Noninvasive Facial Rejuvenation. Part 1: Patient-Directed

Sarah Jane Commander, BS¹ Daniel Chang, MD¹ Abdulla Fakhro, MD¹ Marjory G. Nigro, MD²
Edward I. Lee, MD¹

¹ Division of Plastic Surgery, Baylor College of Medicine, Houston, Texas

² Nigro Dermatology Group, Houston, Texas

Address for correspondence Edward I. Lee, MD, Division of Plastic Surgery, Baylor College of Medicine, 6701 Fannin St., Suite 610.00, Houston, TX 77030 (e-mail: edwardilee@yahoo.com).

Semin Plast Surg 2016;30:129–133.

Abstract

A proper knowledge of noninvasive facial rejuvenation is integral to the practice of a cosmetic surgeon. Noninvasive facial rejuvenation can be divided into patient- versus physician-directed modalities. Patient-directed facial rejuvenation combines the use of facial products such as sunscreen, moisturizers, retinoids, α -hydroxy acids, and various antioxidants to both maintain youthful skin and rejuvenate damaged skin. Physicians may recommend and often prescribe certain products, but the patients are in control of this type of facial rejuvenation. On the other hand, physician-directed facial rejuvenation entails modalities that require direct physician involvement, such as neuromodulators, filler injections, laser resurfacing, microdermabrasion, and chemical peels. With the successful integration of each of these modalities, a complete facial regimen can be established and patient satisfaction can be maximized. This article is the first in a three-part series describing noninvasive facial rejuvenation. The authors focus on patient-directed facial rejuvenation. It is important, however, to emphasize that even in a patient-directed modality, a physician's involvement through education and guidance is integral to its success.

Keywords

- ▶ photoaging
- ▶ noninvasive facial rejuvenation
- ▶ skin care
- ▶ patient-directed facial rejuvenation

The use of topical, noninvasive creams and solutions is increasing in popularity due to their favorable risk profile, ease of use, and increasing efficacy. There are innumerable products on the market aimed to defy age-related skin changes. However, with so many options and little evidence to suggest superiority of one product over the others, choosing the most appropriate intervention can be overwhelming for both patients and physicians alike. Given its popularity, it is becoming increasingly clear that having a sound understanding of this patient-directed, noninvasive form of facial rejuvenation is paramount to a practicing plastic surgeon. Here we will discuss some of the more common skin care products on the market to assist the reader in selecting the most appropriate intervention for his or her patient.

Theory of Aging

Several factors contribute to age-related skin changes such as obesity, smoking, and reduced sex hormones. But photoaging

from sun exposure is the largest contributing factor.¹ Photoaging of the skin is caused by damage to the skin on a molecular level, both directly and indirectly, through exposure to ultraviolet (UV) radiation. Ultraviolet A (UVA; 320–360 nm) and ultraviolet B (UVB; 290–320 nm) exposure directly causes breakage in DNA in the nucleus and mitochondria. Although the nucleus is often able to correct these changes through nucleotide excision repair, the mitochondria have no such mechanism. This leads to decreased mitochondrial function and eventual cellular apoptosis.² Ultraviolet A also indirectly causes damage through the creation of free radicals in the form of reactive oxygen species (ROS). Free radicals damage cells by the peroxidation of lipids in the cell membrane, the breakage of DNA, and organelle damage, ultimately also leading to apoptosis.³ Photoaging is predominantly caused by UVA and sunburn is primarily caused by UVB, but both types of radiation can cause either condition and are responsible for increased carcinogenesis.⁴

Issue Theme Dermatology for Plastic Surgery; Guest Editor, Edward I. Lee, MD

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Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0036-1584820>.
ISSN 1535-2188.

The molecular damages caused by UV light are apparent histologically as flattening of rete ridges, loss of polarity in the epidermis, and apoptosis. The dermis has decreased glycosaminoglycans, collagen, and elastin, but increased fibroblasts and Langerhans cells due to chronic inflammation.^{5,6} Clinically the skin is dry, coarse, loose, has more scaling, telangiectasias, and wrinkles compared with skin protected from sun exposure. Importantly, there is also an increased risk of dysplastic and malignant lesions.⁷ Targeting and reducing these molecular mechanisms of damage is the objective of most age-defying products on the market. Sunscreen attempts to limit the amount of UV light entering the epidermis, whereas retinoids and antioxidants attempt to reduce free radicals.

Patient-Directed Skin Care

Sunscreen

The age-defying mechanism of sunscreen is the total reduction of both UVA and UVB absorption by the skin. Sun protection factor (SPF) is the standard way to measure how much UVA and UVB is blocked. It is a ratio of the UV radiation dose that causes the first sign of erythema of sunscreen-shielded skin to unprotected skin. The American Academy of Dermatology recommends applying SPF of 30 or higher every 2 hours to reduce the risk of photo damage.⁸ Studies have shown that SPF 15 blocks 93.3% of UV radiation, SPF 30 blocks 96.7%, and SPF 60 blocks 98.3%.⁹ In other words, as you double the SPF, the amount of sunlight that is able to penetrate the skin reduces by a factor of one-half (6.7% penetrance for SPF 15 vs. 3.3% for SPF 30 vs. 1.7% for SPF 60).⁹ In addition, studies have shown that to achieve the SPF level of a particular sunscreen, 2 mg/cm² must be applied.¹⁰

To block UV radiation, sunscreens use both organic filters, which use compounds with benzene rings to dissipate light as heat, and inorganic filters, which use refractory filters to reflect light.¹¹ Organic filters that best reflect UVA are benzophenones, anthralinates, ecamsule, and avobenzone. These compounds often dissipate quickly; it is necessary to combine them with photostabilizing agents such as oxybenzone or 2–6-diethylhexylnaphthalate.¹² Organic filters that reflect UVB are often used in combination due to the narrow range of wavelengths each agent is able to block. Common agents used are para-aminobenzoic acid, salicylates, and cinnamates. Organic filters are often combined with inorganic filters for photostabilization. Inorganic filters, such as zinc oxide and titanium dioxide particles, have a white, chalky consistency and are often visually unappealing. As such, these filters are always combined with organic filters. It is important to note that although sunscreen cannot reverse skin damage already present, it is the most effective primary prevention of photo damage.

Moisturizers

Moisturizers, such as petrolatum, dimethicone, and humectant, form the basis of almost all skin care products. They serve as an occlusive barrier for the skin and as a vector for other skin care products. Most of these products are hypoallergenic,

noncomedogenic, and nonacnegenic, making them ideal for use on sensitive areas like the face.¹³

After water, petrolatum is the most common and effective active agent used in products today. It has been used in moisturizers since 1880 and is able to reduce evaporative water loss from the skin by 99%.¹⁴ It penetrates the epidermis and creates an environment ideal for the repair of damaged skin. Healing primarily occurs through the increased production of intracellular lipids and fibroblasts producing collagen.¹⁵ Petrolatum also is able to reduce wrinkle lines by filling the spaces between desquamating keratinocytes, thus acting as an emollient. Although this product is the most-effective moisturizer on the market, patients often do not like the greasy feeling of petrolatum-based products. Therefore, substitutes like humectant and dimethicone are used to reduce this undesirable effect.

Dimethicone, also known as astringent moisturizer, is the second most commonly used ingredient in moisturizers. It is derived of silicone and is used in many skin care products that are water-resistant because it is insoluble in aqueous solutions. It is ideal for sunscreen and cosmetic products as it does not mix with facial sebum and remains on the skin.¹²

Humectants, such as glycerine, are used in moisturizers as agents that draw water from the dermis to the dehydrated stratum corneum.¹³ Humectants allow water to evaporate from the surface of the epidermis, so they are combined with occlusive agents like petrolatum and dimethicone. Humectants are able to induce aquaporins in the skin, thus allowing more water to enter the epidermis.¹² This aids in reducing fine wrinkle lines caused by dehydrated skin.

Retinoids

The retinoid family compounds are derivatives of vitamin A and have been used since the 1940s. Retinol (vitamin A) is usually absorbed through the gastrointestinal tract and stored as retinol esters or oxidized to tretinoin.¹⁶ When applied topically, retinoids must be stored in the active-form tretinoin.³ Histologically, retinoids have been shown to increase collagen in the papillary dermis by inhibiting matrix metalloproteinases and collagenases.¹⁷ These metalloproteinases are usually upregulated by the action of ROS such as the superoxide anion, hydrogen peroxide, and singlet oxygen.¹⁸ They are also upregulated by certain growth factors including tumor necrosis factor, epidermal growth factor, and interleukin-1.

The mechanism of action behind retinoids involves the binding and activation of two nuclear hormone receptors, chiefly the retinoic acid receptors and the retinoid X receptors. These receptors act as nuclear transcription factors, which increase collagen synthesis by up to 80%.¹⁷ They also decrease wrinkles in the skin by inducing epidermal hyperplasia and glycosaminoglycan deposition, and thickening stratum corneum and granulosum.³ In addition, they have been shown to decrease keratinocyte and melanocyte atypia.¹⁷

Topical tretinoin is recommended as the first-line therapy for photoaging. Its benefits are usually seen after 4 months of therapy; therefore, stopping therapy early should be avoided.¹⁹ In addition, the benefits are short lived upon discontinuation.²⁰ Topical tazarotene is an

equally effective alternative in patients who cannot tolerate tretinoin.

It is important to counsel patients before beginning topical retinoid therapy as skin irritation, redness, dryness, scaling, stinging, and peeling are common. These side effects are usually the main reason behind patient noncompliance to therapy.¹⁹ The adverse effects are usually at their worst within the first 2 weeks, especially with higher concentrations, but tend to subside over time. The use of moisturizers is highly recommended during this time to alleviate symptoms.

Alpha-Hydroxy Acids

Alpha-hydroxy acids have been used to rejuvenate skin since the time of Cleopatra. This family is composed of compounds such as glycolic acid, lactic acid, citric acid, and salicylic acid.²¹ The mechanism by which α -hydroxy acids work is unclear, but they are compounds with a terminal carboxy group, which is used to donate the protons of high-energy particles. The strength of the acid is described by the pK_a and the concentration of the specific acid.²² They are believed to remove calcium ions from epidermal corneocytes above the stratum granulosum, which cause desquamation of the stratum corneum.^{23–25} This first thins the skin, but with continued use, causes thickened skin due to increased glycosaminoglycan and collagen deposition, thereby causing firmer, plumper skin and reduced wrinkle lines. This is also accomplished by increasing the skin's water holding capacity due to the charges in the acids applied.²⁶ Mild side effects of α -hydroxy acid use include stinging, burning, pain, and erythema. More serious side effects include blistering, purpura, crusting, hyper- or hypopigmentation, atrophy, ulceration, keloid formation, hypertrophic scarring, and significant pain. These side effects can usually be avoided if the concentration of the acid is $< 20\%$.²⁶

Vitamins

Vitamins are organic compounds that the body cannot synthesize in adequate quantities, but are necessary for vital biochemical pathways. The body is, therefore, reliant on outside sources for these organic compounds. Currently, there are 13 universally recognized vitamins and, of these, vitamins E and C have been shown to have an important antioxidant role in the skin.

Vitamin E is typically found in nuts, vegetable oils, and green leafy vegetables and plays an important role in protecting cell membrane viability. As a fat-soluble vitamin, it is incorporated into the lipid membrane of cells and helps prevent peroxidation of these lipids by donating hydrogen molecules. There are many forms of vitamin E; of these, α -tocopherol is the one most commonly found in skin care products. Alpha-tocopherol as a topical treatment has been demonstrated in randomized, double-blind, placebo-controlled studies, to help reduce UV-induced erythema and prevent sunburn.^{27,28} After donating its hydrogen molecule, vitamin E becomes a tocopherol radical that must regain a hydrogen molecule from glutathione or vitamin C. Accordingly, studies have shown that the combination of topical vitamin E and vitamin C was more effective in reducing UV-induced erythema than each agent alone.²⁹

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin typically found in citrus fruits and dark green leafy vegetables. Vitamin C is necessary for folate metabolism, hormone synthesis, prostaglandin metabolism, and many other systemic functions. Most importantly, vitamin C has long been known to play an essential role in the transcription and posttranslation of collagen synthesis.³⁰ More recently, vitamin C has been shown to act as an important antioxidant in the skin, and topical vitamin C has been shown to reduce inflammation and UV-induced immunosuppression.^{31,32} In double-blind clinical trials, topical vitamin C has demonstrated an improvement in patient- and clinician-assessed skin hydration and suppleness, as well as a reduction of coarse and fine wrinkles.^{33,34}

Although both vitamins E and C are used in many cosmetic products, a lack of regulation leads to many products with low concentrations or unstable preparations that limit their effectiveness. Vitamin E is more stable as vitamin E acetate, but must be hydrolyzed to its active form and vitamin C is often stabilized by esterification. Vitamin E concentrations of 1% and vitamin C concentrations of 15% have been shown to be effective.³⁵ Daily dosing is recommended with improvement typically seen after at least 1 month of therapy. Side effects are limited, but may include dry skin and erythema.

Antioxidants

A popular health term, "antioxidants," is an umbrella term for a wide range of compounds that inhibit oxidation. Antioxidant skin therapies attempt to address the oxidative stress and associated ROS that have been proposed as a major contributor to cellular damage cascades, which lead to premature aging through increased matrix metalloproteinase expression and collagen breakdown.^{36–38} In the skin, UV radiation is the primary extrinsic offender leading to oxidative DNA damage and subsequent photoaging.^{39–41} Therefore, the measure of an antioxidant's effectiveness in skin protection is often measured by its ability to reduce UV radiation-associated erythema, which serves as a proxy for DNA damage. Topical antioxidants directed at preventing these oxidation pathways have been a focus for maintaining healthy youthful skin.^{42–44} In certain forms, these compounds have been shown to have good topical penetration, and evidence supports multiple classes of these compounds working synergistically.

Cellular Antioxidants

Alpha-lipoic acid and ubiquinones, most notably, coenzyme Q10, represent endogenously produced antioxidants. Coenzyme Q10 is a component of the electron transport chain and participates in regenerating adenosine triphosphate (ATP), the primary energy source for cellular functions. Its ability to act as an electron carrier allows it also to act as a potent antioxidant, donating electrons to stabilize free radicals. Although our body produces these compounds, treatments aim to supplement levels of these compounds to increase antioxidant protection. Systemic supplementation of both α -lipoic acids and ubiquinones has been widely studied for various conditions with mixed results. Topical formulations for skin care, however, have shown promise. Alpha-lipoic acid in 3% and 5% creams has

been demonstrated to be effective in reducing UVB-induced erythema and treating photoaging.⁴⁵ A 1 to 4% concentration is recommended with every-other-day application for 3 weeks to determine tolerance prior to daily use.³³ Topical coenzyme Q10 has the ability to penetrate deep into the epidermis and has been shown to suppress collagenase expression after UVA exposure.^{46,47} Currently, the evidence for these compounds is based on in vivo studies showing improved mitochondrial and cellular functions, not on clinical outcomes.

Natural Antioxidants

Polyphenols represent a wide range of compounds found naturally in plants that provide antioxidant properties. Although these compounds have intrinsic reductive properties to stabilize ROS, there is also evidence that they play a role in further activating endogenous cellular antioxidant mechanisms.⁴⁸ Catechins found in green, black, and oolong teas have demonstrated inhibition of carcinogenesis in murine models.⁴⁹ For skin care, topical application of green tea polyphenols has been shown to decrease erythema and DNA damage from UVB radiation.⁵⁰ Pomegranates and grapeseed extract have been found to be rich in anthocyanidin and tannins which, in vitro studies, have demonstrated reduced activation of apoptotic pathways after UV radiation.^{51,52} Ferulic acid is a unique polyphenol found in various grains and greens that is both a mild sunscreen and a potent antioxidant.^{44,53} A double-blind randomized clinical trial of polyphenol-based skin care treatment system showed improvement in fine lines and wrinkles, hyperpigmentation, and erythema, with no reported adverse effects.⁵⁴

Carotenoids are plant pigments that have also been found to have antioxidant properties.⁵⁵ Common carotenoids are lycopene, lutein, and beta-carotene. Although the role of carotenoids in the diet has been studied for many years, topical treatments with carotenoids are less proven. In a study on the effects of lutein on human skin, the combination of oral and topical treatments was found to provide improved antioxidant protection than either treatment alone; however, topical treatment alone was inferior to oral administration.⁵⁶

Other Products

Ecamsule is a novel UVA filter introduced into the United States in the last decade. Although deeper penetrating UVA radiation plays a larger role in photoaging, most sunscreens provide inadequate UVA protection because compounds that block UVA tend to be unstable and dissipate quickly. Ecamsule, however, provides stable and water-resistant coverage. Although available abroad for many years, ecamsule-containing products have only been approved by the Food and Drug Administration since 2006.⁵⁷

Hydroquinone is a chemical known to reduce hyperpigmentation through aromatic benzene amines.⁵⁷ It is commonly used as a bleaching agent in a combination skin care regimen, such as Obagi Nu-Derm (Obagi Medical Products). Combination products generally include a gentle cleanser, a toner, a bleaching agent, tretinoin, and sunblock. Each product is used daily to promote skin rejuvenation. Although individual components of the regimen, such as tretinoin and hydroquinone, have been used for many years, these combination products are touted to

work synergistically for more marked skin improvement.^{24,25} Importantly, these combination products improve patient compliance by being readily available and easy to use.

Professional Recommendation

Although there is a multitude of products available, no single agent has been proven to be more efficacious than others. Therefore, a judicious use of a combination of products is recommended in an attempt to defy age-related skin changes, taking advantage of the strengths and side-effect profile of each class of products mentioned. A balanced regimen should include a barrier (e.g., sunscreen, antioxidants), a maintenance (e.g., moisturizer), and a rejuvenation (e.g., α -hydroxy acids, retinoids) product. Sunscreen provides the first line of defense by inhibiting the penetration of UV radiation into the skin. Antioxidants provide the second line of defense helping to reduce cellular damage. A daily moisturizer will keep the skin well hydrated and reduce wrinkle lines. Alpha-hydroxy acids, retinoids, and newer skin care products can aid in the rejuvenation of the skin. It is hoped that ongoing research will improve the scientific basis for the use of these products as well as improve the safety profile of this ever-popular form of noninvasive facial rejuvenation. Lastly, the importance of physician involvement through patient education cannot be overemphasized. Constant guidance and feedback from a care provider can improve not only the success, but also the safety of patient-directed facial rejuvenation.

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