UK study. This study looked at five antimicrobial acne treatments over an 18-week period. Subjects used either oral oxytetracycline, oral minocycline, benzoyl peroxide, separate administration of topical erythromycin and benzoyl peroxide, or a combination product with containing both topical erythromycin and benzoyl peroxide. The 5% benzoyl peroxide used twice daily had similar efficacy to 100 mg minocycline once daily. This study also carried out a cost-effectiveness analysis and found that the least expensive treatment (benzoyl peroxide) was 12 times more cost-effective than minocycline [18].

Besides being an anti-inflammatory, benzoyl peroxide is also comedolytic. One study utilizing the rabbit ear comedogenicity assay showed a 10% reduction of comedones [19]. Another study compared 5% benzoyl peroxide twice daily with 0.05% tretinoin once daily for 8 weeks. Both treatments were "extremely effective" for all acneiform lesions but significantly reduced both open and closed comedones after only 2 weeks [20].

Benzoyl peroxide is available OTC in 2.5–10% strengths and as either washes or leave-on products (e.g. cream, lotion, gel). Leave-on products reduce *P. acnes* counts more than the washes, although both significantly reduce *P. acnes* on the skin [14]. There is some indication that gel formulations may be more stable and release benzoyl peroxide more consistently than creams and lotions [21]. Equal reductions of acneiform lesions are seen with benzoyl peroxide strengths of 2.5, 5, and 10%. Increasing the strength of benzoyl

peroxide seems only to intensify the irritation [22]. Skin irritation to benzoyl peroxide is one of its greatest barriers to use. Redness, stinging, and dryness may be manifestations of irritation. Many patients describe this as an "allergy" to benzoyl peroxide. However, true allergic contact dermatitis to benzoyl peroxide is estimated at only 1–2.5% of patients with acne [23,24]. Patients should be warned about irritation that may result and should also be told of the propensity for benzoyl peroxide to bleach fabrics and hair.

In addition to being available OTC, benzoyl peroxide is also available as a prescription. These prescription products may contain different formulations that may enhance penetration and decrease irritation, although no head-to-head trials exist comparing prescription with OTC benzoyl peroxide.

Since mouse studies have shown that benzoyl peroxide can produce DNA strand breaks, there has been some question to its carcinogenic potential. However, two case–control studies showed no correlation between benzoyl peroxide use and skin cancer. Additionally, 23 carcinogenicity studies in rodents produced negative results [11]. Epidemiologic evaluations have shown no association between benzoyl peroxide and malignant melanoma [25].

Alfa-hydroxy acids

The hydroxy acids are another common OTC antiacne ingredient found in washes and leave-on products. There are two main classes of hydroxy acids that are used for treating acne: alfa-hydroxy acids and beta-hydroxy acids (Table 60.1). The alfa-hydroxy acids are water-soluble, penetrate the epidermis and even into the dermis at higher concentrations. They act by desquamating the stratum corneum (i.e. exfoliation). Specifically, alfa-hydroxy acids disrupt corneocyte adhesion in the upper stratum corneum, possible by chelating calcium [26]. This results clinically in a smoother appearance to the skin, and may also give the illusion of reducing pore size [27]. Alfa-hydroxy acids also promote epidermolysis, disperse basal layer melanin, and when strong enough to penetrate the dermis they may increase collagen synthesis [28]. These effects may make alfa-hydroxy acids helpful for acne prevention and treatment of postinflammatory hyperpigmentation. The most common OTC alfa-hydroxy acids are glycolic acid (derived from sugar cane) and lactic acid (from sour milk) and are found in less than 10% concentration.

Salicylic acid

The only beta-hydroxy acid used in dermatology is salicylic acid. Unlike the alfa-hydroxy acids, it is lipid-soluble allowing it to penetrate not only the epidermis but also the pilosebaceous unit. This added penetration makes it comedolytic, thus giving it superiority over the alfa-hydroxy acids in treating acne [29]. Salicylic acid also exerts anti-inflammatory effects by inhibiting arachidonic acid.

Multiple studies exist demonstrating the superiority of salicylic acid to placebo or to benzoyl peroxide. One study examined 49 patients who applied either 0.5% salicylic acid or placebo twice daily for 12 weeks. Those who applied the salicylic acid had significantly reduced inflammatory papules and open comedones, but closed comedones were not diminished [30]. One of the two studies submitted to the FDA during the OTC approval phase was a 12-week, double-blind investigation of 180 subjects. It compared the efficacy of 2% salicylic acid solution with a vehicle solution and 5% benzoyl peroxide. Of the subjects treated with the salicylic acid, 40% showed a good or excellent response versus 5% in the vehicle group and only 2% in the benzoyl peroxide group. Salicylic acid was better than either vehicle or benzoyl peroxide in improving total lesions, inflammatory lesions, and open comedones, but not closed comedones.

The second study submitted to the FDA involved 187 subjects and compared 0.5% and 2% salicylic acid solution with the vehicle solution. Both 0.5% and 2% salicylic acid

Table 60.1 Hydroxy acids.

Hydroxy acid	Solubility	Source	Penetration	Action	Over-the-counter strength
Alfa-hydroxy acids	Water soluble		Dermis (at high concentrations)	Exfoliative	Less than 10%
Glycolic acid		Sugar cane			
Lactic acid		Sour milk			
Beta-hydroxy acid	Lipid soluble		Epidermis and pilosebaceous unit	Exfoliative, comedolytic, anti-inflammatory	0.05–5%
Salicylic acid		Willow bark, wintergreen, sweet birch			

were superior to the vehicle in reducing inflammatory lesions, open and closed comedones, and total lesions [31].

There are also several studies that demonstrate the efficacy of salicylic acid formulations other than solution. A cross-over study evaluating a 2% salicylic acid cleanser and a 10% benzoyl peroxide lotion in 30 patients found the salicylic acid cleanser to be superior at improving comedones [32]. Another study demonstrated the efficacy of a 2% salicylic acid scrub in reducing open comedones [33]. Based on these studies, many consider salicylic acid more effective than benzoyl peroxide in treating comedonal acne, but less effective than benzoyl peroxide in treating inflammatory acne [31]. Unlike benzoyl peroxide, salicylic acid does not have the ability to prevent resistance when used in combination with oral or topical antibiotics.

Polyhydroxy acids

A third class of hydroxy acids, polyhydroxy acids, is becoming more popular in OTC dermatologic formulations. Polyhydroxy acids have been shown to be less irritating than alfa-hydroxy acids, but their larger particle size may limit penetration [34]. Lactobionic acid and gluconolactone are polyhydroxy acids most often found in topicals marketed for antiaging purposes but may someday also be found in OTC acne treatments.

Although very little of either the topical benzoyl peroxide or hydroxy acids is absorbed systemically, both of these OTC products are pregnancy category C. Like benzoyl peroxide, the hydroxy acids can cause skin irritation marked by dryness, erythema, and flaking. Use of the hydroxy acids can also lead to greater sun sensitivity. Although generally safe, toxic levels of salicylic acid (known as salicylism) can occur if salicylic acid is used on a large body surface area in patients with icthyosis or excoriations. Use of salicylic acid is contraindicated in any patient with an aspirin allergy [35].

Sulfur

Sulfur is a yellow, non-metallic element that has been used for centuries to treat various dermatologic conditions. A physician in Ancient Rome, Aulus Cornelius Celsus (ca 25 BC – ca 50 BC), wrote *De Medicina*, a medical text which includes the use of sulfur in mineral baths to treat acne [36]. Sulfur continues to be used today for a variety of conditions because of its antifungal and bacteriostatic properties [37]. It is believed by some to also have a keratolytic effect. Although the precise mechanism of action is not known, sulfur is thought to interact with cysteine in the stratum corneum causing a reduction in sulfur to hydrogen sulfide. Hydrogen sulfide in turn degrades keratin, producing the keratolytic effect of sulfur [38]. Although one study has shown sulfur to be comedogenic [39], further studies have not validated this claim [40]. Sulfur is available OTC in concentrations of 3–8% and is often found in combination with resorcinol or resorcinol monoacetate. The malodor and messiness of sulfur limits its use.

Triclosan and triclocarban

Triclosan and triclocarban are two antimicrobials that are found in cleansers marketed for acne treatment and are often labeled as "antibacterial" cleansers. Including having effects against *P. acnes*, both of these antimicrobials are effective against Gram-positive bacteria and triclocarban also is effective against Gram-negative bacteria. Studies are scant, but there is some evidence that these antimicrobials improve acne [41,42].

Retinols

Retinols are a group of vitamin A derivatives that are available topically OTC in various forms such as retinol, retinyl propionate, and retinyl palmitate. Both retinol and retinyl propionate are absorbed by keratinocytes where they are reversibly oxidized into retinaldehyde, wherease retinyl palmitate is inactive. Retinaldehyde is irreversibly converted into all-*trans* retinoic acid (i.e. tretinoin). Tretinoin is transported into the keratinocyte nucleus where it acts by binding to the hormone response elements. There are no large multicenter trials that evaluate the efficacy of the retinols. In general, the retinols are 20 times less potent than topical tretinoin but exhibit greater penetration than tretinoin [43]. 0.25% Topical retinol induces cellular and molecular changes similar to that observed with 0.025% tretinoin without causing the irritation typical of tretinoin. However, it should be noted that most OTC formulations of retinol come in only 0.04–0.07% [44].

Cleansing cloths

Cleansing cloths are disposable, dry towlettes that are impregnated with a cleanser and possibly an antiacne ingredient. Just prior to use, most of them need to be moistened with water. They are manufactured by combining polyester, rayon, cotton, and cellulose fibers through a thermal process. Many cloths are impregnated with triclosan or a hydroxy acid. Their effect on the skin is determined in part by their ingredients but also by the type of weave. The cloths may be either open or closed weave. Cloths with an open weave have 2–3 mm between fibers. This relatively large spacing between the fibers decreases the cloth's contact area with the skin and in turn lessens irritancy. The closed weave cloths have less space between each individual fiber and

are more irritating to the skin [45]. There are no known published trials evaluating the efficacy of cleansing cloths against acne.

Mechanical treatments

In addition to the above-described antiacne ingredients, there are several OTC treatments designed to mechanically rid the skin of acne. Some of these treatments, such as scrubs and cleansing brushes, physically abrade the skin in an attempt to control acne. There are many abrasive scrubs available OTC that patients will often try to combat acne. Scrubs are topical agents that incorporate particles that mechanically abrade the skin and thin the stratum corneum. In general, three classes of scrubs exist. The most abrasive scrubs are made of aluminum oxide particles and ground fruit pits. These particles are the harshest on the skin, in part because of their irregular shape. The second, and milder, class of scrubs is made of polyethylene beads that are smooth and round particles. The mildest class of scrubs is composed of sodium tetraborate decahydrate granules, which soften and dissolve soon after application [45]. To our knowledge, there is only one published study looking at the effect of scrubs on acne. This study showed that scrubs did not improve comedones, but in fact worsened them. The abrasives also caused peeling and erythema. However, resorption of inflammatory lesions was somewhat augmented by the abrasives [46]. Some scrubs also include benzoyl peroxide or a hydroxy acid in order to target the consumer with acne.

In addition to scrubs, another cleansing method designed to thin the stratum corneum is the cleansing brush. Some cleansing brushes (e.g. Sonic™ Skin Care Brush [Pacific Bioscience Labs, Bellevue, MA, USA]) are handheld, battery operator devices with an oscillating brush head while others are simply handheld, coarse pads (Clean and Clear™ Blackhead Eraser [Johnson and Johnson, New Brunswick, NJ, USA]). There are no published trials evaluating the efficacy of either of these devices for removing acne. However, there is a small internally performed study by the makers of the Sonic™ Skin Care Brush demonstrating the brush to remove 2.34 times more foundation than traditional cleansing methods.

There are also adhesive pads (Biore™ [Kao Brands Co., Cincinnati, OH, USA]) on the market that are purported "to get rid of pore clogging buildup and blackheads" [47]. These disposable pads are applied to wet skin and left in place for 10 minutes, over which time the pad will stiffen. The active agent of these pads is polyquaternium 37, a cationic hydrocolloid substance that binds to the anionic component of comedonal plugs [48]. Although no studies exist evaluating the pads' efficacy in treating acne, there is a report of its success in treating trichostasis spinulosa [48].

Besides mechanical agents such as brushes and pads, there is a handheld, electronic heating device (Zeno™ [Zeno Corp., Houston, TX, USA]) designed to speed the resolution of existing acne lesions. The user is directed to apply the device to individual acne lesions for 2.5 minutes, for 2–3 times a day. The device heats to 121°Fahrenheit, killing *P. acnes*. The exact mechanism by which the delivered heat kills this bacterium is unknown. Data from the manufacturer demonstrates that lesions treated with the Zeno device clear on average 1.3 days faster than those treated with a placebo [49].

Essential oils

Patients who are seeking a homeopathic approach to treating acne may seek out essential oils and oral vitamins. Two topical essential oils that can be used are tea tree oil and chamomile. Tea tree oil is derived from the Australian tree *Melaleuca alternifolia*. The oil contains several antimicrobial substances including terpinen-4-ol, alfa-terpineol, and alfa-pinene [50]. A comparative study of 5% tea tree oil versus 5% benzoyl peroxide showed that both substances significantly reduce acne. The tea tree oil had a slower onset but was less irritating than the benzoyl peroxide [51]. It should be noted that the majority of tea tree oil available OTC is no more than 1% concentratioon. Chamomile is derived from the German chamomile plant *Matricaria recutita.* The active ingredient is alfa bisabolol. One study demonstrated that alfa bisabolol has an anti-inflammatory effect in the skin equal to that of 0.25% hydrocortisone [52]. Because of this anti-inflammatory effect, some will try this homeopathic approach to treat their acne.

Oral vitamins

Oral vitamins that have been tried for the treatment of acne include zinc, nicotinamide, and vitamin A. Zinc sulfonate was first used as an acne treatment in 1970. Later, in the 1980s, a different formulation of zinc was developed – zinc gluconate. In patients with acne, zinc inhibits chemotaxis, is bacteriostatic against *P. acnes*, and reduces TNF-α production. *In vitro*, zinc inhibits type I 5-alpha reductase, a key enzyme in the hormonal impact on acne [53]. A randomized, double-blind study of 332 patients compared 30 mg/day zinc gluconate with 100 mg/day minocycline. At 90 days, patients treated with either medication had significant reductions of papules and pustules. However, minocycline-treated subjects had a 17% greater reduction in inflammatory lesions than those treated with zinc [54].

It should be noted that the recommended daily allowance of zinc is 15 mg, half the dose than is often used to treat acne. The most common side effect of zinc supplementation is gastrointestinal upset. Although generally safe at common doses (even safe in pregnancy), side effects can ensue when higher doses are used. In an anecdotal report, a desperate

teenage boy with acne self-medicated with 300 mg/day zinc for 2 years. As a result, he developed severe anemia, leucopenia, and neutropenia, which improved upon cessation of the zinc [55].

Another oral vitamin often utilized for acne treatment is nicotinamide (also known as niacinamide), a water-soluble B vitamin. Nicotinamide can improve acne by both inhibiting white blood cell chemotaxis and by inhibiting the release of lysosomal enzymes by white blood cells which damage the follicular wall [56]. Although the recommended daily allowance of nicotinamide is 20 mg, studies showing its beneficial effect for acne have used 750–1000 mg/day [57]. Supplementation is safe up to 3000 mg/day, at which point it may induce reversible elevations of liver function tests. Oral nicotinamide is also available as a prescription in combination with zinc, copper, and folic acid in a product known as Nicomide (DUSA Pharmaceuticals, Inc., Wilmington, MA, USA) and has shown success in treating acne [58]. Topical nicotinamide has not shown benefit in treating acne [59].

Vitamin A is a fat-soluble vitamin that can be used in high doses to treat acne. Interestingly, those with acne tend to have lower plasma levels of vitamin A than controls [60,61]. Vitamin A binds to some of the same nuclear receptors as isotretinoin (13-*cis* retinoic acid). The recommended daily allowance of vitamin A is 50 000–100 000 IU. It is effective for acne at 300 000 IU/day in females and 400 000–500 000 IU/day in males [62]. At these high doses most patients experience similar side effects to those who are on isotretinoin (e.g. xerosis and cheilitis). High doses of vitamin A also have the potential to induce liver and kidney damage and to cause pseudotumor cerebri.

Conclusions

Because many patients will turn to OTC remedies to treat their acne, it is important that the physician understand what is available to patients. The ability of the physician to speak knowledgeably on OTC remedies instills patient confidence in the physician. Many of these OTC treatments may be used beneficially; however, it is helpful for the physician to advise the patient on both their advantages and shortcomings. Some OTC treatments may enhance the use of prescription medications while others may only cause further irritation. Ultimately, the physician should be educated on merging OTC and prescription acne medications to best help the patient with acne.

References

1 Feldman SR, Fleischer AB Jr. (2000) Role of the dermatologist in the delivery of dermatologic care. *Dermatol Clin* **18**, 223–7.

2 Woodard I. (2002) Adolescent acne: a stepwise approach to management. *Top Adv Nurs Pract eJournal* **2**(2).

3 Malus M, LaChance PA, Lamy L, Macaculay A, Vanasse M. (1987) Priorities in adolescent health care: the teenager's viewpoint. *J Fam Pract* **25**, 159–62.

4 Bowe WP, Shalita A. (2008) Effective over-the-counter acne treatments. *Semin Cutan Med Surg* **27**, 170–6.

5 Agency for Healthcare Research and Quality. (2001) *Management of Acne*. March 2001, Contract No. 01-E018.

6 21 CFR Part 333.350(b)(2), 21 CFR (1991).

7 Clearihan L. (2001) Acne: myths and management issues. *Aust Fam Physician* **30**, 1039–44.

8 Choi JM, Lew VK, Kimball AB. (2006) A single-blinded, randomized, controlled clinical trial evaluating the effect of face washing on acne vulgaris. *Pediatr Dermatol* **23**, 421–7.

9 Abbas S, Goldberg JW, Massaro M. (2004) Personal cleanser technology and clinical performance. *Dermatol Ther* **17** (Suppl 1), 35–42.

10 Subramanyan K. (2004) Role of mild cleansing in the management of patient skin. *Dermatol Ther* **17**, 26–34.

11 Kraus AL, Munro IC, Orr JC, Binder RL, LeBoeuf RA, Williams GM. (1995) Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. *Regul Toxicol Pharmacol* **21**, 87–107.

12 Bojar RA, Cunliffe WJ, Holland KT. (1995) Short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* **132**, 204–8.

13 Pagnoni A, Kligman AM, Kollias N, Goldberg S, Stoudemayer T. (1999) Digital fluorescence photography can assess the suppressive effect of benzoyl peroxide on *Propionibacterium acnes*. *J Am Acad Dermatol* **41**, 710–6.

14 Leyden JJ. (2001) Current issues in antimicrobial therapy for the treatment of acne. *J Eur Acad Dermatol Venereol* **15** (Suppl 3), 51–5.

15 Berson DS, Shalita AR. (1995) The treatment of acne: the role of combination therapies. *J Am Acad Dermatol* **32**, 31–41.

16 Kim J, Ochoa M, Krutzik S, Takeuchi O, Uematsu S, Legaspi A, *et al*. (2002) Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol* **169**, 1535–41.

17 Vowels B, Yang S, Leyden J. (1995) Induction of proinflammatory cytokines by a soluble factor of *Propionibactreium acnes*: implications for chronic inflammatory acne. *Infect Immun* **63**, 3158–65.

18 Ozolins M, Eady EA, Avery AJ, Cunliffe WJ, Po ALW, O'Neill C, *et al*. (2004) Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial. *Lancet* **364**, 2188–95.

19 Tucker SB, Flannigan SA, Dunbar M Jr, Drotman RB. (1986) Development of an objective comedogenicity assay. *Arch Dermatol* **122**, 660–5.

20 Belknap BS. (1979) Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. *Cutis* **23**, 856–9.

21 Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, *et al*. (2003) Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* **49** (Suppl), S1–37.

22 Mills OH Jr, Kligman AM, Pochi P, Comite H. (1986) Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol* **25**, 664–7.

23 Balato N, Lembo G, Cuccurullo FM, Patruno C, Nappa P, Ayala F. (1996) Acne and allergic contact dermatitis. *Contact Derm* **34**, 68–9.

24 Morelli R, Lanzarini M, Vincenzi C. (1989) Contact dermatitis due to benzoyl peroxide. *Contact Derm* **20**, 238–9.

25 Cartwright RA, Hughes BR, Cunliffe WJ. (1988) Malignant melanoma, benzoyl peroxide and acne: a pilot epidemiological case–control investigation. *Br J Dermatol* **118**, 239–42.
26 Berardesca E, Distante F, Vignoli GP, Oresajo C, Green B. (1997) Alpha hydroxyacids modulate stratum corneum barrier function. *Br J Dermatol* **137**, 934–8.
27 Bergfeld W, Tung R, Vidimos A, Vellanki L, Remzi B, Stanton-Hicks U. (1997) Improving the cosmetic appearance of photoaged skin with glycolic acid. *J Am Acad Dermatol* **36**, 1011–3.
28 Tung RC, Bergfeld WF, Vidimos AT, Remzi BK. (2000) Alpha-hydroxy acid-based cosmetic procedures: guidelines for patient management. *Am J Clin Dermatol* **1**, 81–8.
29 Kligman AM. (1997) A comparative evaluation of a novel low-strength salicylic acid cream and glycolic acid products on human skin. *Cosmet Dermatol* **11** (Suppl).
30 Shalita AR. (1981) Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. *Cutis* **28**, 556–8.
31 Chen T, Appa Y. (2006) Over-the-counter acne medications. In: Draelos ZD, Thaman LA, eds. *Cosmetic Formulations of Skin Care Products*. New York: Taylor & Francis, pp. 251–71.
32 Shalita AR. (1989) Comparison of a salicylic acid cleanser and a benzoyl peroxide wash in the treatment of acne vulgaris. *Clin Ther* **11**, 264–7.
33 Pagnoni A, Chen T, Duong H, Wu IT, Appa Y. (2004) Clinical evaluation of a salicylic acid containing scrub, toner, mask and regimen in reducing blackheads. 61st meeting, American Academy of Dermatology, February 2004, Poster 61.
34 Grimes PE, Green BA, Wildnauer RH, Edison BL. (2004) The use of polyhydroxy acids (PHAs) in photoaged skin. *Cutis* **73** (Suppl), 3–13.
35 Brubacher JR, Hoffman RS. (1996) Salicylism from topical salicylates: review of the literature. *J Toxicol Clin Toxicol* **34**, 431–6.
36 Thayer B. (2006) Celsus: De Medicina. Available from: http://penelope.uchicago.edu/Thayer/E/Roman/Texts/Celsus/home.html.
37 Gupta AK, Nicol K, Gupta AK, Nicol K. (2004) The use of sulfur in dermatology. *J Drugs Dermatol* **3**, 427–31.
38 Lin AN, Reimer RJ, Carter DM. (1988) Sulfur revisited [see comment]. *J Am Acad Dermatol* **18**, 553–8.
39 Mills OH Jr, Kligman AM. (1972) Is sulphur helpful or harmful in acne vulgaris? *Br J Dermatol* **86**, 620–7.
40 Fulton JE Jr, Pay SR, Fulton JE 3rd. (1984) Comedogenicity of current therapeutic products, cosmetics, and ingredients in the rabbit ear. *J Am Acad Dermatol* **10**, 96–105.
41 Franz E, Weidner-Strahl S. (1978) The effectiveness of topical antibacterials in acne: a double-blind clinical study. *J Intern Med Res* **6**, 72–7.
42 Lee TW, Kim JC, Hwang SJ. (2003) Hydrogel patches containing triclosan for acne treatment. *Eur J Pharm Biopharm* **56**, 407–12.
43 Duell EA, Kang S, Voorhees JJ. (1997) Unoccluded retinol penetrates human skin *in vivo* more effectively than unoccluded retinyl palmitate or retinoic acid. *J Invest Dermatol* **109**, 301–5.
44 Kang S, Leyden JJ, Lowe NJ, Ortonne JP, Phillips TJ, Weinstein GD, *et al*. (2001) Tazarotene cream for the treatment of facial photodamage: a multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks [see comment]. *Arch Dermatol* **137**, 1597–604.
45 Draelos Z. (2005) Reexamining methods of facial cleansing. *Cosmet Dermatol* **18**, 173–5.
46 Mills OH Jr, Kligman AM. (1979) Evaluation of abrasives in acne therapy. *Cutis* **23**, 704–5.
47 Available from: www.biore.com.
48 Elston DM. (2000) Treatment of trichostasis spinulosa with a hydroactive adhesive pad. *Cutis* **66**, 77–8.
49 Bruce S, Conrad C, Peterson RD, Conrad R, Arambide LS, Thompson J, *et al*. Significant efficacy and safety of low level intermittent heat in patients with mild to moderate acne. http://www.myzenoeurope.com/doc/zenowhite.pdf.
50 Raman A. (1995) Antimicrobial effects of tea-tree oil and its major components on *Staphylococcus aureus, Staph. epidermidis* and *Propionibacterium acnes*. *Lett Appl Microbiol* **21**, 242–5.
51 Bassett IB. (1990) A comparative study of tea-tree oil versus benzoyl peroxide in the treatment of acne. *Med J Aust* **153**, 455–8.
52 Brown DJ, Dattner AM. (1998) Phytotherapeutic approaches to common dermatological conditions. *Arch Dermatol* **134**, 1401–4.
53 Dreno B, Trossaert M, Boiteau HL, Litoux P. (1992) Zinc salts effects on granulocyte zinc concentration and chemotaxis in acne patients. *Acta Derm Venereol* **72**, 250–2.
54 Dreno B, Moyse D, Alirezai M, Amblard P, Auffret N, Beylot C, *et al*. (2001) Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. *Dermatology* **203**, 135–40.
55 Porea TJ, Belmont JW, Mahoney DH Jr. (2000) Zinc-induced anemia and neutropenia in an adolescent. *J Pediatr* **136**, 688–90.
56 Fivenson DP. (2006) The mechanisms of action of nicotinamide and zinc in inflammatory skin disease. *Cutis* **77** (Suppl), 5–10.
57 Niren NM. (2006) Pharmacologic doses of nicotinamide in the treatment of inflammatory skin conditions: a review. *Cutis* **77** (Suppl), 11–6.
58 Niren NM, Torok HM. (2006) The Nicomide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. *Cutis* **77** (Suppl), 17–28.
59 Shalita AR, Smith JG, Parish LC, Sofman MS, Chalker DK. (1995) Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* **34**, 434–7.
60 Vahlquist A, Michaelsson G, Juhlin L. (1978) Acne treatment with oral zinc and vitamin A: effects on the serum levels of zinc and retinol binding protein (RBP). *Acta Derm Venereol* **58**, 437–42.
61 El-Akawi Z, Abdel-Latif N, Abdul-Razzak K. (2006) Does the plasma level of vitamins A and E affect acne condition? *Clin Exp Dermatol* **31**, 430–4.
62 Kligman AM, Mills OH Jr, Leyden JJ, Gross PR, Allen HB, Rudolph RI. (1981) Oral vitamin A in acne vulgaris. Preliminary report. *Int J Dermatol* **20**, 278–85.

Chapter 61: Rosacea regimens

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BASIC CONCEPTS

- Rosacea is a chronic vascular disorder characterized by flushing, redness, telangiectasias, and inflammatory skin lesions.
- Skincare products and cosmetics can improve the skin barrier and also camouflage the underlying erythema.
- Cleansers, moisturizers, and sunscreens can impact the appearance of rosacea.
- Skincare products can be used in conjunction with prescription medications for optimal redness reduction.

Introduction

Rosacea is a chronic vascular disorder affecting the facial skin and eyes which often is characterized by a chronic cycle of remission and flare. Regardless of disease severity (Figure 61.1a–c), there are cosmetic consequences for the patient including flushing, redness, telangiectasia, papules, and/or pustules. Estimates of disease prevalence vary, but it is likely that 14 million people in the USA have rosacea [1]. Because there is no cure for the disease, management consists of the avoidance of disease triggers and the use of both prescription and over-the-counter (OTC) products that work in concert to achieve remission, prevent flare, and camouflage disease manifestations such as flushing and redness.

Physiology of rosacea

Rosacea is found most frequently in fair-skinned individuals with Fitzpatrick type I skin who tend to burn rather than tan. UV radiation damages blood vessels and supporting tissue, and sun exposure may be a causative factor in the disease [2]. Rosacea is most often diagnosed in patients between the ages of 30 and 60 years [2] but it also can begin in adolescence, when it is often mistaken for acne vulgaris, or in persons older than 60 years.

The etiology and pathogenesis of rosacea have not been established, nor are there any known histologic or serologic markers of the disease. However, rosacea is diagnosed by the presence of one or more primary disease features including flushing (transient erythema), non-transient erythema, telangiectasia, papules, and pustules. Secondary diagnostic features include burning/stinging, plaque formation, dryness, edema, ocular manifestations, peripheral location, and/or phymatous changes [3].

Although these disease features often occur in various combinations, four rosacea subtypes have been classified and agreed upon to assist in the diagnosis and selection of appropriate treatment [4] (Figure 61.2a–d). Subtype 1 is erythematotelangiectatic rosacea (Figure 61.2a), which is characterized by flushing episodes lasting more than 10 minutes and persistent erythema of the central face. Telangiectasia is often present. These patients may also complain of central facial edema, stinging and burning, roughness or scaling, and a history of flushing alone is common.

Subtype 2 is papulopustular rosacea (Figure 61.2b), which is characterized by persistent erythema, with transient papules and/or pustules on the central face. Subtype 2 resembles acne, but without comedones; however, acne and papulopustular rosacea can occur simultaneously. Papules and pustules also can occur around the mouth, nose, or eyes, and some patients report burning and stinging.

Subtype 3 is phymatous rosacea (Figure 61.2c), which includes thickening skin and nodularities. Rhinophyma, nose involvement, is the most common presentation; however, ears, chin, and forehead may be involved. Patients may also have telangiectasias and/or patulous follicles in the phymatous area.

Subtype 4 is ocular rosacea (Figure 61.2d), which should be considered if the patient has one or more of the following ocular signs: watery or bloodshot eyes, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, telangiectasia of the conjunctiva and lid margin, or lid and periocular erythema. Blepharitis and conjunctivitis are also found commonly in rosacea patients with ocular manifestations. Ocular rosacea can precede cutaneous signs by years, but it is found most frequently along with cutaneous disease.

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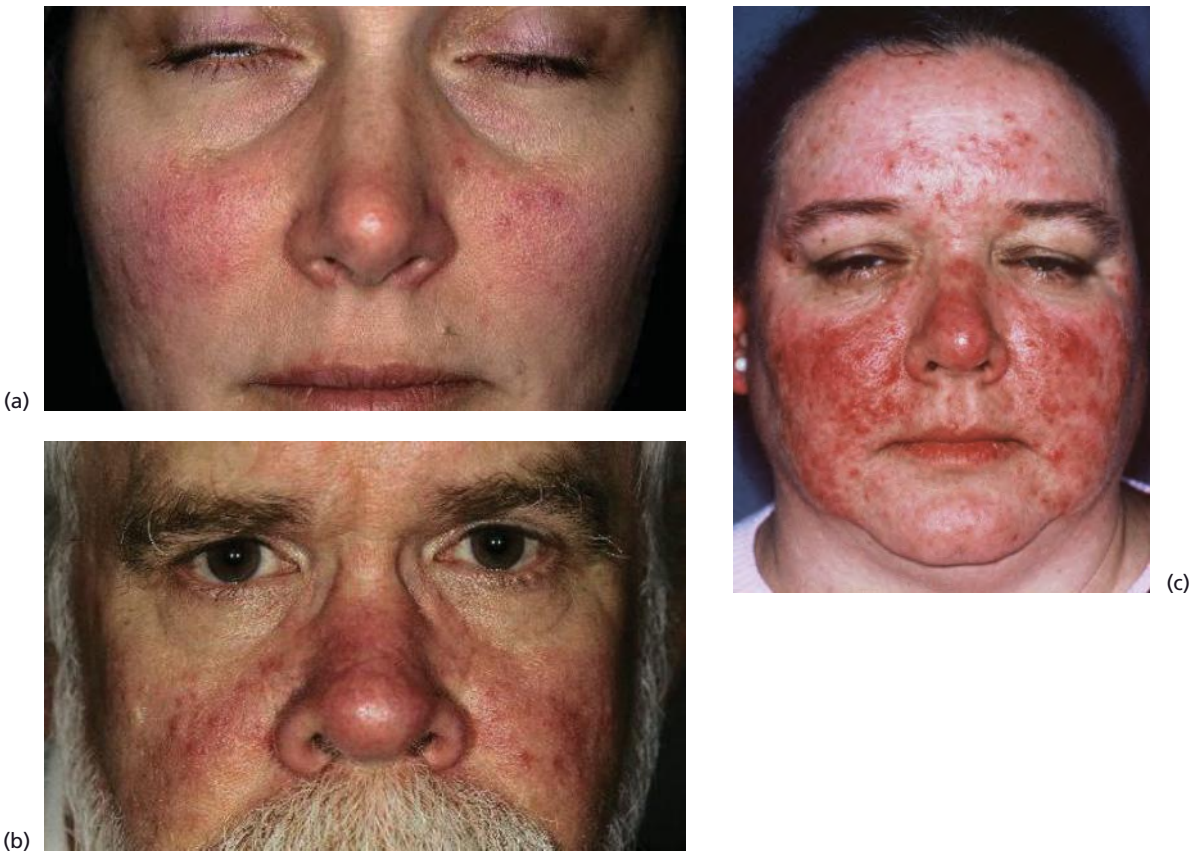

Figure 61.1 Mild (a), moderate (b), and severe (c) rosacea.

Rosacea flare

Beyond these recognized disease stages and presentation, rosacea is characterized by a chronic cycle of remission and flare. Sun avoidance is crucial in avoiding recurrence, but there are numerous other disease triggers. Table 61.1 is only a partial list of flare factors, but it is sufficient to illustrate how challenging flare avoidance is for patients and next to impossible for them to adhere to completely.

Because rosacea pathophysiology has not yet been fully described, treatment targets the signs and symptoms of the disease without a full understanding of disease mechanisms. Disease manifestations and treatment-related cosmetic sequelae necessitate the use of OTC and prescription products for long-term treatment and for camouflaging skin redness, flushing, and blemishes.

Table 61.1 Potential rosacea flare factors. (Adapted from 'Factors that may trigger rosacea flare-ups'. National Rosacea Society website, National Rosacea Society. http://www.rosacea.org/patients/materials/triggers.php. Accessed July 3, 2008.)

Heat Hot baths, saunas, excessively warm environments, overdressing	*Food* Spicy and thermally hot foods Foods high in histamine
Exertion Exercise, lifting	*Alcohol* Red wine, liquor, beer
Emotions Anxiety, stress, embarrassment	*Drugs* Vasodilatators, topical steroids
Medical conditions Chronic cough, menopause	*Topical products* Some cosmetics and hair sprays, especially those containing alcohol; witchhazel or fragrances; hydro-alcoholic or acetone substances
Weather Sun, hot, cold, strong winds, humidity	

Rosacea skincare: available OTC products

Rosacea patients should be counseled to avoid astringents, soaps, fresheners, toners, facial scrubs, masks, and OTC skin-

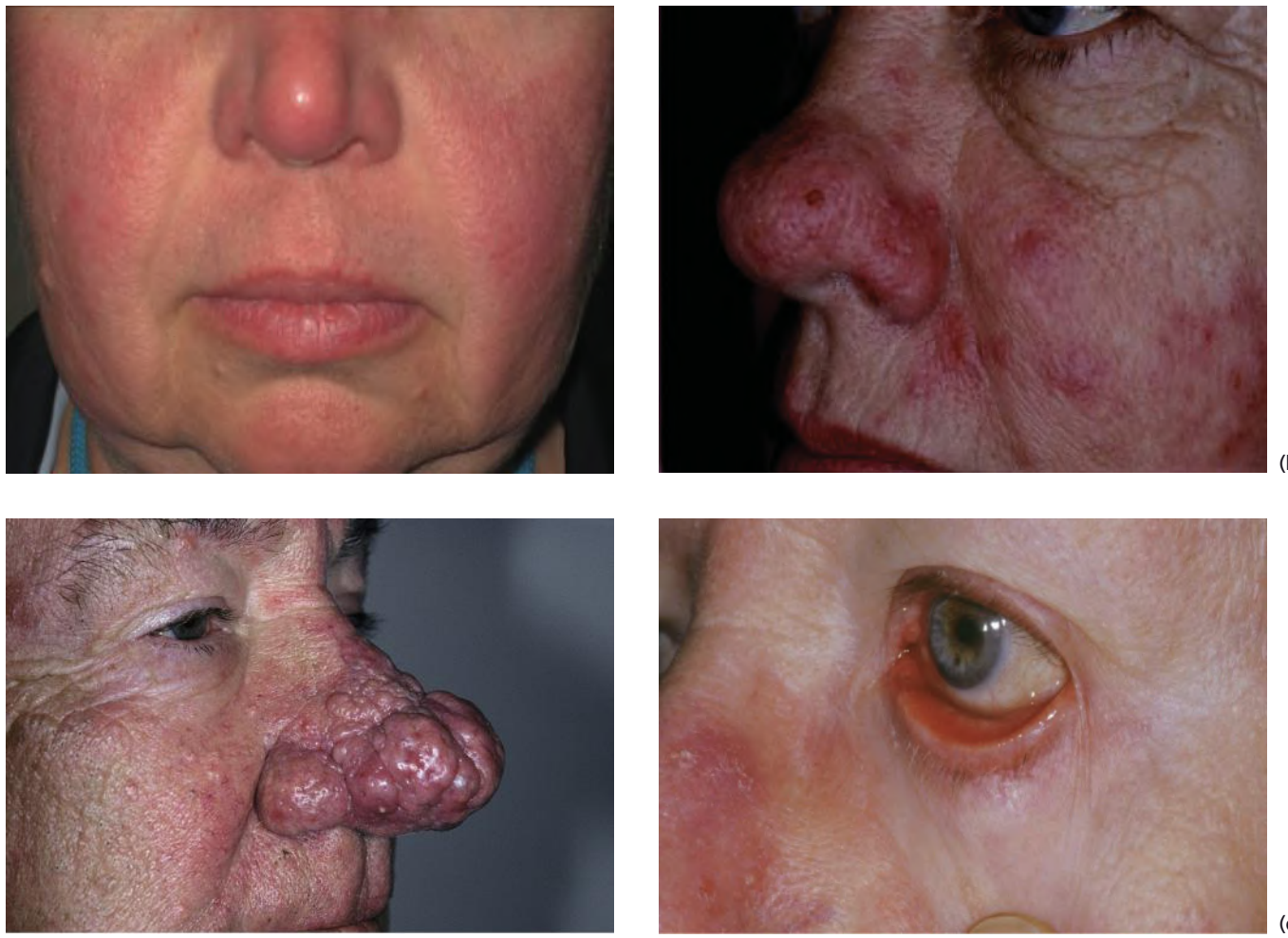

Figure 61.2 Rosacea clinical subtypes: (a) subtype 1; (b) subtype 2; (c) subtype 3; (d) subtype 4.

care programs. However, even though the list of verboten agents is long, there are numerous safe and effective cleansers, moisturizers, sunscreens, and cosmetics available for rosacea patients. Disease management is aimed at achieving synergy between prescription and OTC products to ensure maximum efficacy of active drugs, extend remission, and conceal redness and blemishes. People with rosacea have skin that is extremely sensitive to chemical irritants, so it is important that patients try to avoid all sources of irritation. Furthermore, the skin care regimen of a rosacea patient needs to be simple because the more the skin is specifically manipulated the more opportunity there is for unnecessary irritation.

Cleansing and moisturizing

A proper cleansing and moisturizing routine is an important part of rosacea management. Patients should be counseled that daily cleansing is important to rid the skin of surface dirt, makeup, dead skin, and excess oil, but they should wash with only cool or lukewarm water. The ideal cleanser for rosacea skin is a product that leaves minimal residue, is non-comedogenic and lipid free, and contains non-ionic surfactants with a neutral or slightly acidic pH [4]. Table 61.2 lists some recommended cleansers for rosacea patients.

Moisturizing is important in order to maintain the softness and elasticity of the skin, and therapeutic moisturizers devoid of irritants are important adjunctive therapy in rosacea management [5]. A large proportion of rosacea patients have dry skin, and some topical rosacea medications (e.g. topical metronidazole) can cause further drying and irritation. Moisturizers formulated with a combination of emollients and humectants are recommended to help keep the stratum corneum intact to either repair or prevent skin barrier dysfunction. Furthermore, moisturizing dry skin lessens the itchiness and irritation that rosacea patients often experience as a part of their condition. Table 61.3 lists some moisturizers that can be used as part of a rosacea skin care regimen.

Table 61.2 Recommended over-the-counter cleansers for rosacea skincare.

Cleansers	Benefits
Cetaphil® Gentle Skin Cleanser	Lipid-free, neutral pH, soap-free, non-comedogenic, fragrance-free, leaves no residue, non-irritating
Eucerin® Gentle Hydrating Cleanser	Lipid-free, soap-free, non-comedogenic, fragrance-free, leaves no residue, non-irritating
L'Oréal® Plénitude Gentle Foaming Cleanser	Lipid-free, soap-free, non-comedogenic, leaves no residue, non-irritating
Purpose® Gentle Cleansing Wash	Lipid-free, soap-free, non-comedogenic, soap-free, non-irritating
Eucerin® Redness Relief Soothing Cleanser	Soap-free gel, non-irritating, non-drying, fragrance-free, non-comedogenic, contains licochalcone A

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Table 61.3 Recommended over-the-counter moisturizers for rosacea skincare.

Moisturizers	Benefits
Cetaphil® Moisturizing Cream	Non-greasy, cosmetically appealing, fragrance-free and non-comedogenic. Contains sweet almond oil, which is a source of essential fatty acids
Eucerin® Redness Relief Soothing Moisture Lotion SPF 15 or Daily Protecting Lotion SPF 16	Contains licochalcone A; protects from UVA/UVB; fragrance-free, oil-free, non-irritating, non-comedogenic; Daily Protecting Lotion contains green color neutralizers
Olay® Complete UV Protective Moisture Lotion	Color and fragrance-free; contains vitamin E; SPF 15, protects against UVA and UVB
Rosaliac® Anti-Redness Moisturizer	Contains vitamin C to reduce redness and green tint to conceal redness; expensive

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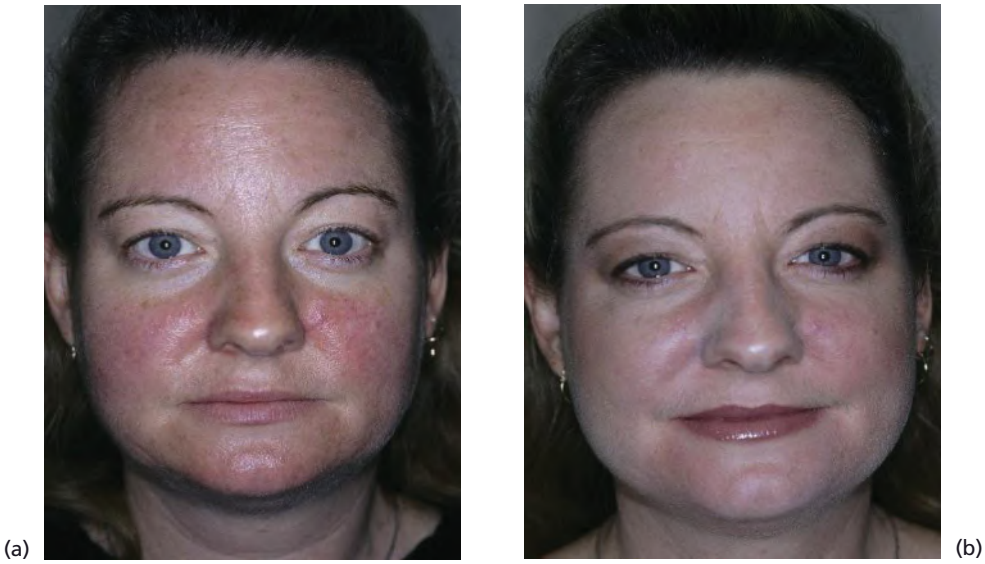

(a) (b)

Figure 61.3 The effect of green-tinted makeup on reddened skin. (a) Patient with rosacea. (b) Camouflage of patient's rosacea using green-tinted makeup.

Cosmetics

Cosmetics are used to camouflage disease signs and symptoms, which is an important part of disease management. Rosacea patients should be counseled to avoid products containing menthol, camphor, or sodium lauryl sulfate, as these can be irritating. It is also recommended that rosacea patients avoid the use of waterproof cosmetics and heavy foundations because they are mechanically harder to apply, and their removal often requires the use of irritating solvents.

Pigmentation irregularities can be camouflaged by applying foundations of complementary colors [6]. For example, red skin can be camouflaged by applying a green foundation, which is the complementary color to red; the combination of green and red creates a brown tone, and this can be covered further, if desired, by a light foundation that spreads easily. Furthermore, a yellow skin tone will turn brown when complemented with purple foundation. Figure 61.3 (a & b) shows how effective green-tinted makeup can be in camouflaging redness. Fortunately, there are an increasing

Table 61.4 Recommended over-the-counter cosmetics for rosacea skincare.

Cosmetics	Benefits
Eucerin® Redness Relief Concealer	Smooth formula blends easily into the skin. Fragrance-free, oil-free, non-irritating, non-comedogenic, contains licochalcone A and has green color neutralizers
Cellex-C® Eye Contour Cream with a 5% L-ascorbic acid	Contains L-ascorbic acid and zinc; lightweight; expensive

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Table 61.5 Recommended over-the-counter sunscreens for rosacea skincare.

Sunscreens	Benefits
L'Oréal® Anthelios SX®	Contains ecamsule; expensive
Neutrogena Helioplex™	Contains avobenzone; protects from UVA/UVB
Active Photo Barrier Complex™	Contains avobenzone; protects from UVA
Dermaplex™	Contains avobenzone; protects from UVA
Titanium dioxide/zinc oxide formulations	Effective options for UVA protection. Older formulations made patients look pale, but newer manufacturing techniques have made these effective products cosmetically elegant

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number of tinted cosmetics and skincare products available to help camouflage rosacea redness, some of which are listed in Table 61.4.

Sunscreens

The daily uninterrupted use of sunscreen is a cornerstone in the long-term management of rosacea. Sun exposure is the leading cause of rosacea flares, and patients should be advised to use a sunscreen daily, irrespective of cloud coverage, with a sun protection factor (SPF) of at least 15. However, patients should be advised that a good sunscreen contains both UVB blockers (e.g. octyl methoxycinnamate, homosalate), as well as UVA blockers (e.g. avobenzone, ecamsule, titanium dioxide, oxybenzone, sulisobenzone, and zinc oxide) [6]. It is also important that the sunscreen be non-irritating, and patients with rosacea may have better tolerance of products containing dimethicone or cyclomethicone [7]. Furthermore, green-tinted sunscreens have the additional benefit of camouflaging erythema. Examples of some recommended sunscreens for rosacea can be found in Table 61.5.

Cleansing, moisturizing, camouflaging, and using sunscreen are the primary features of a rosacea skincare regimen. OTC products that have a green tint or that are cosmetically elegant can be applied during the day, and prescription products used to treat erythema and redness that are less cosmetically elegant can be applied at night. Patients with long-term rosacea often have sensitive skin and can be the most difficult to treat.

Available prescription agents

Oral and topical prescription agents are fundamental in the management of rosacea. Mild to moderate rosacea can be treated with topical monotherapy or topical combination therapy with or without an oral antibiotic. Moderate to severe rosacea necessitates the use of oral antibiotic therapy until remission is achieved, usually for 3–4 months. Remission can often be maintained by continuing the topical therapy alone or in combination with a low-dose oral antibiotic [1]. Because rosacea pathogenesis is so poorly understood, management is focused on treating disease endpoints rather than the underlying disease. In general, inflammation is treated with an anti-inflammatory agent, papules and pustules are treated with antibiotics (with no target organism), flushing is treated with vasoconstrictors, and telangiectasias are treated with light-based therapies.

Oral antibiotic therapy

Papular-pustular rosacea responds well to oral antibiotics, although their efficacy likely is brought about bytheir anti-inflammatory effects more than their antimicrobial effects [2]. Standard antibiotic agents include tetracyclines (tetracycline, doxycycline, and minocycline), erythromycin, and co-trimoxazole, although the latter is usually reserved for use in Gram-negative rosacea or for patients who have not responded to other therapies [8]. These agents have been used for decades and are associated with a relatively good safety profile [8].

Tetracyclines are the most commonly prescribed oral antibiotics for rosacea, but there is apprehension about antibiotic resistance with the long-term use of these and other antibiotic agents. In response to this concern, an anti-inflammatory dose doxycycline (40 mg delayed-release formulation) has been formulated for the treatment of rosacea. Long-term use of this agent did not alter bacterial susceptibility to antibiotics during a 9-month period [9]. Furthermore, a 16-week comparison study showed that both the 40-mg

delayed-release and the 100-mg formulations in combination with 1% metronidazole topical gel are equally effective for the treatment of moderate to severe rosacea with a similar onset of action, and the delayed-release group had a superior side effect profile including fewer gastrointestinal effects [10].

Topical therapy

Topical therapy for rosacea reduces inflammatory lesions (papules and pustules), decreases erythema, improves pruritus, burning and stinging, and reduces the incidence and intensity of flares [1]. Standard topical therapies include sulfacetamide 10%/sulfur 5%, metronidazole, and azelaic acid (AzA), which is the first new therapeutic class of topical agents approved for rosacea in more than a decade. Topical antibiotics erythromycin and clindamycin are second-line agents, but data regarding their efficacy in rosacea treatment are limited [1].

Sulfacetamide-sulfur has anti-inflammatory properties, and the gel comes in a green-tinted formulation, which has the advantage of simultaneously treating inflammation and toning down redness. Sulfacetamide-sulfur also has been combined with avobenzone (UVA filter) and octinoxate (UVB filter) in an SPF 18 formulation, which has shown superior efficacy than topical metronidazole in investigator global severity, percent reductions in inflammatory lesions, and improvement in erythema [11]. Overall, these leave-on products have demonstrated favorable safety and tolerability profiles [1]. Furthermore, sulfacetamide-sulfur cleansers also have demonstrated efficacy as adjunctive therapy in combination with other topical and/or systemic agents [1].

Other treatment modalities

Flushing is a challenging treatment aspect of rosacea management and a source of frustration for most patients. Although there are few data supporting the use of vasoconstrictor agents for flushing, anecdotal reports support the use of low-dose beta-blockers, selective serotonin reuptake inhibitors, and clonidine [12].

Light-based therapies

Many patients also are frustrated with the poor efficacy of oral and topical therapies in resolving telangiectasia and persistent erythema. However, efficacy has been demonstrated in the improvement of vascular disease features from light-based and laser therapies. Pulsed dye laser can be highly effective in reducing telangiectasia, flushing, and erythema by eliminating hemoglobin within increased dilated vessels in rosacea skin. However, efficacy is inconsistent, and treatment can be limited by the frequent occurrence of purpura, which can be long-lasting and difficult to conceal [13].

More recently, intense pulsed light (IPL) therapy has been used with success to treat vascular symptoms of rosacea. IPL utilizes selective photothermolysis with a broad spectrum of light to destroy targeted vessels by coagulation while sparing surrounding tissue [1]. IPL is advantageous because it can penetrate the skin more effectively than lasers. Furthermore, variable light durations can target vessels of different sizes at multiple depths, IPL's increased spot size allows a larger treatment area, and sequential pulsing provides for epidermal cooling between pulses [13].

Natural actives

Cosmetic products with natural actives can be useful to soothe irritation associated with rosacea. Vitamin C is an antioxidant with numerous positive effects on the skin including collagen repair, normalization of photodamage, and anti-inflammatory properties. The use of a 5.0% vitamin C preparation demonstrated efficacy in objective and subjective improvement in erythema, which might be because of its anti-inflammatory effects [2]. There are currently three or four anti-redness products available, and the anti-redness moisturizer listed in Table 61.3 also has a green tint, which heals and conceals redness simultaneously.

Licochalcone A is a major phenolic constituent of the licorice species *Glycyrrhiza inflata* which exhibits anti-inflammatory and antimicrobial effects, and improves redness and irritation [14]. The Eucerin® Redness Relief line has an SPF lotion and spot concealer containing licochalcone A with a green-tinted base, which provides both an anti-inflammatory component and redness camouflage. A study assessing the efficacy of this product line in reducing irritation in patients with mild to moderate facial redness showed that a regimen of cleanser, SPF lotion, spot concealer, and night cream containing licochalcone A improved redness and was compatible with daily metronidazole treatment [15].

Chrysanthellum indicum is a plant-based extract containing phenylpropanoic acids, flavonoids, and saponosids with documented effects on vascular wall permeability and on the increase of the mechanical resistance of capillaries [16]. A cream containing *C. indicum* was recently evaluated in 246 patients with moderate rosacea. Results showed that 12-week, twice daily treatment with the *C. indicum* extract-based cream was significantly more effective than placebo in reducing erythema. Furthermore, this cream has vitamin P properties, which may be responsible for reducing or preventing microcirculation disorders involved in the erythema of rosacea [16].

Alfa-hydroxy acid-based cosmetic peels and at-home regimens also have shown promise for rosacea treatment. A regimen of a daytime cream containing SPF 15 and gluconolactone 8%, and an evening cream with gluconolactone 8% demonstrated significant improvement in texture, fine lines, photodamage, dryness, and erythema, and 80% of patients rated the cosmetic acceptability of these products as

good to excellent [17]. A polyhydroxy acid skin care regimen (cleanser and moisturizer) also demonstrated good tolerability and efficacy in combination with AzA 15% in patients with sensitive skin conditions [18]. This regimen significantly added to the reduction of facial erythema, did not interfere with the efficacy of AzA 15%, and smoothed the skin, which could further enhance patient satisfaction with the products. Glycolic acid peels and topical glycolic acid products added to an antibacterial regimen also have demonstrated dramatic improvement in skin texture and follicular pores, and in the resolution of comedones, papules, and pustules [17]. An additional benefit of these products and procedures is that they provide a treatment option for pregnant women because glycolic acid products, as well as AzA 15%, are not contraindicated in pregnancy.

Conclusions

Management of rosacea includes avoidance of disease triggers and use of oral and topical prescription agents and OTC products to achieve remission, maximize time to flare, and conceal redness. A non-irritating skincare regimen is essential for long-term disease management. A variety of OTC cleansers, moisturizers, sunscreens, and cosmetics are available to keep skin healthy, and an increasing number of OTC products are tinted and/or contain natural anti-redness actives such as vitamin C and licochalcone A, which can be used in combination with prescription agents to maximize response.

Although the pathogenesis of rosacea still has not been elucidated, there is hope that future rosacea therapies will target the disease at the genetic level, which is now common for other inflammatory skin disorders such as atopic dermatitis. There is ongoing research on vascular endothelial growth factor (VEGF) antagonists. It would appear that retinoids can modulate VEGF expression in the skin, and topical retinoic acid has demonstrated beneficial effects on vascular components of rosacea, specifically erythema and telangiectasia. Natural actives and botanicals will continue to be evaluated for their positive effects on the skin, and work remains to be done in optimizing light-based therapy in terms of clarifying treatment parameters, optimal treatment frequency, and the utility of adjuvant light-based therapies.

References

1 Del Rosso JQ. (2004) Medical treatment of rosacea with emphasis on topical therapies. *Expert Opin Pharmacother* **5**, 5–13.

2 Cohen AF, Tiemstra JD. (2002) Diagnosis and treatment of rosacea. *J Am Board Fam Pract* **15**, 214–7.

3 Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, *et al*. (2002) Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol* **46**, 584–7.

4 Bikowski J. (2001) The use of cleansers as therapeutic concomitants in various dermatologic disorders. *Cutis* **68** (Suppl), 12–9.

5 Bikowski J. (2001) The use of therapeutic moisturizers in various dermatologic disorders. *Cutis* **68** (Suppl), 3–11.

6 Draelos ZD. (2007) Cosmetics. Emedicine online journal. Available at: http://emedicine.com/derm/topic502.htm. Accessed June 4, 2008.

7 Nichols K, Desai N, Lebwohl MG. (1998) Effective sunscreen ingredients and cutaneous irritation in patients with rosacea. *Cutis* **61**, 344–6.

8 Del Rosso JQ. (2000) Systemic therapy for rosacea: focus on oral antibiotic therapy and safety. *Cutis* **66** (Suppl), 7–13.

9 Walker C, Webster G. (2007) The effect of anti-inflammatory dose doxycycline 40 mg once-daily for 9 months on bacterial flora: Subset analysis from a multicenter, double-blind, randomized trial. Poster presented at 26th Anniversary Fall Clinical Dermatology Conference; October 18–27, 2007, Las Vegas, Nevada.

10 Del Rosso JQ. (2008) Comparison of anti-inflammatory dose doxycycline (40 mg delayed-release) vs doxycycline 100 mg in the treatment of rosacea. Poster presented at 8th Annual Caribbean Dermatology Symposium, January 15–19, 2008; St. Thomas, US Virgin Islands.

Shalita AR, Dosik JS, Neumaier GJ, *et al*. (2003) A comparative efficacy study of Rosac® cream with sunscreens (sodium sulfacetamide 10% and sulfur 5%) and MetroCream® (metronidazole 0.75%) in the twice daily treatment of rosacea. *Skin Aging* **Oct** (Suppl), 17–22.

11 Baldwin HE. (2007) Systemic therapy for rosacea. *Skin Ther Lett* **12**, 1–5; 9.

12 Bikowski JB, Goldman MP. (2004) Rosacea: where are we now? *J Drugs Dermatol* **3**, 251–61.

13 Kolbe L, Immeyer J, Batzer J, Wensorra U, tom Dieke K, Mundt C, *et al*. (2006) Anti-inflammatory efficacy of licochalcone A: correlation of clinical potency and *in vitro* effects. *Arch Dermatol Res* **298**, 23–30.

14 Weber TM, Ceilley RI, Buerger A, Kolbe L, Trookman NS, Rizer RL, *et al*. (2006) Skin tolerance, efficacy, and quality of life of patients with red facial skin using a skin care regimen containing licochalcone A. *J Cosmet Dermatol* **5**, 227–32.

15 Rigopoulos D, Kalogeromitros D, Gregoriou S, Pacouret JM, Koch C, Fisher N, *et al*. (2005) Randomized placebo-controlled trial of a flavonoid-rich plant extract-based cream in the treatment of rosacea. *J Eur Acad Dermatol Venereol* **19**, 564–8.

16 Tung RC, Bergfeld WF, Vidimos AT, Remzi BK. (2000) Alpha-hydroxy acid-based cosmetic procedures: guidelines for patient management. *Am J Clin Dermatol* **1**, 81–8.

17 Draelos ZD, Green BA, Edison BL. (2006) An evaluation of a polyhydroxy acid skin care regimen in combination with azelaic acid 15% gel in rosacea patients. *J Cosmet Dermatol* **5**, 23–9.

Chapter 62: Eczema regimens

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BASIC CONCEPTS

- Dry skin affected by eczema is characterized by loss of intercellular lipids which results in barrier deficits.
- Moisturizers are an important part of eczema treatment as they provide an environment optimal for barrier repair.
- Moisturizers function by impeding transepidermal water loss with oily occlusive substances, such as petrolatum, mineral oil, vegetable oils, and dimethicone, and by attracting water to the dehydrated stratum corneum and epidermis with humectants, such as glycerin, sodium PCA, propylene glycol, lactic acid, and urea.
- Moisturizing ingredients can be delivered to the skin surface by emulsions, liposomes, and niosomes.
- Careful moisturizer selection is key to the treatment and prevention of eczematous skin disease.

Introduction

Eczematous skin disease is one of the most commonly treated dermatologic conditions. While topical prescription corticosteroids and calcineurin inhibitors are the mainstay of therapy, cosmeceutical moisturizers are key to the treatment and prevention of disease. Moisturizers enhance the skin barrier, decreasing stinging and burning from a sensory standpoint and improving the look and feel of the skin. Moisturizers can also smooth desquamating corneocytes and fill corneocytes gaps to create the impression of tactile smoothness. This effect is temporary, of course, until the moisturizer is removed from the skin surface by wiping or cleansing. From a functional standpoint, moisturizers can create an optimal environment for healing and minimize the appearance of lines of dehydration by decreasing transepidermal water loss. Transepidermal water loss increases when the "brick and mortar" organization of the protein-rich corneocytes held together by intercellular lipids is damaged. A well-formulated cosmeceutical moisturizer can decrease the water loss until healing occurs.

Etiology

Eczema is characterized by barrier disruption, which is the most common cause of sensitive skin. The barrier can be disrupted chemically through the use of cleansers and cosmetics that remove intercellular lipids or physically through the use of abrasive substances that induce stratum corneum exfoliation. In some cases, the barrier may be defective because of insufficient sebum production, inadequate intercellular lipids, or abnormal keratinocyte organization. The end result is the induction of the inflammatory cascade accompanied by erythema, desquamation, itching, stinging, burning, and possibly pain. The immediate goal of treatment is to stop the inflammation through the use of topical, oral, or injectable corticosteroids, depending on the severity of the eczema and the percent body surface area involved. In dermatology, topical corticosteroids are most frequently employed with low potency corticosteroids (desonide) used on the face and intertrigenous areas, medium potency corticosteroids (triamcinolone) on the upper chest and arms, high potency corticosteroids (fluocinonide) on the legs and back, and ultra high potency corticosteroids (clobetasol) used on the hands and feet. Newer topical options for the treatment of eczema-induced sensitive skin include the calcineurin inhibitors, pimecrolimus, and tracrolimus.

However, the resolution of the inflammation is not sufficient for the treatment of eczema. Proper skin care must also be instituted to minimize the return of the conditions that led to the onset of eczema.

Moisturizer mechanism of action

Moisturizers are incorporated into eczema treatment regimens to reduce transepidermal water loss. There are three cosmeceutical ingredient categories that can reduce transepidermal water loss: occlusives, humectants, and hydrophilic matrices [1]. The most common method for reducing transepidermal water loss is the application of an occlusive ingredient to the skin surface. These are oily sub-

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Table 62.1 Occlusive moisturizing ingredients to inhibit transepidermal water loss.

1. Hydrocarbon oils and waxes: petrolatum, mineral oil, paraffin, squalene
2. Silicone oils
3. Vegetable and animal fats
4. Fatty acids: lanolin acid, stearic acid
5. Fatty alcohol: lanolin alcohol, cetyl alcohol
6. Polyhydric alcohols: propylene glycol
7. Wax esters: lanolin, beeswax, stearyl stearate
8. Vegetable waxes: carnauba, candelilla
9. Phospholipids: lecithin
10. Sterols: cholesterol

stances that create a barrier to water evaporation. The more commonly used occlusive ingredients in current formulations and their chemical category are listed in Table 62.1 [2].

The most popular and effective occlusive ingredient is time-tested petrolatum, which blocks 99% of water loss from the skin surface [3]. This remaining 1% transepidermal water loss is necessary to provide the cellular message for barrier repair initiation. If the transepidermal water loss is completely halted, the removal of the occlusion results in failure to repair the barrier and water loss quickly resumes at its preapplication level. Thus, the occlusion does not initiate barrier repair [4]. Petrolatum does not function as an impermeable barrier, rather it permeates throughout the interstices of the stratum corneum allowing barrier function to be re-established [5]. Moisturizers for eczematous disease must contain several occlusive moisturizing ingredients.

In addition to occlusive ingredients, a therapeutic moisturizer for eczema must contain humectants. Humectants are substances that attract water to the viable epidermis and stratum corneum from the dermis. They function as a sponge to hold and release water as necessary. Examples of humectants include glycerin, honey, sodium lactate, urea, propylene glycol, sorbitol, pyrrolidone carboxylic acid, gelatin, hyaluronic acid, vitamins, and some proteins [2,6].

Humectants only draw water from the environment when the ambient humidity exceeds 70%. In environmentally controlled spaces, this does not occur, thus humectants pull water from the deeper epidermal and dermal tissues to rehydrate the stratum corneum. A therapeutic moisturizer for eczema must trap the water in the skin with an occlusive film placed on top of the stratum corneum [7]. Humectants also allow the skin to feel smoother by filling holes in the stratum corneum through swelling [8,9]. Therefore, a moisturizer recommended for eczema must combine both occlusive and humectant ingredients for optimal efficacy and patient esthetics. Occlusive and humectant moisturizers are the formulations most beneficial in the treatment of eczema and include the majority of those found in the dermatologic sample closet (Eucerin Cream and Lotion, Beiersdorf; Norwegian Formula Moisturizers, Neutrogena; Aveeno Cream and Lotion, Johnson & Johnson; Olay Daily Facial Moisturizer, Procter & Gamble, Plentitude, L'Oréal; Cetaphil Cream and Lotion, Galderma; CeraVe Cream and Lotion, Coria).

A third type of moisturizing formulation is known as the hydrophilic matrix. Hydrophilic matrices are large molecular weight substances that create a film over the skin surface thereby retarding water evaporation. The first hydrophilic matrix developed was an oatmeal bath (Aveeno Oatmeal Bath, Johnson & Johnson). The colloidal oatmeal created a film that prevented water from leaving the skin to enter the bath water. Newer hydrophilic matrices include peptides and proteins, but they do not provide meaningful skin moisturization in the eczema patient.

Moisturizer goals in eczema

The goal of all moisturizing emulsions is to accomplish skin remoisturization, which occurs in four steps: initiation of barrier repair, alteration of surface cutaneous moisture partition coefficient, onset of dermal–epidermal moisture diffusion, and synthesis of intercellular lipids [10]. These steps must occur sequentially in order for proper skin barrier repair. Once the barrier has repaired, there must be some substance that holds and regulates the skin water content. This substance has been termed the natural moisturizing factor (NMF). The constituents of the NMF have been theorized to consist of a mixture of amino acids, derivatives of amino acids, and salts. Artificially synthesized NMF has been constructed from amino acids, pyrrolidone carboxylic acid, lactate, urea, ammonia, uric acid, glucosamine, creatinine, citrate, sodium, potassium, calcium, magnesium, phosphate, chlorine, sugar, organic acids, and peptides [11]. Ten percent of the dry weight of the stratum corneum cells is composed of NMF in well-hydrated skin [12]. Cosmeceutical moisturizing emulsions try to duplicate the effect of the NMF.

Moisturizer delivery systems

Another method for optimizing the ability of moisturizers to create an environment for healing in eczema patients is through novel delivery of the ingredients. This has led to the development of delivery systems that can time release substances onto the skin surface and improve product esthetics. For example, petrolatum is the most effective ingredient for skin healing, yet it leaves an easily removed, sticky, greasy film on the skin surface. A delivery system could allow small amounts of petrolatum to be released onto the skin surface avoiding the esthetic drawbacks. Examples of delivery systems relevant to eczema treatment include emulsions,

serums, liposomes, niosomes, multivesicular emulsions, and nanoemulsions.

Moisturizing emulsions

Most moisturizers developed for the treatment of eczema are emulsions [13]. An emulsion is formed from oil and water mixed and held in solution by an emulsifier. Most emulsifiers are surfactants, or soaps, which dissolve the two non-miscible ingredients. The most common emulsions are oil-in-water, where the oil is dissolved in the water [14]. This emulsion is the most popular among patients because the water evaporates leaving behind a thin film of oily ingredients. If the emulsion can be poured from a bottle, it is considered a lotion. These moisturizing products are popular for eczema treatment, but may make the eczema worse as the repeated wetting and drying of the skin results in further maceration. Cream oil-in-water emulsions are preferred because the environment created for barrier repair is far superior.

Water-in-oil emulsions, where the water-soluble substances are dissolved in the oil-soluble substances, are less popular because of their greasy esthetics. Most ointments are water-in-oil emulsions, but they leave the skin feeling warm and sticky. Ointments deliver higher levels of moisturization because the water phase is small, leaving behind a proportionately larger concentration of ingredients capable of retarding transepidermal water loss. Even though their efficacy is greater, most eczema patients prefer more esthetic formulations.

Moisturizing serums

A specialized form of emulsion is a serum. Serums are usually low viscosity, oil-in-water emulsions that deliver of thin film of active ingredients to the skin surface. For example, a high concentration glycerin serum can be placed under a high concentration petrolatum oil-in-water emulsion to provide robust skin moisturization. Sometimes a serum will contain cosmeceutical barrier enhancing ingredients, such as ceramides, cholesterol, and free fatty acids.

Moisturizing liposomes and niosomes

Moisturizing ingredients can be incorporated into structures with unique physical properties on the skin, such as liposomes and niosomes (Table 62.2). Liposomes are spherical vesicles with a diameter 25–5000 nm formed from membranes consisting of bilayer amphiphilic molecules, which possess both polar and non-polar ends. The polar heads are directed toward the inside of the vesicle and toward its outer surface while the non-polar, or lipophilic tails, are directed toward the middle of the bilayer.

Liposomes are based on the natural structure of the cell membrane, which has been highly conserved through evolutionary change. The name is derived from the Greek word "lipid" meaning fat, and "soma" meaning body. Liposomes are primarily formed from phospholipids, such as phosphatidylcholine, but may also be composed of surfactants, such as dioleoylphosphatidylethanolamine. Their functionality may be influenced by chemical composition, vesicle size, shape, surface charge, lamellarity, and homogeneity.

The liposome is an extremely versatile structure. It can contain aqueous substances in its core, or nothing at all. Hydrophobic substances can dissolve in the phospholipid bilayer shell, which allows liposomes to deliver both oil-soluble and water-soluble substances without need for an emulsifier. Thus, the internal moisturizer payload plus the phospholipid membrane can both function as moisturizers.

Table 62.2 Special moisturizer delivery systems.

Delivery system	Structure	Advantages vs. disadvantages
Liposomes	Spherical vesicles consisting of bilayer amphiphilic molecules with polar and non-polar ends	Can deliver hydrophilic and hydrophobic substances to the skin surface without an emulsifier
Multivesicular emulsion (MVE)	Liposome within a liposome within a liposome to form concentric liposomes	Deliver multiple moisturizing ingredients (glycerin, dimethicone, sphingolipids, ceramides) simultaneously
Niosome	Liposome composed of non-ionic surfactants, such as ethoxylated fatty alcohols and synthetic polyglycerol ethers	Non-ionic surfactants do not moisturize the skin surface
Nanoemulsions	Emulsions with 20–300 nm droplets	Allow enhanced skin penetration due to small droplet size

It is unlikely that liposomes diffuse across the stratum corneum barrier intact. The corneocytes are embedded in intercellular lipids, composed of ceramides, glycosylceramides, cholesterol, and fatty acids, which are structurally different from the phospholipids of the liposome. It is postulated that liposomes penetrate through the appendageal structures. They may also fuse with other bilayers, such as cell membranes, to release their ingredients. This is the mechanism by which liposomes can function as moisturizers, supplementing deficient intercellular lipids.

Niosomes are a specialized form of liposome composed of non-ionic surfactants. These are detergents, such as ethoxylated fatty alcohols and synthetic polyglycerol ethers (polyoxyethylene alkylester, polyoxyethylene alkylether). These liposomes do not deliver the moisturizing phospholipids to the skin surface.

Multivesicular emulsions

Another variant of the liposome is a multivesicular emulsion (MVE) (Figure 62.1). The MVE is created through a physical mixing technique, which makes them more stable, but also less expensive to produce. An MVE can be thought of as a liposome within a liposome within a liposome. Thus, with the release of each liposome, additional moisturizing ingredients can be deposited on the skin surface. MVEs can deliver glycerin, dimethicone, sphingolipids, and ceramides to the skin surface simultaneously.

Moisturizing nanoemulsions

Nanoemulsions are similar to regular emulsions with an oil-loving hydrophobic phase and a water-loving hydrophilic, except droplets in these emulsions are on the nano scale of 20–300 nm [15]. If the nano droplets are larger than 100 nm, the emulsion appears white, while nanoemulsions with droplets of 70 nm are transparent. Nanoemulsions offer the ability to deliver highly hydrophobic or lipophilic substances into the skin, which could not otherwise penetrate. The stratum corneum is an excellent barrier to lipophilic ingredients.

For example, new nanoemulsions of ubiquinone have been developed. Ubiquinone, also known as coenzyme Q10, is an important antioxidant manufactured by the body and found in all skin cells. It is found in both hydrophilic and hydrophobic cellular compartments, but topical delivery has been challenging. Nanoemulsions have successfully delivered higher concentrations of ubiquinone into the skin with the goal of enhancing the skin's natural antioxidant capabilities, while leaving beyond a moisturizing film from the other ingredients in the emulsion.

Developing a moisturizer regimen

This chapter has discussed the goals of moisturization, the various types of moisturizers, and some of the unique moisturizer delivery systems. The biggest challenge for the clinician is adding moisturizers or combining moisturizers as part of a treatment regimen.

Patients with eczema require basic hygiene. The face and body must be cleansed. There is no doubt that the synthetic detergent cleansers, also known as syndets, provide the best skin cleansing while minimizing barrier damage. Bars based on sodium cocyl isethionate appear to perform the best (Dove, Unilever; Olay, Procter & Gamble). There are some patients, however, who only require the use of a facial syndet cleanser occasionally, because sebum production and physical activity are minimal. For these patients, a lipid-free cleanser is preferable because it can be used without water

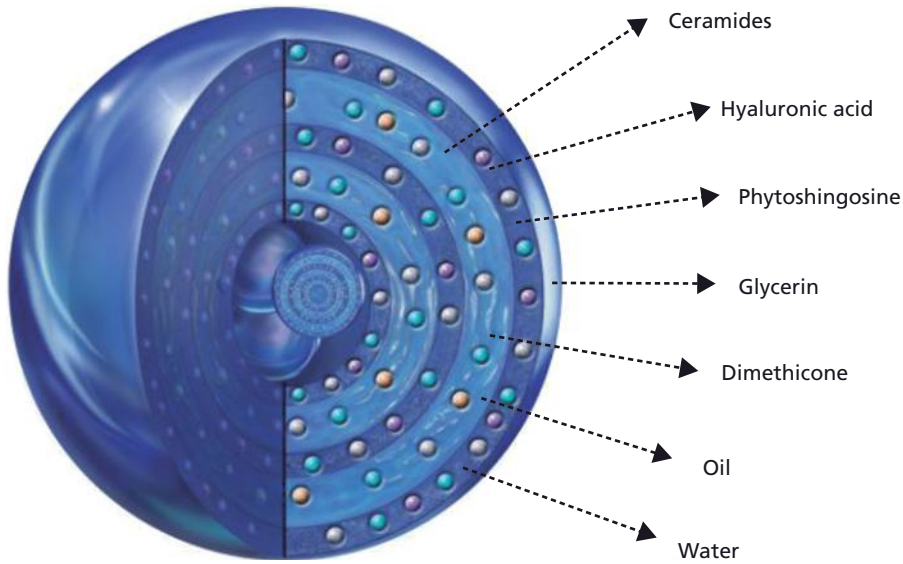

Figure 62.1 A multivesicular emulsion can dissolve many ingredients in the concentric lipsomes.

and wiped away (Cetaphil, Galderma; CerVe, Coria). These products may contain water, glycerin, cetyl alcohol, stearyl alcohol, sodium laurel sulfate, and occasionally propylene glycol. They leave behind a thin moisturizing film and can be used effectively in persons with excessively dry, sensitive, or dermatitic skin. They do not have strong antibacterial properties, however, and may not remove odor from the armpit or groin. Lipid-free cleansers are best used where minimal cleansing is desired.

After completing cleansing, the eczema patient requires moisturization. The moisturizer should create an optimal environment for barrier repair, while not inducing any type of skin reaction. For example, the product should not contain any mild irritants that may present as an acneiform eruption in the eczema patient because of the presence of follicular irritant contact dermatitis. The best moisturizers are simple oil-in-water emulsions. The morning moisturizer should provide SPF 30 photoprotection. A variety of sunscreen-containing moisturizers are on the market for this purpose (Olay Complete Defense SPF 30, Procter & Gamble; Neutrogena Daily Defense SPF 30, Johnson & Johnson). If additional hydration is required, a moisturizer can be applied to the face followed by a second sunscreen-containing moisturizer on top. It is possible to layer moisturizers for additive benefit. The sunscreen-containing moisturizer should be applied last, as it does not need to touch the skin to provide optimal photoprotection.

The evening moisturizer provides the best opportunity for barrier repair, because the body is at rest. The best ingredient for barrier repair is white petrolatum, but dimethicone and cyclomethicone are commonly added to decrease the greasiness of a simple petrolatum and water formulation. Basic night creams containing these ingredients, in addition to glycerin, are the mainstay of therapeutic eczema moisturizers. It is important to remember that fewer ingredients are preferred, because more ingredient exposure creates added opportunities for sensitization or an adverse event.

Conclusions

Eczema treatment requires the use of prescription medications in conjunction with skincare products. Both must be judiciously selected to insure optimal results. Thorough resolution of eczema requires alleviation of the disease, the treatment phase, and prevention of recurrence, the maintenance phase. This chapter has discussed those concepts that are key to designing a maintenance phase regimen for eczema patients.

References

1 Baker CG. (1987) Moisturization: new methods to support time proven ingredients. *Cosmet Toilet* **102**, 99–102.
2 De Groot AC, Weyland JW, Nater JP. (1994) *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd edn. Amsterdam: Elsevier, pp. 498–500.
3 Friberg SE, Ma Z. (1993) Stratum corneum lipids, petrolatum and white oils. *Cosmet Toilet* **107**, 55–9.
4 Grubauer G, Feingold KR, Elias PM. (1987) Relationship of epidermal lipogenesis to cutaneous barrier function. *J Lipid Res* **28**, 746–52.
5 Ghadially R, Halkier-Sorensen L, Elias PM. (1992) Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol* **26**, 387–96.
6 Spencer TS. (1988) Dry skin and skin moisturizers. *Clin Dermatol* **6**, 24–8.
7 Rieger MM, Deem DE. (1974) Skin moisturizers II .The effects of cosmetic ingredients on human stratum corneum. *J Soc Cosmet Chem* **25**, 253–62.
8 Robbins CR, Fernee KM. (1983) Some observations on the swelling of human epidermal membrane. *J Sos Cosmet Chem* **37**, 21–34.
9 Idson B. (1992) Dry skin: moisturizing and emolliency. *Cosmet Toilet* **107**, 69–78.
10 Jackson EM. (1992) Moisturizers: What's in them? How do they work? *Am J Contact Derm* **3**, 162–8.
11 Wehr RF, Krochmal L. (1987) Considerations in selecting a moisturizer. *Cutis* **39**, 512–5.
12 Rawlings AV, Scott IR, Harding CR, Bowser PA. (1994) Stratum corneum moisturization at the molecular level. *Prog Dermatol* **28**, 1–12.
13 Chanchal D, Swarnlata S. (2008) Novel approaches in herbal cosmetics. *J Cosmet Dermatol* **7**, 89–95.
14 Carlotti ME, Gallarate M, Rossatto V. (2003) O/W microemulsions as a vehicle for sunscreen. *J Cosmet Sci* **54**, 451–62.
15 Kaur IP, Agrawal R. (2007) Nanotechnology: a new paradigm in cosmeceuticals. *Recent Pat Drug Deliv Formul* **1**, 171–82.

Chapter 63: Psoriasis regimens

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BASIC CONCEPTS

- Psoriasis is a common condition that can be treated with a variety of over-the-counter skincare products.
- Over-the-counter skincare products helpful for the treatment of psoriasis include moisturizers, keratolytics, tar, hydrocortisone, salicylic acid, and tanning booth radiation exposure.
- Compliance is key in psoriasis therapy, which may be encouraged by over-the-counter skincare products.
- Over-the-counter skincare products can be combined with prescription medications for optimal treatment.

Introduction

Psoriasis affects an estimated 7.5 million people in the USA and 125 million worldwide. Men and women are affected equally. The disease may occur at any age, most frequently starts in the late teens and early twenties, and is most prevalent in the third through fifth decades of life. Caucasians are twice as likely as African-Americans to be diagnosed with psoriasis [1]. The etiology of psoriasis is not yet fully characterized. There is tremendous variation in individual's disease presentation and response to treatment, adding to the complexity of psoriasis treatment.

Most patients with psoriasis have limited, or so-called "mild," disease, covering less than 3% of total body surface area [2]. However, the disease burden does not correlate closely with the extent of disease, and even patients with limited areas of psoriasis can experience significant psychosocial stress and depression [3,4]. Only about 1 in 6 people with psoriasis sees a doctor for their disease in any given year. The remaining patients with psoriasis do not seek treatment by a dermatologist. They may be untreated, or they may self-treat with a variety of over-the-counter (OTC) medications.

The poor quality of life seen in patients with psoriasis is in part brought about by the cutaneous manifestations of the disease and the treatment regimens. Patients claim physical appearance to be a large negative factor in quality of life. The concern over physical appearance increases as the extent of disease spreads. The treatment regimens can also negatively impact quality of life, as they often require multiple daily applications, come in messy, greasy vehicles, and can be very expensive.

This chapter focuses on the role of OTC medications in psoriasis and describes strengths and weaknesses of different OTC products. We briefly discuss the role of OTC medications as part of a combination treatment regimen. Patient compliance is a major factor affecting the effectiveness of psoriasis treatments, and we discuss the future development of OTC medications.

Physiology

Psoriasis is a multifactorial, inherited condition, involving genetics, immune system alterations, and environmental factors. Normal keratinocytes remain in the epidermis for 300 hours, but psoriasis keratinocytes only remain in the epidermis for 36 hours. This shortening of the keratinocyte life cycle is associated with an increased proliferation of keratinocytes and subsequent plaque formation [5]. The pathophysiology behind the shortened keratinocyte life cycle is brought about, at least in part, by a complex immune reaction. This cascade is largely driven by helper T cells and their release of cytokines and tumor necrosis factor α (TNF-α) into the dermis. The presence of cytokines in the dermis triggers infiltration and activation of both polymorphonuclear and mononuclear leukocytes [6]. Many different cytokines have been found in the dermis and epidermis of psoriatic skin, including interleukins IL-4, IL-6, IL-12, IL-23, and transforming growth factor β (TGF-β) [5]. The roles of each of these cytokines have yet to be fully understood.

Genetics impacts psoriasis, as up to 70% of identical twins both develop this disease [7]. Psoriasis has been associated with certain HLA genotypes, and recently researchers have identified a psoriasis risk allele *PSORS1* that codes for HLA-

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Cw6 genotype [8]. However, no single allele can be called the "psoriasis gene" because there are multiple alleles that contribute to the inheritance and risk of developing psoriasis. There are at least seven other genetic loci that have also been identified as psoriasis risk alleles [7]. Complex inherited diseases such as psoriasis require large studies of many affected families in order to begin to identify all the possible genetic loci, a task that has been difficult to achieve.

While there is still much debate about the affect of stress on psoriasis, many retrospective studies have found a correlation between stress and psoriasis flares [9,10]. At baseline, patients with psoriasis have high stress levels and poor quality of life [11]. Up to 80% of patients with psoriasis report that a stressful event triggered a flare during the course of their disease. Most of these stress-related flares occur within 2 weeks of the stressful event [12]. Obesity is a risk factor both for developing psoriasis and for increased severity of psoriasis [13]. Streptococcal type A infections have also been reported to cause psoriasis outbreaks. The link between streptococcal infections and psoriasis has been extensively researched, but no single hypothesis has emerged. Some theories posit there exists molecular mimicry between streptococcal antigens and keratinocytes, while other theories blame bacterial superantigens [5].

These genetic, biologic, and environmental factors combine to create the "perfect storm" of psoriasis. The shortened keratinocyte life cycle results in thick scales that accumulate on the surface of the skin. The inflammatory infiltrates cause dysfunction of the skin's natural barrier. Inflammatory cytokines cause vascular capillary dilatation which results in skin erythema and helps perpetuate the inflammatory process [14]. The end result is dry, cracked, inflamed plaques that can be both painful and pruritic.

Role of OTC medications

Psoriasis education

The first step in any psoriasis treatment regimen is education. Empowering patients with knowledge about their disease allows them to make informed decisions about their care and creates realistic expectations for treatment outcomes. The National Psoriasis Foundation is a great resource for patients. Foundation members feel more satisfied with their treatment and have less disease burden. The Foundation's website has an OTC treatment guide that provides information on many products commonly used for psoriasis. The site also provides information to help patients screen out non-prescription remedies that are touted for their efficacy but which are at best unproven.

Role in self-treating vs. dermatology patients

Patients who self-treat their psoriasis tend to have mild disease and can achieve a measure of control with OTC medications alone. For these patients OTC medications provide symptom relief (reduced pruritus) or improve the skin's cosmetic appearance [15]. Based on their experiences, some dermatologists may feel OTC medications have little efficacy; such an impression may be based on seeing only the patients who have failed to adequately control their disease with OTC medications. People who do achieve adequate control with OTCs alone would be less likely to feel the need to visit a dermatologist. For those patients who do visit a dermatologist for prescription treatment, OTC medications may still have an important role in reducing symptoms and improving appearance. Additionally, OTC medications such as moisturizers and keratolytics can serve to increase the efficacy of prescription topical corticosteroids and phototherapy.

OTC products recommended by physicians

The National Ambulatory Care Survey (NAMCS) provides a representative snapshopt of psoriasis treatment in the USA. Through this survey, prescription and OTC medications prescribed by dermatologists and non-dermatologists are tabulated each year. OTC treatment options for psoriasis are estimated to cost $500 million and to account for 40% of all psoriasis-related expenditures [16]. The NAMCS provides data on the OTC psoriasis treatments most commonly prescribed by physicians. We looked at NAMCS data from 1986 to 2005 and identified the most common OTC prescriptions for psoriasis in each of four 5-year periods.

The most popular classes of OTC medications were hydrocortisone and keratolytics. These were followed by moisturizers and tar (Figure 63.1). When the keratolytics were broken down into individual types, salicylic acid, lactic acid, and urea were the three most commonly prescribed keratolytics (Figure 63.2). Urea was the least commonly prescribed keratolytic. While the prescription frequency of tar, urea, and lactic acid have remained relatively constant over time, salicylic acid and moisturizers show a recent increase in prescription. In contrast, OTC hydrocortisone has dropped in prescription frequency in recent years.

Compliance in psoriasis treatment

Psoriasis patients are among the worst in terms of compliance with treatment regimens [17]. They have levels of depression and anxiety that are higher than other patients with dermatologic disease [3]. Depression and disease burden can negatively affect the patients' ability to adhere to treatment. Adherence to topical medications is worse than adherence to oral medications, with the number of daily applications, the chronicity of treatment, and the complexity of the treatment regimen affecting overall compliance [18].

Topicals have traditionally been messy, greasy, and generally unappealing from a cosmetic perspective. When choosing a topical preparation for a patient, that particular patient's

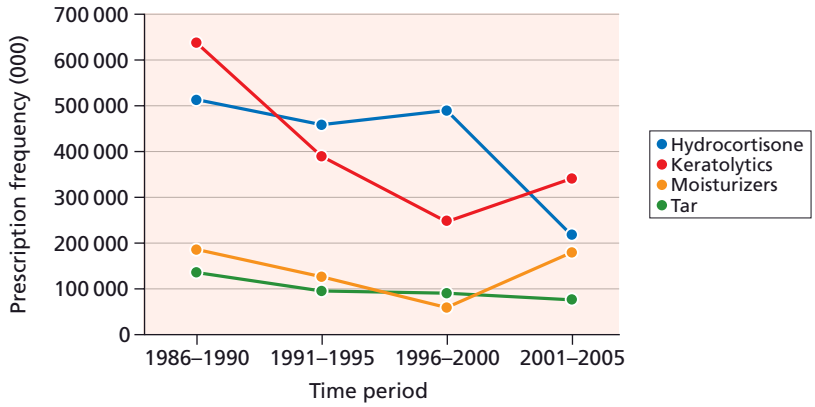

Figure 63.1 Over-the-counter (OTC) psoriasis medications prescribed by physicians 1986–2005. National Ambulatory Care Survey (NAMCS) data was used to find the prescription frequency of OTC medications prescribed by both dermatologists and non-dermatologists. Yearly data was then grouped in four 5-year time periods. OTC medications were grouped in hydrocortisone, keratolytics, moisturizers, and tar preparations.

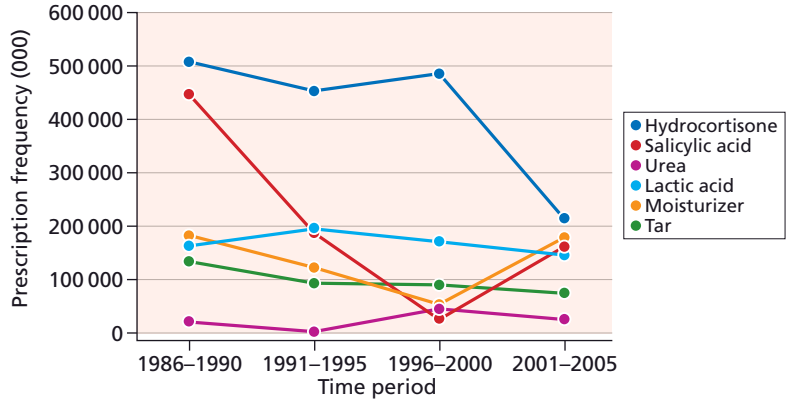

Figure 63.2 Over-the-counter (OTC) psoriasis medications prescribed by physicians 1986–2005. National Ambulatory Care Survey (NAMCS) data was used to find the prescription frequency of OTC medications prescribed by both dermatologists and non-dermatologists. Yearly data was then grouped in four 5-year time periods. OTC medications analyzed included hydrocortisone, salicylic acid, lactic acid, urea, moisturizers, and tar preparations.

preferences are critical to consider. While ointments may be said to be more efficacious for psoriasis, they will not be efficacious for patients who find them too messy to use.

OTC medications allow patients access to a wide variety of treatment options at relatively low cost. Patients can try out different vehicles and different combinations of products to achieve the best improvement. OTC products give patients the independence to experiment with products until they find one they prefer, rather than having to go through a dermatologist every time they want to switch products or try something new.

Moisturizers and keratolytics

Dry skin is often a sign of poor barrier function, as is the case in psoriasis. Symptoms of psoriasis include scaling, itching, and increased sensitivity. Moisturizers can improve the skin's hydration in two ways. First, the hydrophobic emollients such as petrolatum provide occlusive benefits, meaning they create a physical layer of protection on the surface of the skin which acts to slow epidermal water loss. Second, hydrophilic emollients such as glycerine provide humectant benefits, meaning they attract moisture from the air and help skin preserve its water content. Some moisturizers only contain either hydrophobic or hydrophilic elements, but most contain both compounds. The net effect of this increase in moisture on psoriatic skin is a decrease in appearance of scale. Factors such as number of applications and thickness of the applied layer impact success. Moisturizers can often make scale completely invisible by changing the refractive index of scale so less light is reflected.

Keratolytics differ from moisturizers in that they actually dissolve the scales on the skin's surface. Keratolytics help decrease the thickness of the hyperkeratotic plaque from the top surface inward by softening the scaly layers allowing for easy removal [19]. Salicylic acid comes in a wide variety of vehicles from shampoo to gels to creams. OTC concentrations approved for psoriasis use range 1–3%. OTC concentrations exist up to 6%, but concentrations above 3% have not been FDA approved for psoriasis [20]. OTC lactic acid products come in 5–12% concentrations. Other OTC keratolytics include phenol (which is often used in scalp preparations) and urea products. OTC urea preparations range 10–25% in concentration and typically are sold as lotions or creams [20]. Keratolytics such as these can be found OTC in single preparations or in OTC combinations with a moisturizer. Combination products allow the scale to be camou-

flaged by moisturizer as the keratolytics gradually thin the psoriatic plaques. Keratolytics can cause irritant contact dermatitis secondary to their acidic nature. Therefore it is important for patients to find a keratolytic product with a potency that is effective but minimizes irritation.

Tar

Tar is one of the oldest treatments for psoriasis, but its exact mechanism of action remains unknown. Tar is believed to exert anti-inflammatory and antimitotic effects on psoriasis skin. It also has antipruritic effects that can provide a great deal of symptom relief [21]. Tar is developed from coal or wood and can be sold as crude or refined tar products. Most tar products for psoriasis treatment are coal tar products, and are available OTC in concentrations of 0.5–5%. OTC formulations are varied and include shampoos, soaps, lotions, creams, and ointments [20]. Tar shampoos and ointments can be very helpful in the treatment of scalp psoriasis [22].

There are several disadvantages to tar products that prevent them from being used more commonly to treat psoriasis. Traditional tar preparations have been messy, malodorous, and stain skin and clothing. This is especially true of crude tar products. Newer products that use refined tar have tried to minimize these unwanted side effects, increasing the esthetic appeal of tar topicals while maintaining the desired efficacy [22,23]. Despite improvements in the vehicle and odor, patient compliance with tar products may be poor. Tar can also cause unwanted skin reactions such as contact irritation and folliculitis, further decreasing patient compliance. Another component of tar therapy that affects patient use is the fear of its carcinogenic properties. While there is no clear evidence showing an increased risk of cancer in humans, several animal studies have demonstrated an increased risk of cancer with topical tar application [24].

All OTC tar products are covered by an FDA monograph that permits marketing and sales of tar products of certain concentrations for an indication of psoriasis [25]. Other ingredients that are generally regarded as safe may also be in the product. Thus, companies can create and market many different products and claim they are effective for psoriasis as long as the product contains the appropriate concentration of tar. Companies can create all manners of fruit and vegetable extracts and claim their product is FDA approved for the treatment of psoriasis by incorporating tar into the product.

Hydrocortisone

Topical hydrocortisone cream is available OTC in 0.5% and 1% concentrations and is a low-potency corticosteroid with anti-inflammatory and anti-itch properties. In a survey conducted by the National Psoriasis Foundation, psoriasis patients named "scaling," "itching," and "skin redness" as their most common symptoms [26]. Topical corticosteroids help relieve these symptoms. Despite their low potency, OTC hydrocortisone treatments can have an important role in psoriasis management. A benefit of low-potency OTC hydrocortisone is that psoriasis patients can use this corticosteroid to self-treat more sensitive areas of their skin, such as the face, axilla, and genital area.

UV light therapy

Phototherapy has been a mainstay treatment for psoriasis for millenia. Up until the 1990s, broad-spectrum UVB was the treatment of choice. More recently, narrowband (300–313 nm) UVB boxes were introduced, as well as devices designed to provide localized therapy to individual lesions [27]. The addition of PUVA (psoralen and UVA) therapy for severe psoriasis in the 1990s further expanded the use of phototherapy for psoriasis [28]. Many patients with psoriasis realize the benefit of UV exposure before any prescription phototherapy is used, through the seasonal variation in their psoriasis and the beneficial effect of outdoor (and sometimes indoor) tanning on their disease. Benefits of non-prescription phototherapy over prescription phototherapy include greater convenience and lower cost, albeit at the expense of less control over dosimetry. Prescription phototherapy requires patients to travel to the dermatologist's office anywhere from three to five times a week to receive UV treatments. This can be costly and inconvenient to patients, which compromises the overall benefit and accessibility of the treatment.

Sun exposure is the least costly way to obtain phototherapy for psoriasis, although it may be inconvenient or inaccessible (depending on geography). Dosimetry is difficult to control. Commercial tanning beds provide another phototherapy option. Although these devices radiate mostly UVA light, the most widely used commercial tanning bulbs have about 5% of the output that is in the UVB range and this may contribute to tanning bed efficacy. Some dermatologists discourage use of tanning beds for treating psoriasis because of the potential and poorly defined risk of skin cancer and premature aging. However, tanning beds can be an option for psoriasis patients who cannot afford or who do not have access to home or dermatologist-administered UVB therapies. Some dermatologists may not think tanning beds are effective based on their experiences with patients who have tried tanning and seen no benefit. Dermatologists should keep in mind that the people who tried tanning and did find it to be effective for clearing their psoriasis may not come to the dermatologist.

If tanning bed use is recommended by a dermatologist for a particular patient, guidance for use should be provided and realistic expectations about length of time until improvement should be set. Most patients will require multiple tanning sessions over several weeks before seeing improvement in their skin. To help control the dosimetry, patients should use the same tanning bed for each exposure (not switching between tanning establishments or between beds within a single establishment). Tanning bed operators are familiar with their equipment and will likely recommend a safe starting dose, but starting with half that dose may provide a greater degree of safety, particularly if the tanning bed is used in conjunction with oral retinoid treatment (tanning beds should not be used in conjunction with psoralen as life-threatening burns may result). Sunscreen or protective clothing can be recommended to protect unaffected skin, and eye protection should be worn. These measures help patients avoid burning their skin and minimize the risk of developing skin cancer or cataracts [1].

Psoriasis patients may inquire if OTC tanning is safe to use with other psoriasis medications. Topical corticosteroids are safe to use with phototherapy and may even enhance the UV light's effect by thinning the psoriatic plaques, although there is concern that corticosteroids reduce the remission periods associated with phototherapy. Systemic retinoids are not only safe to use with phototherapy, they are frequently prescribed in combination with phototherapy because they can improve the efficacy of phototherapy [29]. While methotrexate is safe to use with phototherapy, cyclosporine should not be used with UVB therapy [30]. UV therapy may inactivate topical calcipotriol, so it is recommended for patients to apply calcipotriol after, rather than before, phototherapy sessions [30,31].

Combination regimens

Most psoriasis treatment regimens do not rely on only one drug to treat psoriasis effectively. Specific combinations of therapies often produce the best results with the least side effects. The caution with combination treatment regimens is that overly complex regimens can confuse and discourage patients and negatively affect treatment adherence. The goal of a dermatologist should be to develop a streamlined regimen that focuses on the individual patient's treatment goals and lifestyle.

OTC medications have a large role in combination psoriasis therapies. Keratolytics are used to enhance the ability of topical corticosteroids to penetrate the epidermis and target dermal inflammation. Topical corticosteroids can penetrate skin two to three times better with keratolytics than without. This results in better relief of symptoms such as scaling and pruritus [19]. Keratolytics have similar effects with tar products and UV phototherapy. Moisturizers can also enhance the efficacy of topical corticosteroids [32]. When prescribing such combination regimens, however, it is essential to consider that complicating the regimen may reduce treatment adherence, resulting in the loss of any potential gains expected from increased penetration.

The classic psoriasis combination therapy is the Goeckerman treatment, which combines topical coal tar and UVB phototherapy. This combination's success was first described by Dr. Goeckerman in 1925, and continues to be one of the most effective psoriasis treatments in use today. The Goeckerman treatment can induce remission even when the most technologically advanced regimens such as biologics fail [33]. Goeckerman treatment is typically administered by a dermatologist in the inpatient or specialized outpatient psoriasis treatment center. Patients can attempt to mimic the effects of Goeckerman by using outdoor or indoor UV therapy followed by prolonged OTC tar ointment used under plastic wrap or sauna suit occlusion.

Conclusions

OTC medications play a large part in the treatment regimen of self-treating patients and those managed by a dermatologist. For the vast majority of people with psoriasis who choose to self-treat their disease, OTC medications provide relief of symptoms such as pruritus, erythema, and dry skin as well as effectively controlling plaque formation. For the minority of patients who require a dermatologist, OTC medications still provide a degree of symptom relief, and are commonly used in combination with prescription medications. The NAMCS data show that dermatologists prescribe OTC hydrocortisone, keratolytics, and moisturizers to supplement prescription psoriasis therapies.

The large percentage of psoriasis patients who rely on OTC medications continues to drive the production of new and improved OTC products. New moisturizers are constantly being developed to increase skin's hydration, and new keratolytics seek to improve the appearance of hyperkeratotic plaques while minimizing skin irritation. Improved vehicles such as foams and sprays for OTC corticosteroids are being developed to increase efficacy and make them more attractive to patients. New tar extracts and derivatives are designed to be less messy and smelly than their older counterparts; by increasing patient adherence such treatments may offer improved efficacy outcomes.

Future trends in OTC psoriasis medications can be considered in two different populations. In those people who entirely self-treat and do not see a dermatologist, there will probably be a continued increase in the use of products such as moisturizers, keratolytics, and tar as the products continue to improve. In patients who see a dermatologist, there

may be a decrease in some OTC use of medications such as keratolytics as more and more topical prescriptions are switching to combination topical products that contain a prescription drug along with an OTC drug. An example of this would be a high-potency topical corticosteroid ointment that also contains salicylic acid. Prescription topicals are now available in new vehicles such as foams and sprays that reduce the messy application process. This movement towards multiple therapies in one product and improved prescription vehicles may result in a decrease in the prescription of OTC topical medications. Biologic agents have revolutionized treatment in a small population of psoriasis patients, inducing rapid and complete remission and thereby reducing their need for complicated combination regimens.

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References

1 National Psoriasis Foundation. http://www.psoriasis.org. Accessed July 18, 2008.
2 Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. (2004) Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc* **9**, 136–9.
3 Evers AWM, Lu Y, Duller P, van der Valk PJ, Kraaimaat FW, van de Kerkhof PC. (2005) Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br J Dermatol* **152**, 1275–81.
4 Gupta MA, Gupta AK. (1998) Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* **139**, 846–50.
5 Nickoloff BJ, Qin JZ, Nestle FO. (2007) Immunopathogenesis of psoriasis. *Clin Rev Allergy Immunol* **33**, 45–56.
6 Linden KG, Weinstein GD. (1999) Psoriasis: current perspectives with an emphasis on treatment. *Am J Med* **107**, 595–605.
7 Valdimarsson H. (2007) The genetic basis of psoriasis. *Clin Dermatol* **25**, 563–7.
8 Nair RP, Stuart PE, Nister I, Hiremagalore R, Chia NV, Jenisch J, *et al*. (2006) Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet* **78**, 827–51.
9 Buske-Kirschbaum A, Kern S, Ebrecht M, Hellhammer DH. (2007) Altered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris. *Brain Behav Immun* **21**, 92–9.
10 Berg M, Svensson M, Brandberg M, Nordlind K. (2008) Psoriasis and stress: a prospective study. *J Eur Acad Dermatol Venereol* **22**, 670–4.
11 Misery L, Thomas L, Jullien D, Cambazard F, Humbert P, Dehen L, *et al*. (2008) Comparative study of stress and quality of life in outpatients consulting for different dermatoses in five academic departments of dermatology. *Eur J Dermatol* **18**, 412–5.
12 Kimyai-Asadi A, Usman A. (2001) The role of psychological stress in skin disease. *J Cutan Med Surg* **5**, 140–5.
13 Azfar RS, Gelfand JM. (2008) Psoriasis and metabolic disease: epidemiology and pathophysiology. *Curr Opin Rheumatol* **20**, 416–22.
14 Joshi R. (2004) Immunopathogenesis of psoriasis. *Indian J Dermatol Venereol Leprol* **70**, 10–2.
15 Proksch E. (2008) The role of emollients in the management of diseases with chronic dry skin. *Skin Pharmacol Physiol* **21**, 75–80.
16 Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, *et al*. (2004) Burden of skin diseases. Available at http://www.sidnet.org/pdfs/Burden%20of%20Skin%20Diseases%202004.pdf.
17 Storm A, Andersen SE, Benfeldt E, Serup J. (2008) One in three prescriptions are never redeemed: primary nonadherence in an outpatient clinic. *J Am Acad Dermatol* **59**, 27–33.
18 Carroll CL, Feldman SR, Camacho FT, Manuel JC, Balkrishnan R. (2004) Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol* **51**, 212–6.
19 Koo J, Cuffie CA, Tanner DJ, Bressinck R, Cornell RC, DeVillez RL, *et al*. (1998) Mometasone furoate 0.1%-salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther* **20**, 283–91.
20 National Psoriasis Foundation Treatment Guide. http://psoriasis.org/treatment/guide/otc/. Accessed July 26, 2008.
21 Roelofzen JH, Aben KK, van der Valk PG, van Houtum JL, van de Kerkhof PC, Kiemeney LA. (2007) Coal tar in dermatology. *J Dermatolog Treat* **18**, 329–34.
22 Dodd WA. (1993) Tars: their role in the treatment of psoriasis. *Dermatol Clin* **11**, 131–5.
23 Mefford L. (2008) NeoStrata® announces the launch of Psorent™ Psoriasis Topical Treatment. http://www.reuters.com/article/pressRelease/idUS169492+04-Feb-2008+PRN20080204. Accessed August 10, 2008.
24 van Schooten FJ, Godschalk R. (1996) Coal tar therapy. Is it carcinogenic? *Drug Saf* **15**, 374–7.
25 Kessler DA. (1991) Food and Drug Administration. Dandruff, seborrheic dermatitis, and psoriasis drug products for over-the-counter human use: final monograph. *Federal Register* **56**, 63554–63569. Available at http://www.fda.gov/cder/otcmonographs/Dandruff&Seborrheic_Dermatitis&Psoriasis/dandruff_seborrheic_dermatitis_psoriasis_FR_19911204.pdf.
26 Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. (2001) The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol* **137**, 280–4.
27 Stein KR, Pearce DJ, Feldman SR. (2008) Targeted UV therapy in the treatment of psoriasis. *J Dermatolog Treat* **19**, 141–5.

28 Kostović K, Pasić A. (2004) Phototherapy of psoriasis: review and update. *Acta Dermatovenerol Croat* **12**, 42–50.
29 Carlin CS, Callis KP, Krueger GG. (2003) Efficacy of acitretin and commercial tanning bed therapy for psoriasis. *Arch Dermatol* **139**, 436–42.
30 Zanolli MM. (2004) Phototherapy arsenal in the treatment of psoriasis. *Dermatol Clin* **22**, 397–406.
31 Adachi Y, Uchida N, Matsuo T, Horio T. (2008) Clinical effect of vitamin D3 analogues is not inactivated by subsequent UV exposure. *Photodermatol Photoimmunol Photomed* **24**, 16–8.
32 Ghali FE. (2005) Improved clinical outcomes with moisturization in dermatologic disease. *Cutis* **76** (Suppl), 13–8.
33 Soares TF, Davis MD. (2007) Success of Goeckerman treatment in two patients with psoriasis not responding to biological drugs. *Arch Dermatol* **143**, 950–1.