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INTRODUCTION

The pursuit to prevent or reverse human aging is as old as time itself. The surgical specialties have made great strides to this effect, but they all too often overlook the usefulness of topical skin care. This review aims to familiarize the reader with the biological processes of skin aging and evidence-based clinical outcomes afforded by topical skin care.

INTRANISC AGING AND PHOTOAGING OF SKIN

Etiology

Skin aging is the result of both an intrinsic phenomenon and the cumulative effect of environmental stress, mainly ultraviolet (UV) radiation. No cell line can continue to replicate indefinitely, and with each cell cycle, the telomeres shorten and deoxyribonucleic acid (DNA) replication errors build in number. Despite DNA repair mechanisms, these changes ultimately result in atypia, arrest of the cell cycle, apoptosis, or malignant transformation. In non-photoprotected skin, these changes are accelerated.

Intrinsic Aging

Intrinsic aging, unrelated to environmental stress, is caused by errors in DNA replication and oxidative stress from cellular metabolism. Human keratinocytes are limited to 50 to 100 cell doublings. Subsequently, they are arrested in the G1 phase of the cell cycle or undergo apoptosis. However, keratinocytes have been shown to have higher thresholds for apoptosis induction. An increased lifespan allows for greater accumulation of DNA damage and protein damage. DNA damage results from errors in replication and from endogenous agents, such as reactive oxygen species (ROS), which are generated by all aerobic species. During the lifespan of a keratinocyte, the accumulation of DNA damage affects genes and their associated proteins, leading to compromise in function and eventual cell death.

Photoaging

UV radiation causes direct and indirect damage to skin. Direct damage results from absorption of UV energy. The two most important UV spectrum chromophores in skin are DNA and urocanic acid. DNA maximally absorbs radiation at 300
The energy is converted into abnormal DNA bonds between adjacent pyrimidine bases whereby cyclopyrimidine dimers and (6-4) photoproducts are formed. Although UVB (290–320 nm) light is most likely to induce pyrimidine base changes, UVA (320–400 nm) light can also directly damage DNA. Both nuclear and mitochondrial DNA are affected by UV radiation, although mitochondrial DNA repair mechanisms are not as efficient and therefore are more susceptible to permanent damage. Defects in mitochondrial DNA impair oxidative phosphorylation, leading to further oxidative stress on the entire cell. Defects in nuclear DNA usually are repaired by excision DNA repair enzymes, but, if the damage is great, p53-mediated apoptosis can result. If DNA mutations occur in the p53 coding sequence, quality control is impaired and clonal expansion can give rise to actinic keratosis. Damage to the second p53 gene is the hypothesized cause of squamous cell carcinoma. Mutations in the hedgehog family of genes are thought to induce basal cell carcinoma.

Although UVA has been shown to directly induce DNA changes, its main route of cell damage is indirect through the creation of ROS and free radicals. Counterintuitively, the indirect damage from UVA-induced free radicals has been found to be more cytotoxic. ROS, such as molecular oxygen, singlet oxygen, and hydrogen peroxide, can directly cause oxidative reactions in addition to free radical creation. In addition to causing damage to the genome, ROS directly damage lipids and proteins. Urocanic acid, which is found in high concentrations in skin, has been identified as a primary chromophore for UVA with peak absorption at 345 nm. Excited urocanic acid can produce singlet oxygen and superoxide anion, both highly reactive ROS. The superoxide anion can be produced by UV stimulation of nicotinamide adenine dinucleotide−/nicotinamide adenine dinucleotide phosphate (NADH−/NADPH), tryptophan, and riboflavin.

Cells are designed to tolerate an oxidative environment and protect themselves with DNA repair enzymes, enzymatic reduction proteins, and antioxidants. The antioxidants in high concentration in skin are glutathione, ascorbic acid, vitamin E, and ubiquinol-10. However, high metabolic demand, UV radiation, smoking, decreased cellular function with age, and other factors can overwhelm the system and result in oxidative damage.

In the milieu of oxidative stress, activation protein (AP-1), nuclear factor-κ B (NF-κB), and c-Jun transcription factors are upregulated. AP-1, among other things, induces several matrix metalloproteinases (MMP), namely MMP-1, MMP-2, MMP-3, and MMP-9. NF-κB stimulates neutrophil migration and subsequent release of neutrophil-derived MMP-8. These proteases combine to degrade the collagen extracellular framework. At the same time, production of procollagen is decreased related to the c-Jun transcription factor activation and feedback inhibition by the degraded collagen products. While the collagen framework is being dismantled, oxidative stress in fibroblasts stimulate an increase in elastin production. Cell membrane lipids are also affected by ROS. UVA has been found to have a 10-fold higher rate of lipid peroxidation than UVB through the creation of ROS. The resulting cell membrane oxidation has notable consequences on fluid homeostasis. The mechanism for hyperpigmentation or hypopigmentation is not yet completely understood. It is thought that endothelin and its related cytokine signaling pathway are directly affected by UV light. Although less researched, some evidence for direct DNA damage in melanocytes stimulating increased pigment production has been reported.

**Clinical Findings**

On a clinical level, the most common findings in intrinsically aged or photoprotected skin is thin, dry, smooth, and unblemished skin. Photoaged skin is characterized by fine and coarse wrinkles, roughness, laxity, sallowness, scaling, dryness (increased transepidermal water loss), telangiectasia, and dyschromia. The frequency of benign,
premalignant, and malignant lesions is increased in photoaged skin.\textsuperscript{21,22} Seborrheic keratoses are commonly associated with sun-exposed, aged skin.\textsuperscript{23} Syndromes associated with sun exposure have also been described, namely actinic or solar elastosis and Favré-Racouchot syndrome. Favré and Racouchot\textsuperscript{24} described a phenotype with nodular elastosis, large pores with keratin cysts, and comedones.

**Histological Findings**

**Epidermis**

Photoprotected epidermis usually is thinner than normal, with deceased cellular turnover. The keratinocyte maturation entails minor abnormalities but a normal stratum corneum. The contour of the rete pegs is flattened, increasing fragility and susceptibility to shear stress forces.\textsuperscript{2}

Photodamaged keratinocytes are characterized by atypia, loss of polarity (non-orderly maturation), slowed proliferation, lessened cell signaling, and less response to signaling.\textsuperscript{25−27} Histologically, the epidermal thickness might decrease or remain unchanged in the sun when protected but is increased in the sun when unprotected. However, concomitant flattening of the rete ridges can render the appearance of decreased thickness or atrophy.\textsuperscript{25} On the whole, melanocytes decrease in number, have shortened life spans, and respond less to growth factors, resulting in guttate hypomelanosis.\textsuperscript{28} However, there can also be regions of increased melanocyte concentration, increased capacity for melanin production, and increased melanin deposition into keratinocytes (e.g., solar lentigines).\textsuperscript{29}

**Dermis**

It is important to remember that UVB light is almost completely absorbed by the epidermis; thus, dermal photodamage is solely caused by UVA. In photoprotected skin, all cell type density and extracellular matrix contents decrease. Collagen, elastin, glucosaminoglycans (GAG) content, fibroblast, and Langerhans cell counts are all decreased.\textsuperscript{2}

The histological picture of photoaged dermis on the cellular level is one of chronic inflammation. Fibroblast and Langerhans cells are decreased and surrounded by abundant inflammatory infiltrate, a condition called beliodermatitis.\textsuperscript{30,31} Fibroblasts are morphologically abnormal and produce less collagen. However, cultured photoaged fibroblasts are able to produce collagen in vitro, similar to aged photoprotected controls.\textsuperscript{16} Thus, the decreased biosynthesis is likely caused by impaired signaling (lessened response to transforming growth factor beta [TGF-β]). Additionally, it is normal for fibroblasts to respond to degraded collagen and decreased tissue tension with decreased procollagen biosynthesis.\textsuperscript{16,32}

Langerhans cells decrease in number and undergo functional and morphological changes after UV exposure.\textsuperscript{31} Their depletion has implications in local and systemic immunosuppression, including the improved conditions for cutaneous malignancy proliferation.\textsuperscript{33}

Solar elastosis is the term used to describe the histological appearance of the photoaged dermal extracellular matrix. This condition is characterized by an accumulation of amorphous, abnormal elastin material surrounding a decreased volume and disorganized array of wavy collagen fibrils.\textsuperscript{22,25} It is hypothesized that the abnormal elastin results from overproduction of normal elastin, which is subsequently degraded by the chronic inflammatory state.\textsuperscript{22}

The other major components of extracellular matrix, glycoproteins and glycosaminoglycans, tend to diminish with age but are increased in photoaged skin.\textsuperscript{34} However, the increased GAG are not found in the papillary dermis and epidermis as usual; instead, they are deposited in the reticular dermis within the elastotic material.\textsuperscript{35} In this location, the GAG are not able to regulate hydration, leading to dry and leathery appearing skin.\textsuperscript{36}

UV radiation has been shown to increase
angiogenesis, mediated through increased vascular endothelial growth factor, increased platelet-derived endothelial cell growth factor, and decreased thrombospndin-1.\textsuperscript{37,38} These changes likely account for the telangiectases seen in sun-exposed skin and might promote the growth of skin malignancies.

**PROTECTION FROM THE SUN**

The most cost-effective and, some would argue, only way to prevent premature skin aging is sun protection. Sun protection can be as simple as avoiding sunlight altogether during peak UV exposure. Clothing, hats, and sunglasses are other simple solutions to photoprotection. Unfortunately, tanned skin has become a sign of youthfulness, vitality, and health. Multiple generations have exposed their skin to years of photodamage to achieve a tanned appearance, and sun avoidance continues to be an unrealistic expectation for most. Sunscreen is the least effective methodology for photoprotection, but it has gained a great deal of acceptance because of recommendations by the medical community and marketing actions from the skin care industry.

The ozone blocks 100% of UVC, 90% of UVB, and almost none of the UVA rays. Depletion of the ozone layer is known to directly increase UVB penetration and increase skin malignancy rates.\textsuperscript{39} The percentage of UV rays reaching the skin is also affected by time, season, altitude, latitude, and environmental surroundings. Peak UV exposure occurs between 10 AM and 4 PM. For every 300 m of elevation, UV radiation increases by 4%. For every degree of latitude closer to the equator, UV radiation increases by 3%.\textsuperscript{40} Fog, clouds, and air pollution can decrease UV transmission, and water, snow, sand, and concrete can reflect UV radiation to the skin.\textsuperscript{41} Avoiding environments with heightened levels of UV radiation or taking more precautions when in such environments should be advised to all patients.

**Photoprotective Clothing**

Wearing hats, sunglasses, and clothing is an important method to achieve photoprotection, with many advantages compared with sunscreen application alone. UVA and UVB protection is more uniform with clothing and hats compared with most sunscreens, which primarily block UVB. Wearing clothes and hats obviates the issues of appropriate application and reapplication of sunscreen. Clearly, the duration of UV protection exists as long as the clothing is worn. Clothing is much more cost-effective than sunscreen and devoid of any contact or photoallergic complications.

Not surprisingly, different materials offer different degrees of UV protection. Most regulatory agencies have adopted the UV protection factor (UPF) as the standard with which to assess the ability of a material to block radiation transmission. Standards in labeling are highly regulated in Europe and Australia but are currently self-regulated by industry in North America.\textsuperscript{42} Therefore, clothing bought in the United States with a UPF rating might not always be reliable, despite most producers’ claims of following the international UPF testing and labeling standards.

The UPF rating is a score that is based on two end points: UV transmission and skin response. First, UV light at multiple wavelengths is applied to a material and the percentage of UV transmission is measured using a spectrophotometer. Second, the amount of UV transmission associated with an erythema response by skin is used to create a final UPF rating (Table 1).\textsuperscript{43} Because UVA does not incite an erythema response, UPF does not directly measure UVA protection. In 2003, the European Committee for Standardization required all clothing with a UPF label to block a minimum 95% of UVA radiation. Additionally, to use a UPF label, the committee requires a minimum of 40 UPF and complete coverage from the neck to hip, across the shoulders and three-quarters of the upper extremity.\textsuperscript{44}

Several post-production factors can change the ability of a material to block UV transmission. Many materials, such as cotton, rayon, and flax,
shrinking has the effect of decreasing gaps between fibers and will increase the UPF. However, most light colored materials reflect or scatter light and lose this ability when worn wet. Dark colored clothing primarily absorbs UV radiation and is therefore less affected by wetness.

Many household laundry detergents contain optical brightening agents, UV absorbers, and bleach. Optical brightening agents absorb UV energy and release light in the visible range, increasing the UPF. UV absorbers, Tinosorb FD (Ciba Specialty Chemicals, Basel, Switzerland) for example, bind to clothing fibers in a cumulative fashion with each application and will also increase the UPF. Bleach and other harsh chemicals can enlarge fiber gaps in materials, which decreases the UPF.

Sunscreen

Sunscreens have been in existence for more than 70 years. Sunscreen products are regulated by the U.S. Food and Drug Administration (FDA) as over-the-counter drugs. A wide variety of products have been approved for use and are available in combinations and formulations. The efficacy of these products is graded by the sun protection factor (SPF) and, more recently, by the ability to filter UVA radiation. SPF testing is accomplished by in vivo UV exposure of 20 volunteers’ skin with and without sunscreen. The end point of the test is to find the minimal erythema dose (MED) in both. SPF is calculated by dividing the MED with sunscreen by the MED without sunscreen.

In practical terms, UV radiation doses increase linearly with exposure time. Assuming a particular person would have an erythema response within 10 minutes, application of SPF 10 would allow for 100 minutes of exposure before an erythema response.

Long considered the “gold standard” of photoprotection, sunscreen is now considered the third line of defense behind shade and protective clothing. Inadequacy of sunscreen use results primarily from inappropriate or inadequate use. SPF of sunscreen is tested 30 minutes after an application dose of 2 mg/cm². Sunscreen should be reapplied at 2-hour intervals or more frequently if exposed to water. Controlled studies of real-life sunscreen application have found average doses of 0.5 mg/cm² or less with variable timing before sun exposure and reapplication. Sunscreen dosing has a logarithmic relationship with effective SPF (Fig. 1). Thus, even with SPF 50 application, the prolongation before erythema response is only 3-fold.

The evidence-based support of sunscreen use has been limited by several factors. As discussed above, inappropriate, inadequate, and inconsistent uses of sunscreen are substantial limitations. Furthermore, until recently, sunscreen protection was limited to the UVB exposure. The protection from UBV and the associated erythema response further encouraged increased duration of unprotected UVA exposure.

<table>
<thead>
<tr>
<th>UPF</th>
<th>Protection Category</th>
<th>% of UV Radiation Blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–24</td>
<td>Good</td>
<td>93.3–95.8</td>
</tr>
<tr>
<td>25–39</td>
<td>Very good</td>
<td>95.9–97.4</td>
</tr>
<tr>
<td>40–50+</td>
<td>Excellent</td>
<td>≥97.5</td>
</tr>
</tbody>
</table>

Table 1

Ultraviolet Protection Factor Ratings

UPF, ultraviolet protection factor; UV, ultraviolet.
Because UVA exposure does not cause an erythema response, SPF is not a useful way to measure UVA protection. There is an in vivo measurement for UVA exposure, currently used in Japan and the European Union, which measures persistent pigment darkening of skin after UVA exposure. Other governing agencies use in vitro UVA filtering tests to assess the level of UVA protection.

In the summer of 2012, the FDA mandated new labeling restrictions. First, any sunscreen with SPF <15 will have a warning label that reads, “Skin Cancer/Skin Aging Alert: Spending time in the sun increases your risk of skin cancer and early skin aging. This product has been shown only to help prevent sunburn, not skin cancer or early skin aging.” Second, water resistance claims will be limited to the water submersion times for which SPF will be maintained: only 40 minutes or 80 minutes will be allowed. Third, sunscreen labels cannot use the following language: “waterproof,” “sweatproof,” or “instant protection” nor can they identify their products as “sunblocks” or claim protection for more than 2 hours without reapplication. UVA protection will be signified as “Wide Spectrum” in sunscreens with SPF >15 that have been shown to provide UVA protection proportional to UVB protection.

Inorganic Sunscreen

Currently, two inorganic sunscreen components have been approved by the FDA: titanium dioxide (TiO$_2$) and zinc oxide (ZnO). They work by scattering or reflecting UV radiation. Before the 1990s, they were available only as large particles (100 to 300 μm). Sunscreens made with these large particles where thick pastes. Not only were they not cosmetically ideal, but they also had a tendency toward comedogenesis and stained clothes. More recently nano- and micro-scale particles have been available. The smaller particle size has increased the cosmetic appeal (invisibility on the skin) but has unfortunately decreased the UVA absorption.

Both TiO$_2$ and ZnO offer protection from the complete range of UVB light, although the magnitude of ZnO protection is less. In terms of UVA protection, TiO$_2$ blocks only UVA II (315–340) whereas ZnO affords the complete range of UVA protection.

When compared with organic sunscreens, the inorganic agents have several advantages. They are photostable, which means that their protection is predictable and stable after UV exposure. They have no allergenic or skin-irritating qualities. Also, the inert chemical profile of the inorganic sunscreens allows them to be easily combined with organic sunscreens to increase SPF and/or increase UVA protection. ZnO and TiO$_2$ have traditionally been considered very safe; however, some concern was raised with decreased particle size formulations. Theoretically, the smaller particles would have an increased risk of systemic absorption. This issue has since been resolved after a large number of studies using human skin have shown that the nano-sized ZnO and TiO$_2$ particles remain at the stratum corneum level.

Organic Sunscreen

Organic sunscreens offer UV protection by absorbing the energy and releasing it as heat. The primary issues when comparing these compounds are spectrum of radiation absorbed, photostability,
effectiveness after exposure to water and perspiration (substantivity), and skin irritation or photoallergic potential.

Aminobenzoates—Para-aminobenzoic acid (PABA) was the first UVB filter widely used in the United States. Although PABA has a high level of substantivity, 4% of the general population has photoallergic reactions. Combined with a tendency to stain clothing, PABA is no longer practical for continued consumer use.

Cinnamates—Cinnamates are a class of UVB-absorbing organic sunscreens composed of octinoxate and cinoxate. Octinoxate is widely used in the United States because of its low irritancy potential and water-resistant properties. Additionally, it is the most potent UVB absorber. However, the use of octinoxate is limited by its incompatibility with avobenzone, a common UVA filter. When combined, both filters become extremely photoliable.

Octocrylene—Octocrylene is a UVB-absorbing compound that causes very little skin irritation. In the past, this compound was limited in use because of the cost of production and very low substantivity. More recently, octocrylene has been increasingly used because it is the best photostabilizer of avobenzone available in the United States.

Salicylates—Octisalate, homosalate, and trolamine salicylate are all FDA-approved UVB filters. Generally speaking, they are weak UVB absorbers and high concentrations would be necessary to achieve desirable SPF ratings. Salicylates are still commonly used in combination with other filters because of their low skin irritancy potential and high substantivity.

Benzophenones—Oxybenzone is a member of the benzophenones class of UVA filters. It is commonly used in the United States, but, because of several drawbacks, it is rarely used elsewhere. When used in European sunscreens, a warning label is mandated: “contains oxybenzone.” Oxybenzone effectively blocks UVA II but not UVA I. The main drawbacks to its use are high rates of contact and photoallergic dermatitis, release of oxygen radicals with UV exposure, and systemic absorption. The presence of oxybenzone in urine and blood has raised serious safety concerns; however, no evidence of pathological implications has been shown to date. With new UVA filters on the horizon of FDA approval, it is predicted that oxybenzone will soon become an historical footnote.

Avobenzone—In the United States, avobenzone is the most potent and broad-spectrum UVA-blocking organic agent. UVA protection afforded by avobenzone extends well into the UVA I spectrum. It does not have any systemic absorption and relatively little skin irritation. Avobenzone does suffer substantial photoinstability, especially when combined with octinoxate, as previously discussed. Therefore, photostabilizers have been combined in commercial formulations, such as octocrylene and diethylhexyl 2,6-naphthalate. Neutrogena Corporation (Los Angeles, CA) has patented the formulation of avobenzone, octocrylene, oxybenzone, and diethylhexyl 2,6-naphthalate under the trade name Helioplex.

Ecamsule—Commonly referred to as Mexoryl SX (La Roche-Posay, Poitou-Charentes, France), ecamsule is a broad-spectrum UVA filter that is photostable, is water-resistant, and has little systemic absorption. Because of its limited FDA approval, ecamsule is permitted in only certain formulations. Ecamsule combined with avobenzone, octocrylene, and TiO₂ has been marketed under the trade names Anthelios by La Roche-Posay and Capital Soleil by Vichy (Vichy, France).

Clinical Evidence
As previously discussed, studies supporting routine sunscreen use have been difficult to conduct
and interpret. Sunscreen use is often irregularly or inappropriately applied. In addition, and perhaps more importantly, sunscreens have only recently begun to protect against UVA radiation. Although no study has been published proving that regular sunscreen use in humans protects or reverses photoaging, it seems a relatively intuitive conclusion. Two studies performed by Kligman et al.\textsuperscript{52,53} did show protection and improved repair from UV damage in a hairless mouse model.

It has similarly been difficult to prove cutaneous malignancy risk reduction with sunscreen use. To date, Green and his colleagues\textsuperscript{54−56} are the only groups to have conducted a large randomized controlled trial exploring this topic. The authors randomized 1646 participants in Australia to daily SPF 16 sunscreen application or discretionary sunscreen application. The study took place over 4.5 years, from 1992 to 1996.

The initial study\textsuperscript{54} showed a statistically significant reduction in the number of squamous cell carcinoma tumors (39%) but not in the number of people affected (rr = 0.61; 95% confidence interval [CI], 0.46–0.81). As for basil cell carcinoma tumors, sunscreen use had no protective effect. Believing that the beneficial effect of sunscreen might be delayed, the participants were subsequently followed. In a 2006 study\textsuperscript{55} (12.5 years after trial initiation), sunscreen use showed a statistically significant reduction in both the incidence (35%) and the total number (39%) of squamous cell carcinoma tumors. Again, no statistically significant reductions were observed in the incidence or number of basic cell carcinoma tumors ($P = 0.42$). In a 2010 follow-up study\textsuperscript{56} (15 years after trial initiation), patients were specifically compared for melanoma rates. The sunscreen group had a statistically significant (50%) reduction in risk for developing new primary cutaneous melanomas ($P = 0.05$; hazard ratio [HR], 0.5; 95% CI, 0.24–1.20). In addition, the invasive melanoma incidence had a more substantial (73%) reduction in risk (HR, 0.27; 95% CI, 0.08–0.97).

### RETENOID THERAPY

Retinoids are a family of compounds composed of vitamin A, its derivatives, and synthetic molecules acting through the same pathway. Since the 1940s, they have been administered topically and orally for a multitude of skin conditions, primarily acne. The ability of retinoids to rejuvenate photoaged skin was popularized in the 1980s, largely because of the work conducted by Kligman and colleagues.\textsuperscript{57−59}

The retinoid family can be classified based on chemical makeup (presence of aromatic groups), generation, natural versus synthetic, and prescription versus over-the-counter availability. Table 2 displays an exhaustive list of retinoids using many existing classifications.\textsuperscript{60}

### Mechanism of Action

Retinoids pass through cell membranes through non-receptor endocytosis.\textsuperscript{61} The retinoids are then carried to the nucleus by cellular retinoic acid binding protein (CRABP) types I and II, with type II being predominate in human keratinocytes.\textsuperscript{62} Within the nucleus, retinoids bind to retinoic acid receptors (RAR) and retinoid X receptors (RXR). Each receptor has three subtypes—alpha, beta, and gamma—although RAR-γ and RXR-α represent approximately 90% of their family in the epidermis.\textsuperscript{63} These receptors form hetero- or homodimers before binding to the genome at retinoic acid response elements. Retinoic acid response elements are in the promoter region of genes. Thus, transcription of specific genes is upregulated by specific retinoid×homo- and/or heterodimer complexes.

Retinols are naturally existing elements acquired through diet. Retinol (vitamin A) is absorbed through the small intestine and transported to be stored as a retinol ester (palmitate, propionate, acetate) or oxidized to tretinoin through a two-step process with retinaldehyde serving as the intermediate. Tretinoin represents 50% of the active cellular form with its metabolites (4-hydroxy retinoic acid) and stereoisomers 9-cis.
retinoic acid (alitretinoin) and 13-cis retinoic acid (isotretinoin) making up the difference. Thus, in topical application, retinol, retinol esters, and retinaldehyde have to be converted to a more active form (tretinoin), whereas isotretinoin, alitretinoin, adapalene, tazarotene, and seletinoid G are applied in their active form.

Retinoid effects on the molecular level are known primarily through research using tretinoin, which binds with all RAR (via 13-cis retinoic acid) and all RXR (via 9-cis retinoic acid). These effects may or may not be found with the topical use of synthetic retinoids depending on their individual RAR binding properties (adapalene, RAR-β; tazarotene, RAR-β and RAR-γ; seletinoid G, RAR-γ).

**Tretinoin**

*Molecular and Histological Evidence*

Kligman was the first to demonstrate the antiaging effects of tretinoin using an animal model. After 10 weeks of topical treatment on a photoaged hairless mouse, significant deposition of

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**Table 2**

*Classification of Retinoids*60

<table>
<thead>
<tr>
<th>Generation</th>
<th>Retinoid</th>
</tr>
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<tbody>
<tr>
<td>First (non-aromatic and naturally occurring)</td>
<td>Retinol (all-trans retinol, vitamin A)*</td>
</tr>
<tr>
<td></td>
<td>Retinyl-palmitate*</td>
</tr>
<tr>
<td></td>
<td>Retinyl-propionate*</td>
</tr>
<tr>
<td></td>
<td>Retinyl-retinoate*</td>
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<tr>
<td></td>
<td>Retinyl N-formyl aspartamate*</td>
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<tr>
<td></td>
<td>Retinyl-acetate*</td>
</tr>
<tr>
<td></td>
<td>Retinaldehyde*</td>
</tr>
<tr>
<td></td>
<td>Tretinoin (all-trans retinoic acid)*†</td>
</tr>
<tr>
<td></td>
<td>Isotretinoin (13-cis retinoic acid)*†</td>
</tr>
<tr>
<td></td>
<td>Alitretinoin (9-cis retinoic acid)*†</td>
</tr>
<tr>
<td>Second (mono-aromatic)</td>
<td>Etretinate†</td>
</tr>
<tr>
<td></td>
<td>Acitretin†</td>
</tr>
<tr>
<td>Third (poly-aromatic)</td>
<td>Adapalene*†</td>
</tr>
<tr>
<td></td>
<td>Tazarotene*†</td>
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<tr>
<td></td>
<td>Bexarotene†</td>
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<tr>
<td>Fourth (pyranone)</td>
<td>Seletinoid G*†</td>
</tr>
<tr>
<td></td>
<td>Arotinoid†</td>
</tr>
<tr>
<td></td>
<td>Eretin†</td>
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*Studied for effects on skin aging.
†Available through prescription only.
‡U.S. Food and Drug Administration approval retracted.
collagen and wrinkle effacement were observed \((P < 0.05)\). Since that time, the effect of tretinoin on the molecular level has been further elucidated.

The increased collagen content in the upper papillary dermis is the result of both inhibition of collagen degradation and increased collagen synthesis. Topical tretinoin application before UV radiation has been shown to block AP-1 transcription, which in turn prevents MMP production and collagen degradation.\(^68\) New type I procollagen biosynthesis is mediated by inhibiting UV-induction of c-Jun and altered TGF-\(\beta\) expression.\(^{15,69}\) Histologically, increased collagen types I, III, and VII (dermal-epidermal anchoring fibrils) and reorganization of the dermal collagen into new woven bundles can be seen.\(^70\) Topical tretinoin has been shown to increase production of type I collagen by 80\% in photoaged skin.\(^71\) It is thought that the increased collagen content indirectly stimulates normalization of the elastic tissue organization.\(^72\)

Increased smoothness of skin or wrinkle effacement from tretinoin topical treatment results from epidermal hyperplasia, compaction of the stratum corneum, thickening of the granular layer, and increased epidermal and dermal glycosaminoglycan deposition. On the molecular level, increased epidermal proliferation is accomplished via epidermal growth factor (EGF) receptor activation. Specifically, the heparin-binding EGF and amphiregulin ligands of the EGF-receptor are activated. Increased epidermal differentiation results from expression of transglutaminase, involucrin and filaggrin.\(^{73,74}\)

The molecular etiology of the effect of tretinoin on dyschromic skin is less understood. Several mechanisms have been suggested, including inhibition of tyrosinase activity, reduction in melanocyte Golgi apparatus and endoplasmic reticulum size, inhibition of melanosome transfer, and enhanced shedding of melanin-laden keratinocytes.\(^{75}\) Regardless, improvement in cutaneous coloration and reduction of mottled pigmentation have been well documented.

Tretinoin therapy has also been shown to improve wound healing. Improved wound healing is most likely the effect of improved cutaneous circulation, which has been demonstrated by laser Doppler velocimetry.\(^76\) Animal studies have also shown tretinoin to have an effect on cytokeratin 16, which is an important modulator of the wound-healing process.\(^77\) However, to date, a direct cause-and-effect relationship has not been established.

**Clinical Evidence**

**Time to Effect**—The concentration and dosing regimen of topical tretinoin is a balancing act between side effects and treatment effectiveness, both of which are dose dependent. The typically studied treatment protocol is 0.05\% tretinoin cream applied nightly. Using this protocol, epidermal thickening and improvement in fine wrinkles can be seen as soon as 1 to 3 months (Level II evidence).\(^{78,79}\) After 6 months of therapy, improvements in fine and coarse wrinkling, sallowness, dyschromia, roughness, and laxity have been observed (Level I evidence).\(^{80-84}\) However, at 6 months, improvement is limited to the epidermis; no changes in dermal collagen or elastosis were observed. Bhawan et al.\(^85\) confirmed that dermal changes were not seen at 6 months and continued treatment for 12 months, at which point, formation of new collagen fibers and reduction in elastotic material were observed (Level I evidence).

The so-called *retinoid reaction* consists of erythema, scaling, xerosis, and pruritus. These side effects are dose dependent. They occur in the majority of patients using 0.05\% concentrations daily and in more than 90\% of patients treated with 0.1\% concentrations. However, the side effect severity tends to subside over time in a patient-dependent manner.\(^78\)

To reduce the incidence of the retinoid reaction, several studies have been conducted with lower concentrations of tretinoin. After 6 months of therapy, two large, vehicle-controlled, double-blind, randomized trials showed superior epidermal
improvement using 0.05% concentration compared with 0.01% concentration (Level I evidence).\(^{82,83}\) Griffiths et al.\(^{86}\) compared 0.1% and 0.025% in a similarly designed 8-month study and found no statistically significant difference in epidermal changes \((P > 0.05)\). Not surprisingly, the 0.025% concentration had much fewer adverse effects (Level I evidence). It therefore seems that 0.025%, but not 0.01%, is an appropriate option for patients with lower side-effect tolerance.

Lower concentrations of tretinoin have also been studied with longer treatment durations. Olsen et al.\(^{87}\) followed 298 patients randomized to daily application of 0.05%, 0.01%, or vehicle for 11 months. Statistical improvement over the vehicle preparation was identical for both tretinoin concentrations in clinical and histological evaluations (Level I evidence) \((P < 0.001)\). Similarly, Nyirady et al.\(^{88}\) conducted a double-blind, vehicle-controlled comparison of 0.02% and 0.05% tretinoin cream for 24 months and found no statistically significant difference in clinical improvement (Level I evidence) \((P > 0.05)\). Thus, after 6 months of therapy, using concentrations greater than 0.01% has no apparent advantage.

Because of the delayed gratification of clinical improvement and concurrent incidence of adverse effects, patient noncompliance and discontinuation of therapy are not uncommon with tretinoin therapy. This has stimulated investigation of high-strength tretinoin treatment. Kligman et al.\(^{89}\) have been the strongest proponents of this style of therapy. In 1998, their group studied 50 women using 0.25% tretinoin cream every other night for 2 weeks followed thereafter by nightly application. Not only did they find the therapy to be well tolerated by patients but also the clinical and histological improvement after 4 to 6 weeks was similar to the results achieved in patients who underwent 12 months of 0.05% daily application. Specifically, fine wrinkling, hyperpigmentation, elasticity, hydration, vascularity, and new collagen deposition were observed (Level III evidence). In 2004, Kligman and Draelos\(^{90}\) studied 32 women with 0.25% tretinoin for 4 weeks. Again, early onset of epidermal and dermal changes was observed with a process they have coined rapid retinization. Perhaps more interesting, the retinoid reaction was markedly diminished within only 2 weeks of treatment (Level III evidence). To date, randomized controlled trials using rapid retinization concepts have yet to be conducted.

**Maintenance of Effect**—The safety and efficacy of long-term tretinoin use is less well understood; no study to date has a follow-up duration of longer than 6 years. Several issues are worthy of discussion. After 48 months of 0.05% cream, Olsen et al.\(^{91}\) randomly assigned 126 patients to once weekly application, three times per week application, or discontinuation of therapy. Three times per week therapy was found to preserve fine wrinkle improvement better than once weekly application. Discontinuation of therapy resulted in significant reversal of the antiaging effect \((P < 0.05)\). Therefore, discontinuation or marked truncation of tretinoin therapy will result in reversal of effect to some extent (Level I evidence).

Ellis et al.\(^{92}\) followed patients using 0.1% and 0.05% concentrations for 22 months. First-year results were similar to those of the above noted studies. However, epidermal thickness gradually decreased from its 6-month peak (although greater than pretreatment), mitotic figures decreased, and the compact stratum corneum reverted to its pretreatment basket-weave pattern (Level III evidence).\(^{92}\) A 4-year study of patients using variable concentrations of tretinoin but all using 0.025% for the last 19 months found slightly different results.\(^{93}\) Epidermal thickness did slightly decrease between 1 and 4 years, but the granular layer thickness and stratum corneum compaction were unchanged (Level III evidence). Kligman and Graham\(^{94}\) followed patients for 5 to 6 years using 0.05% concentration daily. In this group of patients, the authors found continued improvement in the dermis and epidermis over time. Specifically, a widening grenz layer, decreased elastotic tissue, increased fibroblast density, and decreased dermal GAG (Level III evidence).
No conclusion can be made regarding the best maintenance therapy dosing or concentration of tretinoin. Current evidence of the long-term effect of tretinoin on epidermal thickness and compaction of the stratum corneum is contradictory. However, evidence does suggest that continued tretinoin therapy is necessary to prolong, maintain, or possibly improve early clinical gains in dyschromia and reversal of solar elastosis.

Isotretinoin

**Molecular and Histological Evidence**

Isotretinoin (13-cis retinoic acid) is a stereoisomer of retinoic acid. It is known to bind to CRABP intracellularly and to bind all RAR subtypes directly. However, some debate exists regarding whether its topical effect is, in some part, caused by conversion to tretinoin in vivo. 95

**Clinical Evidence**

The clinical evidence of the effect of isotretinoin on photoaging is less than that of tretinoin but is nonetheless substantial. In 1990, Cunningham 96 was the first to show clinical improvement (decreased mottled pigmentation and fine wrinkles) in photoaged skin with the use of topical 0.1% isotretinoin cream (Level II evidence). Since that time, three groups have performed large (n = 326, n = 776, and n = 800) double-blind, vehicle-controlled, randomized trials using 0.1% cream for 9 months. 97−99 All study participants achieved statistically significant clinical improvement in wrinkling pigmentation, sallowness, and texture compared with controls starting at 12 weeks (Level I evidence) (P < 0.05 through < 0.01). Maddin et al. 99 additionally demonstrated histological improvement in epidermal thickness. However, no substantial changes were found in the dermis in terms of elastosis reduction or fibroblast density. It should be noted that the study’s duration was only 9 months; thus, long-term dermal effects are unknown. Side effects were local and severe in only 5% to 10%. Plasma concentration of isotretinoin was not increased during the 36-week study period.

Alirezai et al. 100 studied the effect of twice daily 0.1% isotretinoin cream on actinic keratoses. In a vehicle-controlled study, two-thirds of the patients were found to have a greater than 33% reduction in precancerous growths in 6 months (Level II evidence).

More recently, oral isotretinoin therapy has been investigated for efficacy in the treatment of photoaging. Hernandez-Perez et al. 101 randomized 60 women to facial rejuvenative procedures only, orally administered isotretinoin (10 mg thrice weekly) with rejuvenative procedures, or orally administered isotretinoin (20 mg thrice weekly) with rejuvenative procedures. The authors found significant observational improvement in wrinkles, skin tone, and pigmentation in the isotretinoin groups when compared with controls (Level II evidence) (P < 0.01). Kalil et al. 102 conducted a similar study using 20-mg doses during 3 months in an open, noncontrolled study. Clinical and histological improvements were “optimal” in two-thirds of the study participants (Level II evidence). However, Begatin et al. 103 called these results into question with their 2010 Phase II trial on oral isotretinoin for facial photoaging. The authors conducted a controlled trial of 32 women randomized to sunscreen and moisturizer only or to 20 mg of isotretinoin administered orally three times a week plus sunscreen and moisturizer. The group receiving isotretinoin was found to have no clinical benefit shown by profilometry, corneometry, or skin elasticity tests or by histological examination (Level II evidence). Regardless of the notable side effect and safety concerns associated with oral isotretinoin therapy, current evidence is discouraging for the efficacy of oral isotretinoin for treatment of facial aging.

Alitretinoin (9-cis Retinoic Acid)

**Molecular and Histological Evidence**

Alitretinoin is a naturally occurring retinoid that binds and activates all known RAR and RXR subtypes.
Clinical Evidence

Although well studied for beneficial effects on Kaposi sarcoma and chronic hand dermatitis, only one small trial has been conducted to elucidate the effect of alitretinoin on aging skin. In 2005, an open pilot study that included 20 patients with photoaged skin was conducted using 0.1% topical alitretinoin. Seborrheic keratoses, actinic keratoses, and other signs of photoaging improved and the treatment was well tolerated (Level IV evidence).\textsuperscript{104}

Retinol (Vitamin A)

Molecular and Histological Evidence

Retinol is commonly used as a component in cosmeceutical products. According to Han et al.,\textsuperscript{105} the potential of retinol in the treatment of antiaging was realized in 1995 when its ability to induce epidermal thickening with little irritation was shown. The induction occurred mostly because of its hydroxyl end group drastically reducing the retinoid reaction observed with retinoic acid’s carboxyl end group. Unfortunately, retinol is very unstable in light, oxygen, heat, lipid peroxidation, and water, which limits its bioavailability. Furthermore, retinol must be converted to tretinoin in vivo to become biologically active.\textsuperscript{106} From these shortcomings, it has been speculated that retinol is 20-fold less effective than tretinoin, and the dermal concentration of tretinoin is anecdotally considered to be 1000-fold less than that used when topically applying the proper drug.\textsuperscript{107} Some have hypothesized that if retinol were applied at concentrations high enough to have similar effects as tretinoin, the side effect profile would be similar. Despite the shortcomings of retinol, substantial retinoid-mediated changes have been documented, including inhibition of UV induction of MMP, stimulation of collagen synthesis, increase in GAG production, epidermal thickening, and wrinkle reduction.\textsuperscript{105,107}

Clinical Evidence

To date, evidence of the use of retinol to improve photoaged skin is limited to small controlled trials of limited duration. Pierard-Franchimont et al.\textsuperscript{108} conducted the first controlled clinical trial with retinol and reported significant improvement in fine wrinkles after 12 weeks of treatment (Level II evidence) ($P < 0.05$). Varani et al.\textsuperscript{109} studied the effects of 1% retinol on 53 patients with photoaged skin compared with a vehicle control. The authors found statistically significant histological improvement in 7 days (Level II evidence) ($P = 0.009$). Kafi et al.\textsuperscript{110} conducted a randomized, double-blind, vehicle-controlled study of 0.4% retinol applied to the upper arm skin of 23 patients. The authors found subjective fine wrinkle and histological improvements (Level II evidence). It should be noted that the commonly researched retinol concentrations range from 0.4% to 1%, compared with 0.08% or less for the average over-the-counter products.\textsuperscript{111}

Similar positive but poor quality evidence for the use of retinol comes from combination therapy studies. Retinol (0.4%) and Vitamin C (3.5%) were applied topically twice daily to the photoaged arm skin of eight volunteers in a double-blind, vehicle-controlled study. The authors found histological evidence of decreased elastosis and a thickened grenz layer with little epidermal effect.\textsuperscript{112} Dralezos\textsuperscript{113} conducted a trial of retinol (0.3%) and hydroquinone (4%) compared with 0.05% tretinoin. The tretinoin group was found to be inferior in terms of subjective assessment of dyspigmentation, fine wrinkles, and tactile roughness at 4 months (Level II evidence).

Retinyl Esters and Derivatives

Molecular and Histological Evidence

Like retinol, its esters and derivatives must undergo in vivo conversion to the active form: tretinoin. Creation of the retinyl esters and derivatives has been stimulated by compliance, reducing side effects of tretinoin therapy and the instability of retinol.

Clinical Evidence

Retinyl propionate was the first clinically studied retinol ester. Green et al.\textsuperscript{114} were encouraged by
an animal model study and conducted a double-blind, randomized, placebo-controlled trial with 80 patients using retinyl propionate cream. Fifty-nine patients completed the 48-week study. No subjective or objective data suggested improvement compared with the vehicle control (Level II evidence).

Retinyl palmitate was studied indirectly by Watson et al. who compared commercially available skin creams, one containing retinyl palmitate (concentration of <0.2%). The authors concluded that it was unclear whether retinyl palmitate was responsible for any of the favorable histological changes that were observed (Level II evidence).

Retinyl N-formyl aspartamate is a relatively new photostable and temperature-stable retinol derivative. In a prospective trial, the faces of 24 Korean women received twice daily applications of an unknown concentration of retinyl N-formyl aspartamate on one facial half and a vehicle control on the other. Although not randomized and lacking power, statistically significant improvement in objective and subjective skin surface characteristics were observed, with only one patient reporting skin irritation (Level III evidence) \( (P < 0.001) \).

Most recently, the photostable retinyl retinoate has been investigated. Retinyl retinoate is a new synthetic retinoid that combines retinol and retinoic acid molecules with an ester bond. In a small \( (n = 46) \) randomized controlled trial, 0.06% retinyl retinoate was compared with 0.075% retinol during 3 months. Statistically significant improvement was noted in subjective and objective surface characteristics without any reported skin irritation (Level II evidence) \( (P = 0.025 \) and 0.005, respectively).

**Retinaldehyde**

*Molecular and Histological Evidence*

Retinaldehyde is the natural occurring intermediate compound formed when retinol is oxidized to tretinoin through a two-step process. Thus, as with the other retinol esters, its clinical activity depends on in vivo conversion to tretinoin. Intrinsic to the retinaldehyde molecule is an antibacterial and comedolytic effect, but this has yet to be proven in an in vivo model.118

Using histological, immunohistochemical, and electron microscopic techniques, Saurat et al.119 studied varying concentrations of retinaldehyde, retinoic acid, retinol, and altretinoin. The induction of CRABP-2 messenger ribonucleic acid and associated protein was greatest in tretinoin, with its being next greatest in retinaldehyde, altretinoin, and retinol, in rank order.119

*Clinical Evidence*

In the group of retinol esters and derivatives, retinaldehyde has the greatest amount and quality of evidence for reversal of skin aging. In a randomized controlled trial of 229 volunteers using the forearm model, morphological changes from 0.5% retinaldehyde and 0.1% tretinoin were similar (Level I evidence). Creidi et al.120 conducted a similar randomized trial that included 125 patients. The authors compared 0.05% retinaldehyde, 0.05% tretinoin, and vehicle. Retinaldehyde and tretinoin had similar improvements on profilometric scores at 18 and 44 weeks, although retinaldehyde was better tolerated throughout the study period (Level I evidence). The evidence supporting retinaldehyde for the reversal of photodamaged skin is promising, although long-term trials against tretinoin therapy still need to be conducted.

**Adapalene**

*Molecular and Histological Evidence*

Adapalene is a synthetic retinoid with selectivity for the RAR \( \beta \) and \( \gamma \) receptors. It has been shown to reverse abnormal desquamation of the skin by modulating cellular differentiation, and it has also been shown to possess anti-inflammatory properties.121
**Clinical Evidence**

Adapalene is most commonly used for acne treatment and has only recently been studied for effect on photoaged skin. Kang et al.\(^{122}\) conducted a randomized, vehicle-controlled, investigator-blinded study of 83 patients with photoaging. Adapalene gel (0.1% or 0.3%) or vehicle was applied to facial skin daily for 4 weeks and then twice daily for a total of 9 months. Subjective improvement in wrinkles, lentigines, and actinic keratoses were observed (\(P < 0.05\)). Conversely, histological specimens found no statistically significant differences among groups (Level II evidence) (\(P > 0.05\)). Too little evidence is available to make definitive conclusions, but the lack of histological changes after 9 months of therapy is discouraging.

**Tazarotene**

**Molecular and Histological Evidence**

Tazarotene is a synthetic retinoid and is pro-drug. The active form, tazarotenic acid is rapidly created in the skin. Thereafter, tazarotenic acid selectively binds to RAR \(\beta\) and \(\gamma\) receptors. Histological evidence of photoaging reversal shows no statistical difference compared with that of 0.05% tretinoin in terms of improved cell proliferation, differentiation, epidermal polarity, epidermal thickness, mottled hyperpigmentation, new collagen formation, and decreased dermal elastosis.\(^{123,124}\)

**Clinical Evidence**

Also effective in treating psoriasis and acne, tazarotene has shown substantial ability to reverse photodamaged skin. The landmark study was performed by Kang et al.\(^{125}\) in 2001. In a multicenter study, 349 study participants with photoaged skin were randomized to varying concentrations of tazarotene (0.01%, 0.025%, 0.05%, and 0.1%), 0.05% tretinoin, or vehicle. Clinical improvement in terms of epidermal thickness, fine wrinkling, lentigines, elastosis, and mottled hyperpigmentation were similar between the 0.1% tazarotene and 0.05% tretinoin groups at 24 weeks. However, 0.1% tazarotene showed a greater degree of improvement at 12 and 20 weeks compared with the tretinoin group (Level I evidence). Lowe et al.\(^{126}\) confirmed the findings of this study (faster onset, but similar result at 24 weeks) in a randomized, multicenter trial of 0.1% tazarotene and 0.05% tretinoin in 153 patients (Level I evidence).

Phillips et al.\(^{127}\) studied the long-term effect of tazarotene treatment with a vehicle-controlled, multicenter, double-blinded, randomized trial of 563 patients. Tazarotene 0.1% cream was applied blindly for 24 weeks and then unblinded during a 28-week extension. Continued improvement was observed and did not plateau by 52 weeks. Irritation was mild and decreased with continued use (Level I evidence).

Since the study by Phillips et al.\(^{127}\) was published in 2002, two double-blind, randomized, vehicle-controlled trials have been conducted (\(n = 50\) and \(n = 568\)).\(^{124,128}\) Significant clinical and histological improvements were observed, with mild skin irritation (\(P < 0.01\)). Both trials showed early onset of clinical improvement, as early as 4 weeks after treatment initiation (Level I evidence).

**Seletinoid G**

Seletinoid G is the newest retinoid to show promise in reversal of skin aging. It is selective for RAR-\(\gamma\), which is the predominant epidermal receptor. To date, one Phase II trial has been conducted to assess topical effects on skin.\(^67\) In 23 patients of variable age, the effects of seletinoid G was compared with the effects of tretinoin. The histological improvements in the dermis and epidermis were very similar between the two groups, with the exception of skin irritation (Level III evidence). When applied under an occlusive dressing, seletinoid G produced no irritation and tretinoin caused severe irritation.
Complications

The most common complication and reason for noncompliance is the retinoid reaction, characterized by pruritus, burning, erythema, and peeling. The retinoid reaction occurs much more commonly in association with use of tretinoin and tazarotene because of their exposed carboxylic acid group. Accordingly, local irritation is relatively uncommon in association with use of isotretinoin, adapalene, retinol, retinaldehyde, and other synthetic derivatives.\textsuperscript{129} In the majority of cases, the retinoid reaction occurs early in treatment and gradually resolves. It was originally thought that the erythematous reaction was required and was directly related to the improvements in photoaged skin, much like topical 5-FU therapy. However, the etiology of retinoid actions on keratinocytes and other dermal cells has been found to be independent the inflammatory state.

The most important predictive feature of those likely to suffer retinoid reaction is sensitive skin. Types of sensitive skin have been outlined by Kligman\textsuperscript{130} as Fitzpatrick type 1 skin; skin with historical intolerance of other topicals (perfumes, sunscreens, or astringents); skin that blushes or feels hot after embarrassment; skin chronically exposed to large amounts of cosmetics; and skin with other dermatological disease (eczema, rosacea, or seborrheic dermatitis). Commonly used strategies to reduce the retinoid reaction are dermal moisturization (at least 30 minutes after retinoid application) and a gradual introduction to retinoid therapy (lower concentrations or less frequent application). Conversely, Kligman and colleagues\textsuperscript{89,90} promoted high-concentration retinoid treatment, which, in their experience, was associated with quicker resolution of local side effects.

Concomitant application of other medications and other naturally occurring compounds has also been advocated for reduction of local side effects. Although treating a drug side effect with another medication is less than desirable, 3\% indomethacin and/or 1\% hydrocortisone have been described to treat those who are severely affected.\textsuperscript{131} Additionally, gingko extracts, magnolia flos, \(\beta\)-glycyrrhetinic acid, scleroglucan, raspberry extract, Schisandra extract, Enna complex, Vegetol red grapevine extract, cola extract, and \(\beta\)-sitosterol might have some potential to combat local side effects.\textsuperscript{132}

The medium or vehicle with which retinoids are delivered through the epidermis has a powerful effect on the local side effects. Leyden et al.\textsuperscript{133} studied the commonly used delivery vehicles for tazarotene, adapalene, and tretinoin. The authors found microsponge gel for tretinoin, cream for tazarotene, and gel for adapalene to be the least reactive vehicles for each retinoid. More recently, liposome and nanoparticle carriers have been studied, mostly in animal models. Nanoparticle delivery systems have shown the most promise not only by decreasing local side effects but also by increasing drug efficacy.\textsuperscript{134}

Photosensitivity is the other commonly associated side effect of topical retinoid therapy. Much like the retinoid reaction, photosensitization normally occurs at the beginning of therapy and resolves after several months.\textsuperscript{131} Patients are advised to avoid excessive sun exposure and include daily sunscreen application to their skin care regimen.

Systemic side effects have not been reported during the 3 decades of topical retinoid use. Although teratogenicity of topical retinoid use has not been reported, pregnant patients should be advised to discontinue use based on lack of concrete evidence. Interestingly, one retrospective case-controlled study of 215 mothers exposed to tretinoin during the first trimester had lower rates of birth defects compared with the control group (1.9\% versus 2.6\%, respectively).\textsuperscript{135}

Summary

1. Tretinoin is the gold standard for retinoid-based skin care therapy.

2. During the first 6 months of therapy, tretinoin should be applied nightly at concentrations of at least 0.05\%.
Patients with sensitive skin should be advised to decrease frequency until tolerance of the retinoid reaction has been obtained.

3. Maintenance tretinoin therapy does not require concentrations greater than 0.25% to 0.01% applied daily or 0.5% applied three times weekly.

4. Retinoid therapy does not seem to cause permanent change. Discontinuation of use will cause regression of clinical gains.

5. Among the over-the-counter retinoids, retinaldehyde 0.05% to 0.1% is the only one with significant evidence supporting its use.

6. During the short term, tazarotene 0.1% is superior to tretinoin 0.05%, but no difference is observed at 1 year. Longer follow-up is unavailable.

7. Newer retinoids, such as seletinoid G, retinyl N-formyl aspartamate, and retinyl retinoate are showing promise via their lack of side effects, allowing for greater drug concentrations.

Hydroquinone

Hydroquinone has been the gold standard in treating disorders of hyperpigmentation. Hydroquinone inhibits the enzyme tyrosinase, blocking the conversion of dihydroxyphenylalanine to melanin. Other likely mechanisms of action include selective cytotoxicity toward melanocytes and inhibition of DNA and ribonucleic acid synthesis.

Hydroquinone can be obtained in 2% concentration over the counter and in 4% to 10% concentrations with prescription. Four percent concentration applied to the whole face twice daily is the standard for melasma and PIH treatment. When used in this manner, results can be seen at 4 months and plateaus at 6 months. Lightening of non-hyperpigmented skin will be evident; even application is therefore important. Spot treatment of acne PIH will leave the patient with characteristic “bull’s eye” or “halo” areas of discoloration.
Irritation is not uncommon with hydroquinone use. Patients should be educated to stop treatment if irritation and erythema arise, especially considering that irritation can cause further PIH.\textsuperscript{141} A rare, but serious side effect of hydroquinone use is exogenous ochronosis. Ochronosis is characterized by erythema leading to blue-black patches of discoloration. In severe cases, darkly pigmented papules and nodules can form.\textsuperscript{141} Sun exposure, prolonged use, darker skin phenotypes, and high concentrations are the main risk factors. Many experts currently advocate treatment cycles of 3 months on and 3 months off for prevention of this devastating side effect.\textsuperscript{140}

**Hydroquinone in Combination**

For melasma that is unresponsive to monotherapy, hydroquinone combined with tretinoin has been advocated. Pathak et al.\textsuperscript{142} studied multiple concentration combinations in a study group of 300 Hispanic women with melasma. The authors concluded that 2% hydroquinone and 0.05% to 0.1% tretinoin had the best results. Both tretinoin and hydroquinone are known to cause skin irritation, and, once again, patients should be informed to discontinue treatment if irritation occurs. To combat the irritating effects, the formulation known as Kligman formula, which combines 5% hydroquinone, 0.1% tretinoin, and 0.1% dexamethasone, has been used with success.\textsuperscript{143} The addition of a topical steroid adds to the bleaching effect through an unknown mechanism and blunts the irritation of the tretinoin and hydroquinone. However, prolonged use is not advisable considering the inherent side effects of topical steroid use.\textsuperscript{144} A less severe triple therapy known as Tri–Luma (Galderma USA, Fort Worth, TX) contains 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide. Tri–Luma has been shown to be effective in treating melasma and PIH.\textsuperscript{145}

**Mequinol**

Mequinol is a derivative of hydroquinone that competitively inhibits tyrosinase. It is available by prescription in 2% concentration alone and in combination with 0.01% tretinoin. One comparative study randomized patients to 4% hydroquinone or 2% mequinol and 0.01% tretinoin.\textsuperscript{146} The mequinol and tretinoin combination was found to be much less irritating to the skin and equal in depigmentation of solar lentigines compared with hydroquinone.

**Kojic Acid**

Kojic acid is another tyrosinase inhibitor. It frequently is used in cosmeceutical over-the-counter formulations in low concentration. Clinically, it is available in 1% and 4% concentrations. Lim\textsuperscript{147} found 2% kojic acid combined with hydroquinone and glycolic acid (GA) to be an effective treatment for melasma. Despite being recently banned in Japan for mutagenicity concerns, kojic acid continues to be used frequently in cosmeceutical preparations in low concentration.

**Azelaic Acid**

Azelaic acid is a naturally occurring substance created by tinea versicolor. Azelaic acid is a competitive inhibitor of tyrosinase and has an effect on DNA synthesis and mitochondrial enzymes.\textsuperscript{148} Lowe et al.\textsuperscript{149} showed that the 20% cream is effective in treating darker skin types that have PIH and melasma. Allergic reactions and skin irritations were rare. Azelaic acid has also been found to be effective in a preparation in combination with GA.\textsuperscript{150}

**Arbutin**

Arbutin is a naturally derived compound and derivative of hydroquinone. It inhibits tyrosinase and also inhibits melanocyte maturation. In a 12-week clinical trial, arbutin was found to be moderately effective in lightening solar lentigines in patients with lighter skin; however, it was much less effective on darker skin phenotypes.\textsuperscript{151} The study
also found that the response is dose dependent, but in high concentration, counterintuitive hyperpigmentation can occur.

**Niacinamide and N-Acetylglucosamine**

Niacinamide is the biologically active form of vitamin B3 (nicotinic acid). Niacinamide is thought to induce skin lightening by blocking melanosome transfer to keratinocytes.\(^\text{152}\) \(N\)-acetylglucosamine inhibits tyrosinase glycosylation, an important step in melanin production. As a monotherapy, neither niacinamide nor \(N\)-acetylglucosamine has been found to be effective in darker phenotypes. However, in combination, effective treatment of the dyschromia of aging has been achieved. In an 8-week, double-blind, randomized, split-face clinical trial, 2\% \(N\)-acetylglucosamine with 4\% niacinamide demonstrated significant improvement in facial hyperpigmentation in 29 Japanese women \((P = 0.002)\).\(^\text{153}\) Two to five percent niacinamide and 2\% \(N\)-acetylglucosamine is a common formulation in cosmeceutical products.

**Ascorbic Acid**

Ascorbic acid (vitamin C) has many actions in the skin, mainly through its role as an antioxidant. Ascorbic acid can inhibit melanin formation by reducing \(\sigma\)-quinone formation, reducing oxidized melanin (changing its color from black to tan), and preventing UV-induced free radical formation.\(^\text{154}\) During many of these steps, vitamin C works synergistically with vitamin E.\(^\text{155}\) Espinal-Perez et al.\(^\text{156}\) compared topical 5\% L-ascorbic acid with 4\% hydroquinone. Good or excellent subjective improvement was observed in 93\% of the hydroquinone group compared with only 63\% in the L-ascorbic acid group. Notably, skin irritation was experienced by 68\% of the hydroquinone group and only 6\% of the ascorbic acid group.

Because it is an antioxidant, ascorbic acid is quickly oxidized in solution. Magnesium-L-ascorbyl-2-phosphate (MAP) was synthesized to solve this problem, as skin phosphatases readily convert it to L-ascorbic acid in the dermis.\(^\text{157}\) However, MAP has difficulty penetrating the skin. In the last step in its evolution, iontophoresis was used to increase the ability of MAP to penetrate skin. In a split-face, double blind, placebo-controlled, randomized trial, iontophoresed vitamin C demonstrated significant improvement compared with controls \((P = 0.002)\).\(^\text{158}\)

**Licorice**

Flavonoids from licorice extract have shown depigmenting ability, namely glabridin, liquiritin, and licochalcone A. Of those, only liquiritin has been studied in a randomized controlled trial. In a split-face, vehicle-controlled trial, 20 women applied 2\% liquiritin cream for 4 weeks. Eighty percent of patients experienced excellent response, with nearly 75\% reduction in pigmented areas.\(^\text{159}\)

**Combination Therapies**

As previously described, hydroquinone is the gold standard monotherapy for hyperpigmentation disorders. Because of the risk of exogenous ochronosis, an alternative therapy is desirable. Two combination therapies have been found to be effective. In a split-face, blinded, 8-week trial, the combination of GA, antioxidants, and licorice root was shown to be as effective as 4\% hydroquinone.\(^\text{160}\) Additionally, a combination of kojic acid, \(\alpha\)-hydroxy acids (AHA), and emblica was as effective as 4\% hydroquinone at 12 weeks.\(^\text{161}\)

**COSMECEUTICALS**

The term *cosmeceutical* describes a topical product sold as a cosmetic product but having effects suggestive of pharmaceutical action. The FDA does not recognize any such category as cosmeceuticals. A product can be considered a cosmetic, a drug, or both. A drug is defined by the FDA as “those products that cure, treat, mitigate, or prevent disease or that affect the structure or function of the
human body.\textsuperscript{162} Although drugs are subject to an intensive review and approval process by the FDA, cosmetics are not approved by the FDA before they are available to the public. This has important implications for cosmetic products, considering the FDA review process can be very costly and time-consuming and can have devastating consequences if a product is denied approval.

**Growth Factors**

The use of growth factors, specifically TGF-\(\beta_1\), has been studied in the treatment of chronic wounds, with some success.\textsuperscript{163} The use of growth factors for skin rejuvenation is a logical next step and is a relatively new focus of research. Because of the novelty of these products and lack of regulation, little is known of their efficacy and safety profiles.

The formulations known as *Tissue Nutrient Solution (TNS) Recovery Complex* (SkinMedica, Carlsbad, CA) and *Citrix Cell Rejuvenation Serum (CRS) with Growth Factor* (Topix Pharmaceuticals, Amityville, NY) are the only peer-reviewed growth factor applications studied to date. TNS is a product containing NouriCel-MD (SkinMedica): a proprietary blend of several growth factors and cytokines, including vascular endothelial growth factor, fibroblast-derived growth factor A, granulocyte colony-stimulating factor, hepatocyte growth factor, interleukin 6, interleukin 8, and TGF-\(\beta_1\). Citrix CRS with Growth Factor contains TGF-\(\beta_1\) combined with L-ascorbic acid and *Cimicifuga ramosa* (black cohosh) extract.

TNS was invented and first reported by Fitzpatrick and Rostan.\textsuperscript{164} Fourteen healthy adults applied the product twice daily for 60 days. Subjective improvement in wrinkling was seen. Wrinkle depth was also measured by optical profilometry. Histologically, a 30\% increase in epidermal thickness, a 37\% increase in grenz zone collagen, and a decrease in elastotic material were observed. In subsequent review publications, Fitzpatrick and colleagues\textsuperscript{165,166} noted a multicenter, double-blind, vehicle-controlled, split-face study that used the TNS complex for 90 days; however, that work has not been published. The authors claimed that the research yielded similar histological and clinical results that were maintained during a 90-day follow-up period.

Ehrlich et al.\textsuperscript{167} conducted a two-armed trial of Citrix CRS with Growth Factor. In the first arm of the study, 12 patients applied Citrix with Growth Factor and Citrix alone to each facial half for 3 months. In the second arm of the study, 20 patients applied TNS Recovery Complex and Citrix CRS with Growth Factor to each facial half for 3 months. Statistically significant improvement in subjective and objective wrinkling scores for both the TNS Recovery Complex and Citrix CRS with Growth Factor were observed (versus Citrix alone and pretreatment) (\(P = 0.003\)). No difference was observed between the two growth factor products.

Atkin et al.\textsuperscript{168} conducted a 3-month, open-label, single-center study on TNS Essential Serum, which combines the above growth factors with several antioxidants and depigmenting agents. Thirty-seven patients applied the product twice daily for 3 months. Subjective improvement in fine and coarse rhytides were seen. Cutometer readings showed decreased skin extensibility and increased resiliency.

The short-term safety profile of over-the-counter topical growth factor is very good. Irritation and erythema are relatively rare occurrences.\textsuperscript{164−168} However, little is known about chronic use. A recent study on platelet-derived growth factor (PDGF) application to diabetic pressure sores has raised theoretical concern for topical growth factor application.\textsuperscript{169} In the study, patients received PDGF in dosages almost 1 million-fold higher than those described above. The PDGF was administered into tissue that had undergone débridement. Likely because of high rates of systemic absorption, the increased mortality rates occurred as a result of various malignancies that are remote to the site of treatment. However, no new malignancies arose.
Antioxidants

Topical antioxidants are a class of cosmeceutical products that contain botanicals, vitamins, and essential minerals. In concept, the ability of these products to quench free radicals will protect cells from continued damage and allow self-repair. There are several ways to quantitate the ability of a particular substance to quench free radicals. The oxygen radical absorption capacity (ORAC) assay is the best in vitro test. ORAC defines the ability of a molecule to absorb ROS. The sunburn cell assay is most commonly used in in vivo testing. Conducted in the same manner as SPF testing, the sunburn cell assay quantifies the ability of the product to protect the skin from sunburn.

Vitamins and Essential Minerals

Vitamin C

L-ascorbic acid (vitamin C) is one of the main antioxidants in the body. Topical L-ascorbic acid has been shown to increase native antioxidant capabilities by reducing erythema and sunburn cell formation in a porcine skin model. In addition to its antioxidant role, L-ascorbic acid has a role in many other cellular functions, namely: cofactor for collagen synthesis, transcriptional regulator for collagen synthesis, inhibition of elastic synthesis, inhibitor of melanin production, stimulator of sphingolipid production (improves epidermal barrier function), and maintenance of the function of vitamin E.

Through its many roles described above, topical vitamin C has been shown to be clinically effective in several small randomized trials. Traikovich performed a split-face, randomized trial of 10% ascorbic acid versus vehicle applied to the faces of 19 patients. Substantial improvements in wrinkling, roughness, course rhytides, laxity, and sallowness were indicated by clinical and subjective scores. Humbert et al. reported the ability of 5% ascorbic acid to clinically improve photoaged skin and wrinkling after 6 months of application. Another double-blind study with 10 patients showed significant improvement in photoaging scores after 3 months of application of 10% ascorbic acid (P = 0.01).

The main limitation of the use of topical vitamin C is delivery. Pinnell et al. noted that delivery of L-ascorbic acid into skin depends on protonation of the charged molecule, which occurs at a pH value of less than 3.5. To avoid this acidic preparation and increase bioavailability, ascorbic acid derivatives were created: magnesium ascorbyl phosphate, ascorbyl-6-palmitate, and dehydroascorbic acid. These derivatives then rely on in vivo mechanisms to revert back to the active form, L-ascorbic acid. However, Pinnell et al. showed that L-ascorbic acid levels in the skin are not increased with topical application. Despite the lack of evidence-based support, form stable ascorbic acid derivatives continue to be included in a wide array of cosmeceutical applications.

Vitamin E

Vitamin E has eight naturally occurring forms: four tocopherols and four tocotrienols. Alpha-tocopherol is the most active and most important in protecting the viability of the cell membrane. In this section, vitamin E refers to alpha-tocopherol. Vitamin E is incorporated into cell membranes to prevent lipid peroxidation. Vitamin E also functions directly by quenching singlet oxygen and superoxide anions. Oral supplementation and topical application of vitamin E have been shown to increase dermal concentrations. However, no in vitro benefit has been observed with increased dermal vitamin E levels alone. When vitamins E and C are supplemented, orally or topically, a significant increase in the MED, cytokine production, thymine dimer formation, and p53 upregulation occurs (P < 0.04 and P < 0.02, respectively).

Topically applied concentrations of alpha-tocopherol ranging from 0.2% to 1% in
combination with ascorbic acid will likely be effective in improving antioxidant protection of the skin barrier. What this antioxidant effect means for reversal or prevention of photoaged skin has yet to be elucidated.

Selenium—Selenium acts as a cofactor for vitamin E regeneration through glutathione peroxidase and thioredoxin reductase. Selenium deficiency can mimic vitamin E deficiency. In animal studies, oral selenium supplementation has been shown to be protective against UV-induced cytotoxicity, DNA oxidation, DNA damage, and lipid peroxidation. In human trials, topical L-selenomethionine increased the MED in a dose-responsive manner.

Botanicals
Botanicals constitute a large and growing percentage of cosmeceutical products. To date, there are no double-blind, placebo-controlled, human studies defending the inclusion of botanicals in topical formulations. Again, the lack of data could be related to FDA-avoidant behavior (e.g., companies are content with marketing and selling the products as cosmetics and not as drugs). Commonly used antioxidant ingredients include açai berry extract, α-lipoic acid, coffee berry (ferulic acid), curcumin, ginkgo, grape seed, licorice extract (also discussed in depigmenting agent section), pomegranate, pine bark extract, silymarin, soy isoflavones, and tea polyphenols.

H Y D R O X Y A C I D S

Hydroxy acids are a group of relatively weak acids used in many cosmeceutical products. AHA are group of organic acids with a hydroxyl group in the α position. The group is composed of many acids, but lactic acid and GA are the most commonly used and studied. β-Hydroxy acids are composed of salicylic acid and its derivatives (i.e., C8-lipoxyhydroxy acid [C8-LHA]).

The method of action for these acids is not yet completely understood but likely involves direct and indirect effects. The direct action is breaking the desmosomes in the outer stratum corneum. Breaking desmosomes directly results in “peeling” of the outermost layers and, in turn, indirectly stimulates increased epidermal cell division. The compaction and increased turn over the epidermal layers clinically results in smooth, flexible skin that is less prone to wrinkling and cracking. The indirect increase in epidermal cell turnover rates is different for each acid, and a rank order has been established based on a retinoic acid control: 0.05% tretinoin > 2% C8-LHA > 5% salicylic acid > 10% GA.

Hydroxy acids also cause increased dermal and epidermal collagen and base substance production. This could be because of keratinocyte released cytokines or changes in mechanical forces acting on the compact stratum corneum. Clinically, this results in thicker dermis. It is unclear which hydroxy acid (and in what concentration) has the strongest dermal effect.

In the treatment of photoaged skin, hydroxy acids have effects that are similar to, but less potent than, those of tretinoin. In randomized controlled trials, AHA have shown the ability to decrease epidermal atypia, induce epidermal hyperplasia, disperse melanosomes, and increase elastin fiber thickness. The trials included 8% GA and 8% lactic acid for 6 months, 5% GA for 3 months, and short duration 50% GA cream for 4 weeks.

AHA have other documented benefits, including improving barrier function, enhancing the effect of tretinoin, and improving the effect of hydroquinone when treating dyschromia of photoaging. The side effects of AHA are local irritation, although rare at concentrations below 10%, and increased UV sensitivity, especially with GA. Salicylic acid at concentrations of 3% or less and C8-LHA are not photosensitizers nor do they induce much skin irritation.
PEPTIDES
Cosmeceutical peptides are a group of small sequence amino acid chains designed to improve the signs of skin aging. By their method of action, this group can be subdivided into three subgroups: signal peptides, carrier peptides, and neurotransmitter peptides. Signal peptides directly stimulate fibroblasts to increase collagen and ground substance production while inhibiting collagenase function and production. Carrier peptides, like the name implies, are designed to deliver essential cofactors for dermal homeostasis through the epidermis. Neurotransmitter peptides inhibit muscle contraction by blocking neuromuscular signaling, similar to botulinum neurotoxin.

Carrier Peptides
The tripeptide glycyl-L-histidyl-L-lysine (GHK) spontaneously binds copper and facilitates copper uptake by cells. To date, it is the only carrier peptide with in vitro and in vivo evidence for reversal of skin aging. Copper downregulates MMP, reduces the activity of collagenase, increases GAG production, and is an essential cofactor for collagen and elastin production. GHK is found on the α chain of procollagen and directly stimulates fibroblast activity alone (see the next section on Signal Peptides).

Abdulghani et al. performed a small clinical trial comparing the effects of topical vitamin C, a naturally occurring copper complex of GHK (GHK-Cu), and tretinoin. After 1 month of anterior thigh application, GHK-Cu was associated with the most consistent procollagen formation.

Leyden et al. conducted a 12-week facial study of GHK-Cu-containing face and eye creams. Subjective improvement in skin laxity, clarity, and appearance; reduced fine lines; and depths of wrinkles were noted compared with placebo and vitamin K cream. However, although this study was presented to the American Academy of Dermatology, it has not been published in the peer-reviewed literature.

Signal Peptides
As previously mentioned, GHK also has qualities of a signaling peptide. A study of cultured fibroblasts showed that GHK without copper stimulates collagen production. Marketed as Biopeptide CL (Sederma, Paris, France), GHK is combined with palmitic acid to better penetrate the epidermis. Various non-peer-reviewed in vitro and in vivo studies by Sederma claimed collagen production, GAG synthesis, and wrinkle reduction.

Palmitoyl oligopeptide is a common component of many cosmeceutical products. This peptide is a derivative of elastin and has been shown to increase fibroblast production, downregulate elastin production, and chemotactically attract fibroblast migration in the in vitro setting.

The best clinical data for skin rejuvenation exists for Matrixyl (Sederma). Matrixyl is a combination of palmitic acid and a type 1 procollagen derivative: lysine-threonine-threonine-lysine-serine (KTTKS). Robinson et al. conducted a 12-week, double-blind, placebo-controlled, split-face trial with 93 Caucasian women as study participants. Palmitoyl-KTTKS was shown to achieve subjective and objective improvement in wrinkle reduction.

Neurotransmitter Peptides
Topical neurotransmitter-affecting peptides aim to raise the threshold for muscle contraction. Thus, more signal is required for movement, theoretically reducing subconscious muscle movement. Although promising, it has yet to be proven whether topically applied peptides can effectively reach the neuromuscular junction. There are several commercially available neurotransmitter peptides with little if any peer-reviewed clinical evidence. Pentapeptide-3, marketed as Vialox (Cellular Skin Rx, Alameda, CA), is a competitive antagonist for the postsynaptic acetylcholine receptor-like curare. Leuphasyl (The Lubruzol Corporation, Wickliffe, OH) is proposed to modulate calcium channels. Tripeptide-3, marketed as Syn-Ake (The Lubruzol Corporation), acts similarly to temple viper...
venom, reversibly antagonizing the postsynaptic acetylcholine receptors. Actyl hexapeptide-3, marketed as Argireline (Lipotech, Barcelona, Spain), works similarly to botulinum neurotoxin by preventing vesicle docking in the presynaptic neuron. In vivo and in vitro clinical studies for all exist on the companies’ web sites, purportedly showing decreasing muscle function and reducing wrinkle depth.

PROBIOTICS AND PREBIOTICS

Probiotics and prebiotics are relatively new classes of cosmeceutical products. Originally designed and used for changing or maintaining the microbial homeostasis in the intestinal and urogenital tracts, applications have now been established for the microbiota of the skin. Probiotics have been defined by the World Health Organization as, “Live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Prebiotics are feed supplements that beneficially affect the host by improving or normalizing the microbial environment. The normal microbiota of the skin are likely involved in the competitive exclusion of pathogens. It is unclear whether the normal microbiota of the skin have additional benefits (e.g., the release of cytokines or other cell signaling molecules). Additionally, little to no peer-reviewed evidence supports their use in topical skin care lines.

SURGICAL AND RESURFACING WOUND HEALING

Chronic and Surgical Wounds

Vitamin A has a well-known role in wound healing. Because of toxicity of excessive vitamin A oral supplementation, topical treatment with its derivatives is a logical step. To date, two human studies have been conducted and the results have been encouraging. Tom et al. randomized 24 diabetic lower extremity wounds to 0.05% tretinoin solution or vehicle control for 4 weeks. Statistically significant healing was observed in the tretinoin group ($P < 0.02$). Similarly, Paquette et al. reported a 0.05% retinoic acid solution that promoted healing of venous stasis ulcers.

Pretreatment with tretinoin has also been shown to promote healing of surgically created wounds. Popp et al. pretreated photodamaged forearm skin with 0.05% to 0.1% tretinoin or vehicle control for 4 months. Subsequent 4-mm punch biopsy wounds were 50% smaller in diameter in the pretreatment group at 1 week compared with the control group.

Skin Resurfacing

The skin is commonly preconditioned before undergoing resurfacing procedures. The aim of preconditioning is to enhance wound healing, regulate pigmentation, and create consistent epidermal thickness for even penetration of chemical peeling solutions. The life cycle for a basal layer keratinocyte to reach the stratum corneum is 6 weeks. Therefore, preconditioning should be at least 6 weeks in duration and longer for darker skin types. The usual topical regimen during this preconditioning period includes tretinoin (0.5–1% nightly), hydroquinone 4% (twice daily) and a topical AHA for thick or sebaceous skin. The evidence, or lack thereof, for the dogmatic regimen is reviewed.

Chemical Peel

In a randomized controlled trial, Hevia et al. studied pretreatment with 0.1% tretinoin cream 2 weeks before a 35% trichloroacetic acid peel of the arms and face. Tretinoin sites displayed earlier, more intense, and uniform frosting because of the compacted stratum corneum. Additionally, the pretreated group had a statistically significant increase in the area of re-epithelialized skin after 1 week ($P < 0.05$).
**Dermabrasion**

Mandy\textsuperscript{220} studied pretreatment with 0.5% tretinoin cream for 2 weeks before full- or half-face dermabrasion for acne scarring. Compared with the control group, pretreated faces completely re-epithelialized 2 days earlier. Additionally, pretreated patients suffered less PIH and had no milia formation.

**Laser Resurfacing**

Encouraged by the results from pretreating patients before chemical peels and microdermabrasion, animal studies were performed to evaluate the role of retinoid pre-CO\textsubscript{2} laser resurfacing. Using a guinea pig model, McDonald et al.\textsuperscript{221} achieved faster re-epithelialization and more rapid healing. Theoretically, retinoid pretreatment would decrease postoperative milia, decrease postoperative hyperpigmentation, and increase laser penetration through the thinner stratum corneum.\textsuperscript{221} These beliefs were so well accepted that a survey of the American Society for Laser Medicine and Surgery showed that 80% of dermatologists and plastic surgeons recommended treatment with retinoids before CO\textsubscript{2} laser resurfacing.\textsuperscript{222}

In 2004, Orringer et al.\textsuperscript{223} challenged these widely held beliefs. They studied CO\textsubscript{2} resurfacing for photodamaged forearm skin after 3 weeks of pretreatment with 0.05% tretinoin cream or vehicle control. No benefit was found histologically or in terms of re-epithelialization. Around the same time, West and Alster\textsuperscript{224} randomized patients to topical GA, 0.25% tretinoin and 4% hydroquinone, or placebo for 2 weeks. None of the pretreatments substantially affected the rates of post-CO\textsubscript{2} laser hyperpigmentation. These results are not without a logical explanation. At 2 or 3 weeks, retinoids are known only to affect the epidermis, especially at a relatively low dose. The epidermis is completely removed with ablative CO\textsubscript{2} resurfacing, along with all the pretreatment benefits. Based on this understanding, retinoid pretreatment might prove more advantageous with erbium lasers, fractionated resurfacing, or increased pretreatment duration.
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growth factor beta 1 and in the appearance of wrinkles with topical transforming factors. 


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