Photoaging and Topical Rejuvenation

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KEYWORDS

• Photoaging • Skin rejuvenation • Sunscreen • Tretinoin • Hydroquinone • Alpha hydroxy acid • Topical niacinamide • Topical vitamin C

KEY POINTS

- Photoaging is a complex process of skin changes including rhytids, lentigines, telangiectasias, mottled pigmentation, coarse texture, and laxity caused by chronic ultraviolet exposure.
- Strict photoprotection with sunscreen is the best defense for photoaging.
- Topical retinoids are the cornerstone for an antiaging topical regimen.
- Combination topicals should be used with caution as the stability and absorption are questionable when compounded.
- Hydroquinone, the most commonly used and studied lightning agent, should be used with physician oversight due to possible adverse effects.

INTRODUCTION

The skin is the most visible indicator of aging. Ultraviolet (UV) light, specifically UVA, and the cumulative exposure are the main culprits of photoaging. Clinically, photoaging can be appreciated as rhytids, telangiectasias, dyspigmentation, volume loss, and even malignancy.[1] On a microscopic level, there is a reduction in epidermal thickness, pigment heterogeneity, dermal elastosis, collagen degradation, ectatic vessels, and mutagenesis of keratinocytes and melanocytes.[1] The purpose of topicals is to help reduce and reverse these signs of aging and restore the organ to its highest functioning level. Although easily overlooked, a topical regimen is the foundation for facial rejuvenation. The number of topicals and the claims of efficacy can be overwhelming especially with the number of over-the-counter cosmeceuticals. It is impractical for a physician to be familiar with all available products on the market so focus will be placed on a core group of medical grade, evidence-based topicals including retinoids, lightning agents, and other vitamin/antioxidant agents. We will discuss our approach for optimal skin care regimens and routines.

SUNSCREEN

Up to 80% of aging can be attributed to UV exposure.[2] Thus, limiting sun exposure and protecting the skin from UV radiation is paramount for the prevention of facial aging and maintenance of rejuvenation measures. Solar UV radiation consists of UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). UVC fails to reach the Earth's surface as it is completely absorbed by the ozone layer.[3] Historically, UVB was thought to be the major contributor to photoaging. It is predominantly absorbed by the epidermis, and it composes the major portion of UV radiation that induces sunburns and erythema.[3] However, UVA, which is 20 times more abundant than UVB at the level of the Earth's surface,[4] has a longer wavelength. This leads to deeper dermal penetration and has been found to be the primary driver of photoaging.[5] For example, when there is chronic, asymmetric exposure of the face to UVA radiation, the exposed side has a clinically increased level of skin wrinkling and roughness .[6] Additionally, in

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skin of color patients, UVA radiation leads to irregular skin pigmentation, which is associated with photoaging in this population.[5] Currently there is mounting evidence that both visible and infrared light also play a role in photoaging and pigmentary changes. The visible light spectrum extends from 400 to 700 nm and has been found to stimulate matrix metalloproteinase production, which leads to the degradation of dermal collagen.[7] Furthermore, studies suggest a synergistic effect between UVA radiation and visible light in driving age-related pigmentary changes.[8,9]

Although the skincare market often focuses on products that reverse skin aging, it is much more efficacious to focus on prevention .[10] Sun avoidance and sun-protective clothing, such as hats and shirts may be helpful, in limiting UV damage, but sunscreens remain the mainstay of facial photoprotection. Sunscreens have historically been split into two major categories, physical (inorganic) and chemical (organic) blocking agents. Both types of agents work via absorption of UV radiation. Spectrums of absorption vary in chemical agents and typically a combination of organic filters is necessary in order to provide protection across the full range of UV radiation. As visible light is now implicated in photoaging and dyspigmentation, there is an increased interest in protection against these wavelengths. However, this can be difficult to achieve with cosmetically acceptable results, as these sunscreens must be opaque in order to block visible light.[11,12] Notably, only pigmentary grade zinc oxide and titanium dioxide protect against visible light and not the micronized forms.[12] Iron oxide and pigmentary titanium dioxide are the most commonly used visible light filters, and they are used in tinted formulations that may be matched to an individual's skin tone.[11,12]

Sun protection factor (SPF), is the standard for measuring the protective ability of a sunscreen. This is based on UV-induced erythema, which, is mostly UVB driven. In order to account for UVA radiation, sunscreens can be labeled as broad spectrum if greater than 90% of UVA is absorbed at $\geq$ 370 nm.[13] There are currently no guidelines for visible light protection, and as iron oxide is not an Food and Drug Administration (FDA) approved inorganic filter, it is listed as an inactive ingredient on sunscreen labels.

There is high-quality evidence that daily sunscreen prevents of photoaging.[14,15] A study including 903 adults randomized to daily sunscreen application versus discretionary sunscreen application tracked participants over 4.5 years. At the end of the study period, the daily sunscreen group showed no detectable increase in skin aging, which was 24% less than skin aging in the discretionary sunscreen group.[14] Daily sunscreen application has been suggested to reverse signs of extrinsic aging.[16] A study of 32 patients who applied daily broad-spectrum SPF 30 sunscreen over a 1 year period showed significantly improved skin clarity, pigmentation, and texture in all subjects.[16] Studies examining the benefit of visible light protection have been primarily performed in the setting of melasma.[17,18] In a double-blind study of 68 female subjects with melasma, there was a significant improvement in Melasma Area Severity Index (MASI) and Physician's Global Assessment scores in those who applied UV and visible light filters, including iron oxides, versus UV filters alone.[18]

Although there has been recent controversy over the safety of sunscreens due to systemic absorption,[19,20] a systematic review in 2020 showed no evidence of human health risk,[21] and its benefits are thought to outweigh the theoretic risks. There has also been concern over the environmental impact on coral reefs, but most studies have shown sunscreen concentrations are lower than the required threshold for coral reef toxicity.[22] However, there have been a few studies that demonstrated oxybenzone and octinoxate, which are both organic sunscreens, have some risk on coral reef health.[23] Sunscreens with these filters are banned in certain locations. This is an area that requires further research. It is important to note that physical blockers, such as zinc oxide and titanium dioxide, have not demonstrated health or environmental risk, and they have achieved Category I- generally recognized as safe and effective (GRASE) by the FDA.[24]

It is generally recommended that a tinted, broad spectrum, SPF 30+ sunscreen be used on a daily basis to provide protection against UV radiation and visible light in order to reduce the effects of photoaging.[25] Even if one is mostly indoors, sunscreen application is still critical, as UVA radiation penetrates through glass,[4] and visible and blue light are ubiquitous in our environment. Additionally, sunscreen should be reapplied every 2 hours, as well as after sweating or water exposure.

RETINOIDS

Topical retinoids, used as monotherapy and in combination, are the cornerstone of treatment for photoaging. Its efficacy and use in photoaging have been well reviewed.[26–28] As a class of compounds related to vitamin A (eg, retinol, retinyl esters, retinaldehyde), it is converted to its most biologically active form, trans-retinoic acid. The mechanism of action involves diffusion into the cell and transportation into the nucleus by the

cellular retinol-binding proteins or cellular retinoic acid-binding proteins. Within the nucleus, the retinoid binds to the retinoic acid receptor or to the retinoid X receptor, which act as ligand-dependent transcription factor. This allows either increases or decreases in the expression of specific proteins and enzymes.[28]

Historically, tretinoin was used to treat several dermatologic conditions, most commonly acne, and it was observed to have an effect on photoaging.[29] Evidence demonstrating the effectiveness of topical retinoids for aging has been shown clinically, histologically, and at the molecular level.[28] Clinically, it reduces the appearance of fine/coarse lines, improves skin texture, improves tone and elasticity, and slows photoaging.[26,30] Histologically, it has been shown to increase collagen production,[31] induce epidermal hyperplasia, and decrease keratinocyte and melanocytic atypia.[32] Molecularly, it increases collagen syntheses via inhibition of UV-induced c-Jun and alternation of TGF-beta expression, inhibition of collagen degradation via matrix metalloproteinases (MMP) inhibition, increased epidermal proliferation and differentiation, inhibits tyrosinase activity, and increases glycosaminoglycans (GAG), which binds water, increasing epidermal hydration.[33]

Of the topical compounds, tretinoin is the most widely used and studied compound. As the beneficial effects of tretinoin on photodamaged skin cease after discontinuation , it is recommended that initial topical treatment is maintained by long-term use. The most studied concentration of tretinoin is 0.05%. In one study, tazarotene compared with tretinoin 0.05% provided a more rapid response; however, at the conclusion the study period there was no difference in overall improvement.[34] Topical over- the- counter retinols have been shown to improve photodamage such as epidermal thickening and increase collaged synthesis.[35] However, its potency is 20-fold less compared with retinoic acid. Although retinols can be less irritating than retinoic acid, it is also very unstable, degrading into inactive metabolites.[36] That is important to keep in mind when recommending over-the-counter products.

Many patients often abandon the use of topical retinoids before reaping the beneficial effects. A minimum of 3 months use is required to appreciate epidermal changes. Dermal changes are not seen until 9–12 months. Therefore, it is important to prescribe the correct formulation, coach patients through the side effects, and manage their expectations (**Table 1**). Retinoid dermatitis and photosensitivity can be seen in the beginning of treatment. Common side effects include erythema, burning, stinging, dryness, and scaling. To improve tolerability, initiate retinoid at the lowest strength of 0.025%. Encourage moisturizer use at least 30 minutes after retinoid application and start with thrice-weekly application and increase to daily as tolerated. There also are novel vehicle delivery systems that improve tolerability such as liposomes, controlled-delivery systems, and nanoparticles.[26]

HYDROQUINONE

Hydroquinone is the gold standard of depigmenting agents and is effective in the treatment of melasma and hyperpigmentation. Hydroquinone acts by binding histidines on the active site of tyrosinase.[37] Tyrosinase is the rate-limiting step in melanin production by melanocytes. Furthermore, hydroquinone reduces DNA and RNA synthesis by glutathione depletion, resulting in melanosome degradation.[38] It has also been shown to selectively damage melanosomes and melanocytes.[39]

Hydroquinone comes in a variety of concentrations, but the 4% strength is most commonly used in dermatology practices. A randomized, placebo-controlled trial of 48 patients showed significant improvement in pigmentation in hydroquinone 4% treated patients compared with placebo.[40] Additionally, 40% of hydroquinone patients had complete resolution of their hyperpigmentation. Klingman first proposed that hydroquinone's skin lightning effects may be further enhanced by the addition of corticosteroids and retinoids.[41] His original formulation was hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%, and this combination of active ingredients has been continually replicated. Corticosteroids decrease irritation caused by hydroquinone and tretinoin and tretinoin stimulates cell turnover and hydroquinone penetration.[42] A multicenter, randomized controlled trial of 260 subjects over 8 weeks showed that a triple combination cream of fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% had superior efficacy in comparison to hydroquinone 4% alone in the treatment of melasma.[43] However, the triple therapy group did have a higher rate of skin irritation. In addition, a 2010 Cochrane systematic review including 2125 participants showed that triple combination cream was more effective at lightning melasma than hydroquinone cream alone.[44] Although more high-quality studies are needed to further determine the ideal formulation and parameters for clinical use.

In addition to skin irritation, the most common side effect, there are several more concerning adverse effects. Although uncommon, exogenous ochronosis, the permanent deposition of yellow-

Table 1
Side effects of topical retinoids and ways to increase tolerance

Side Effect	Advice
Dryness	• Emollient moisturizer 30 min AFTER application of retinoid • Emollient moisturizer with SPF in the morning
Irritation	• Wait 30 min after washing face • Apply every other night to build up tolerance eventually increasing to every night • Apply after the face is completely dry • Avoid chemical or physical scrubs • Pea-size amount to the whole face
Redness	• Strict sun protection
Stinging	• Avoid chemical or physical scrubs • Liposome or nanoparticle carrier
Sensitive skin (eg, Fitzpatrick type 1, historical intolerance to perfumes, chemical sunscreens, or astringents, atopic dermatitis, rosacea)	• Initiate tretinoin at0.025% qHS

pigmented fibers within the dermis is a feared complication. This clinically appears as reticulated blue-grey macules in treated areas. It can be almost prevented with the appropriate use of hydroquinone.[45] A systematic review showed that the development of exogenous ochronosis occurred after a median duration of use of 5 years, and only four cases were reported when using hydroquinone for 3 months or less.[45] Additionally, exogenous ochronosis was more frequently reported when hydroquinone concentrations were greater than 4%. Additional risk factors include Black race and Fitzpatrick skin types V and VI, both being associated with greater than 50% of exogenous ochronosis cases. Although extremely rare, there is a risk of permanent depigmentation due to oxidative damage to membrane lipids in melanocytes.[46] Only eight cases have been reported in the literature of hydroquinone causing permanent leukoderma.[47] There have been significant safety concerns with hydroquinone due to it being a benzene derivative and reports of animals developing malignancy after being treated for extended periods with high oral doses.[48] It is currently banned in Europe, Australia, and Japan although there have been no reports of cutaneous or internal malignancy associated with hydroquinone in humans over its 40 to 50 years of clinical use.[49]

Up until 2020, hydroquinone was available over the counter in a 2% formulation. As part of the Coronavirus Aid, Relief, and Economic Security Act, hydroquinone was categorized as not non-GRASE, eliminating over-the-counter sales. It remains available as a prescription product and is commonly compounded into a triple therapy cream. Of note, there is only one FDA-approved product containing hydroquinone (Tri-Luma, Galderma Labs), which also contains tretinoin and fluocinolone. When compounding hydroquinone, it can be difficult to formulate in a stable preparation as it rapidly oxidizes. Hydroquinone will change from a creamy color to dark yellow or brown as oxidation occurs, making it less efficacious. Therefore, any products with color change should be replaced.[50]

We feel that hydroquinone applied topically as a thin layer one to two times daily for up to 3 months has a good safety profile. Being mindful to avoid overtreatment and ensuring drug holidays may be helpful in preventing side effects. Additionally, concomitant use of sun protective measures to prevent further hyperpigmentation is critical.

NIACINAMIDE

Niacinamide is an active form of vitamin B3 that has become increasingly popular in skincare products. Its physiologic role is as a precursor to nicotinamide adenine dinucleotide and its phosphate derivative (NADPH). These cofactors and their reduced forms (NADH and NADPH) function as coenzymes in many redox reactions. The reduced forms also act as antioxidants in the skin. It has been shown that topical niacinamide readily penetrates human skin and increases local levels of NADH after topical application.[51] It has also been shown to increase collagen and GAG production, which can help to decrease wrinkling by boosting these dermal matrix components. Additionally, niacinamide increases ceramide levels of the skin, as NADPH is a cofactor in the synthesis of

fatty acids and lipids, which in turn enhances the skin's barrier function.[52]

Clinical studies have supported the effectiveness of niacinamide on improving visible signs of aging.[53,54] In a randomized, double-blind, placebo-controlled trial of 50 white females with clinically apparent photodamage, niacinamide 5% was applied twice daily for 12 weeks to half of the face, although a vehicle control was applied to the other half. The niacinamide-treated skin showed significantly reduced redness, lightning of hyperpigmentation, and decreased sallowness.[55] Sallowness, or age-related yellowing of the skin, is due to the Maillard reaction. This reaction involves spontaneous oxidation and glycation of proteins, the rate of which increases with age. The resulting cross-linked proteins lead to a yellow tint to the skin. Niacinamide is specifically beneficial in the reduction of sallowing, as its antioxidant forms, NADH and NADPH, inhibit the Maillard reaction, and thus, reduce skin sallowing.[54] This has been supported clinically by several studies that showed a significant reduction in sallowness after the application of topical niacinamide.[53,55]

Daily to twice daily application of niacinamide-containing products is typically well tolerated. Concentration varies based on formulation, and there is evidence that the antiaging effects of niacinamide are dose dependent, as improvement with niacinamide 5% was significantly better than 2%.[56] Although topical niacinamide has not shown the same efficacy in photoaging improvement as retinoids, it lacks skin irritation and is thus suitable for patients with sensitive skin.[53] It can also be used in addition to a regimen with other potentially irritating products. Furthermore, it has not been shown to have any inflammatory or carcinogenic properties.[57]

VITAMIN C

Vitamin C is a popular cosmeceutical ingredient and is the most plentiful and important antioxidant in the skin.[58] Vitamin C plays an essential role in transcription and post-translation collagen synthesis and has been shown to downregulate MMP responsible for collagen degradation.[59] Vitamin C also reduces inflammation and UV-induced immunosuppression.[58] Moreover, vitamin C inhibits melanogenesis and resulting hyperpigmentation by inhibiting copper ions on tyrosinase active sites.[59]

Several studies have shown that topical application of vitamin C improves the appearance of photoaging and dyspigmentation[59–63]; however, oral supplementation remains controversial.[64] In one double-blind, placebo-controlled trial, subjects who applied 10% topical vitamin C over 12 weeks had a statistically significant reduction in photoaged scores and skin wrinkling.[62] Skin biopsies also revealed increased grenz zone type 1 collagen. Another double-blind, placebo-controlled trial involving 6 months of vitamin C 5% application looking at structural improvements revealed improved skin furrowing on histology, along with improved clinical appearance.[61]

Most studies evaluating topical vitamin C benefits in dyspigmentation have evaluated its use in melasma. An open-label study evaluating 40 melasma patients applying L-ascorbic acid 25% for 16 weeks revealed a significant decrease in MASI scores, improvement in skin pigmentation as evaluated by mexameter and improvement in melasma specific quality of life index.[65] When compared to hydroquinone 4%, ascorbic acid 5% had similar improvements in colorimetry; however, more patients in the hydroquinone group had good and excellent results based on photography and patient report.[66]

Vitamin C most commonly occurs in its active form, L-ascorbic acid, which is unstable and hydrophilic. Therefore, L-ascorbic acid has poor skin penetration due to the hydrophobic nature of the stratum corneum.[67] Reducing the pH of L-ascorbic acid by the addition of ferulic acid improves stability and permeability due to transformation into a hydrophobic molecule.[67,68] Additional studies have looked at the use of vitamin C esters, which are active and have an added benefit of being nonirritating.[69] Regardless of formulation, vitamin C must be in its active form and should have a concentration of 8% to 20% in order to have a biologically significant effect.[67] In concentrations greater than 20%, there is no improved d cutaneous absorption and higher concentrations are associated with increased irritation.[67]

ALPHA HYDROXY ACID

The use of alpha-hydroxy acids is a centuries-old practice to improve skin appearance, dating back to ancient Egyptian medicine and initially described in the Ebers Papyrus in 1550 BC..[70] Queen Cleopatra was famously known to bathe in sour milk to improve the texture and cosmesis of her skin.[71] Unbeknownst to her, the active ingredient was lactic acid, an alpha-hydroxy acid. Alpha hydroxy acids include glycolic acid, lactic acid, malic acid, citric acid, pyruvic acid, tartaric acid, and other less commonly known acids. They are hydrophilic organic acids with a carboxylic acid moiety and an adjacent hydroxyl acid group in the alpha position. Although the exact mechanism of action remains unknown, they are

Table 2
Additional products for specific complaints

Patient Concern	Addition to Topical Routine
Dull/sallowness	• Vitamin C q am before sunscreen
Sensitive skin	• Niacinamide q am • Sunscreen with physical blockers only
Pigment (melasma; lentigines; postinflammatory hyperpigmentation)	• Hydroquinone q pm (can be compounded with tretinoin)
Coarse/roughness	• Alpha hydroxy acid

[a]Core topical regimen involves sunscreen in the morning and retinoid in the evening.

thought to function via epidermolysis. By removing calcium ions from epidermal cell adhesions via chelation, they result in the weakening of adhesions resulting in an exfoliative effect.[72] Additionally, they have been shown to increase collagen and hyaluronic acid within the dermis.[73]

Although most studies involving the use of alpha hydroxy acids have been performed with chemical peeling, evaluation of their use in leave-on products has also been performed in small studies. Ditre and colleagues recruited 17 volunteers in a split arm study with moderate to severe photoaging.[74] They applied a 25% glycolic acid, lactic acid, or citric acid lotion to one forearm versus vehicle on the other arm. After 6 months, they found the alpha hydroxy acid group had increased skin thickness, reversal of basal cell atypia, melanin dispersal, normal rete, increased papillary dermal thickness with increased collagen density, and improved elastic fiber quality. Further studies have also reported improvement in wrinkling, roughness, and dyspigmentation with the daily application of leave-on alpha hydroxy acids.[75–77]

The daily application of alpha hydroxy acid-containing compounds in concentrations up to 20% appears to be well tolerated.[78] Adverse effects depend on the concentration and pH of the product used. Potential mild negative side effects include skin irritation, stinging, burning, pain, and erythema. Side effects become more frequent and severe with increasing concentration; therefore concentrations up to 70% and a pH 2 or less should be restricted to professional use.[78]

OUR APPROACH

Topicals have a role in priming the skin before other surgical rejuvenation procedures.[27] It has been shown that pretreatment with retinoid creams before chemical peels and dermabrasion improved the uniformity of frosting and reepithelialization. However, short-term pretreatment before carbon dioxide laser has not demonstrated benefit in reepithelialization or hyperpigmentation. Moreover, although some providers recommend hydroquinone pretreatment before rejuvenation procedures in those with an increased risk of postinflammatory hyperpigmentation, there is insufficient data to demonstrate that pretreatment hydroquinone can diminish this risk.

The essential components of a topical skincare routine are sun protection and a retinoid. Although seemingly straightforward, achieving routine use of these products is easier prescribed than done by patients. Furthermore, the number of over-the- counter cosmeceuticals is overwhelming and challenging to assess efficacy. As they are not classified as drugs, they are not subject to the rigorous testing and regulation of the FDA. Many of the combination creams are proprietary so it can be difficult to compare products. As indicated above, many of the components discussed can become unstable and inactivate easily. Although the over- the- counter anti-aging creams can serve as moisturizers, we tend to recommend bland, emollient moisturizers to combat the irritation of the prescription strength retinoids. Combined sunscreens and moisturizers are convenient to use in the mornings and establish a routine. As for retinoids, our recommendation is to familiarize oneself with a few retinoids for the different skin types and common complaints that prevent adherence. Other agents can be added for specific concerns (**Table 2**). In our experience, a simple routine increases compliance and tolerability, which is key as these topicals are intended for lifelong maintenance and prevention.

SUMMARY

The skin is the most visible indicator of aging. The major extrinsic factor that causes aging is UV light. Optimizing skin health with a topical routine with photoprotection and retinoid is the foundation of facial rejuvenation. Due to the irritability of prescription strength retinoids and length of time needed for results, adherence is an issue even though their efficacy has been demonstrated on

the clinical, histologic, and molecular levels. Coaching patients through the side effects and choosing a well-tolerated retinoid is key. Furthermore, without strict photoprotection, any topical will be counterproductive.

CLINICS CARE POINTS

- Regardless of the skin type or pigmentation, daily photoprotection best prevents the aging effects of UVA.
- Long-term use of topical retinoids can reduce the appearance of fine/coarse lines, improves skin texture, improves tone and elasticity, and slows photoaging.
- Hydroquinone inhibits melanin production and can treat hyperpigmentation. Caution must be used when determining the concentration and length of time used.
- Niacinamide, an active form of vitamin B3, can lessen redness, hyperpigmentation, and sallowness, reducing signs of photoaging. Although not a potent as retinoids, it is less irritating.
- Topical application of vitamin C improves the appearance of photoaging and dyspigmentation. The active form is unstable and has poor penetration of the stratum corneum.
- Alpha hydroxyl acids have an exfoliative effect and can reduce coarseness.
- Keep topical routines simple to reduce irritation and augment compliance.

DISCLOSURE

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