

# The Mechanism of Action of Topical Retinoids for the Treatment of Nonmalignant Photodamage, Part 1

Patricia K. Farris, MD; Marta I. Rendon, MD

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Photodamage or photoaging refers to the skin changes that are induced by cumulative exposure to UV radiation and are superimposed on the signs of chronologic aging. Histologically, photoaged skin is characterized by keratinocyte atypia, a loss of polarity (orderly maturation of skin layers), degeneration of collagen, and deposition of abnormal elastotic material. These changes can be attributed to the effects of chronic exposure to UVA, including reduction in the amount of type I collagen in the skin, induction of a low-grade inflammatory response and the enzymes responsible for matrix degradation, and impairment of barrier function.

The 2 main categories of treatment for photodamage include topical agents and resurfacing procedures. The latter includes chemical peels, dermabrasion, and laser resurfacing, all of which can produce rapid results but are also associated with patient downtime, risk for complications, and significant cost. Topical therapies are simple to use but require good adherence to treatment for some months before measurable improvement is seen.

Of all topical therapies available to date, the retinoids, and in particular tretinoin at concentrations of 0.02% or higher, can be prescribed with the most confidence, as the clinical evidence underpinning their use far outweighs that available for other compounds such as antioxidants and  $\alpha$ -hydroxy acids. Retinoid therapy has consistently been shown to attenuate and reverse the signs of photodamage, including coarse wrinkling, in controlled trials. The mechanisms of action of retinoids in the attenuation of photodamage include inhibition of the UV-induced upregulation of matrix metalloproteinases, increased production of type I collagen, increased epidermal proliferation and epidermal thickening, compaction of the stratum corneum, and the deposition of glycosaminoglycans.

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*Dr. Farris is Clinical Assistant Professor, Tulane University School of Medicine, New Orleans, Louisiana. Dr. Rendon is dermatologist, private practice, The Dermatology and Aesthetic Center, Boca Raton, Florida, and Clinical Associate Professor, Department of Biomedical Sciences, Florida Atlantic University, Boca Raton.*

*Dr. Farris is on the advisory board of Neutrogena Corporation, is a consultant for Ortho Dermatologics, and is a spokesperson for Guthy-Renker. Dr. Rendon is an advisor, researcher, and speaker for Johnson & Johnson Services, Inc.*

*Correspondence: Patricia K. Farris, MD, 701 Metairie Rd, Ste 2A205, Metairie, LA, 70005; Marta I. Rendon, MD, The Dermatology and Aesthetics Center, 880 NW 13th St, Boca Raton, FL, 33486.*

**P**hotodamage (dermatoheliosis) is the term used to describe the alterations in the structure, function, and appearance of the skin that result from prolonged or repeated excessive exposure to UV radiation from the sun or other sources. Photodamage is also referred to as photoaging or extrinsic aging and is seen on sun-exposed areas of the body. Conversely, intrinsic or chronologic aging of the skin is a normal part of the aging process and is seen regardless of sun or other environmental exposure.

Although photodamage should ideally be prevented through photoprotection, excessive exposure to UV radiation is difficult to avoid consistently, particularly for persons involved in outdoor occupations and activities. Concerns about the effects of aging in general are also becoming increasingly prevalent, particularly in societies where aging populations are growing and the maintenance of a youthful appearance is deemed important. Moreover, in some instances, concerns over appearance can lead to difficulties with self-esteem, relationships, and employment opportunities.<sup>1</sup> Skin aging and photodamage have in the past been thought to be irreversible, but clinical experience has indicated that this is not necessarily so. It is now widely recognized that various topical therapies used in combination with in-office procedures can alleviate age-related and sun-related skin damage.

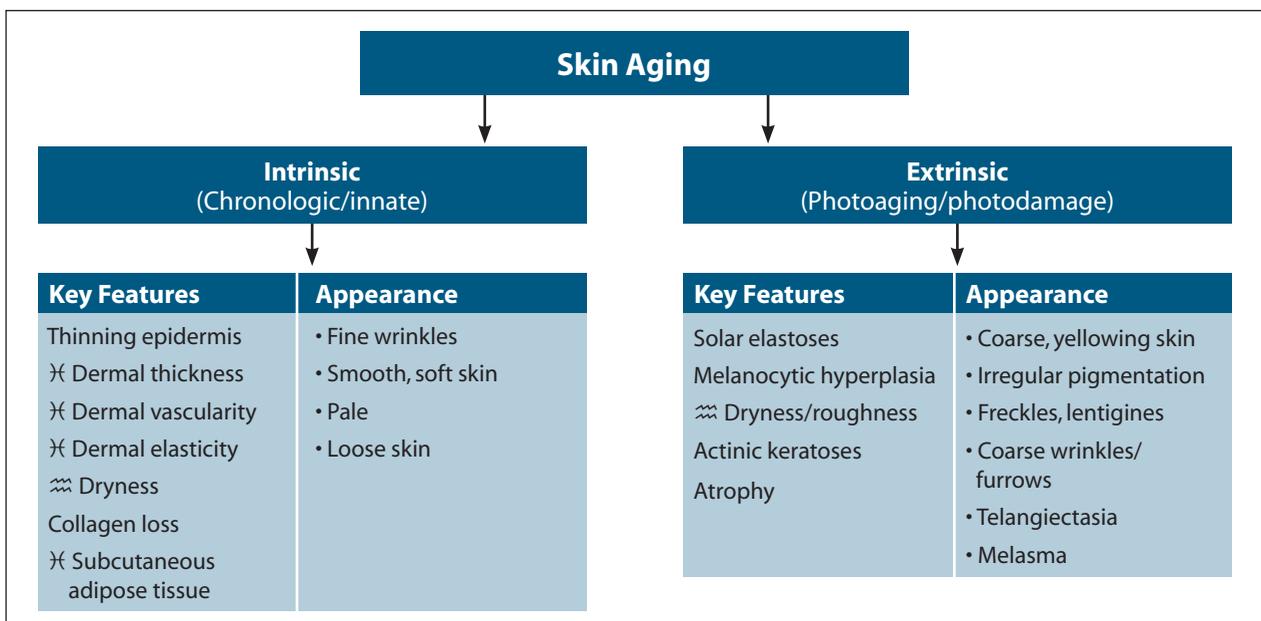
This article examines the use of topical retinoids in the treatment of photodamage during routine clinical practice, using an illustrative case study, and describes the mechanism of action of these agents in the context of the pathophysiology of photodamage.

**WHAT IS PHOTODAMAGE?**

The characteristics of photoaged skin may include irregular pigmentation, deep wrinkles, roughness or dryness, actinic (solar) keratoses, elastoses, telangiectasia (most commonly on the nose and cheeks), and atrophy (Figure 1).<sup>2-4</sup> Histologically, photoaged skin is characterized by keratinocyte atypia, a loss of polarity (orderly maturation of skin layers), degeneration of collagen, and deposition of abnormal elastotic material.<sup>2,5</sup> Eventually, in severe cases, there is a large quantity of degraded, tangled, and thickened elastic fibers.<sup>5</sup> In severe photodamage, there are changes to the thickness of the epidermis; thickening and thinning may occur simultaneously corresponding to areas of hyperplasia and atrophy, respectively.<sup>2,5</sup> Vessels in the microcirculation twist and dilate and eventually become sparse in number.<sup>5</sup>

In contrast, intrinsically aged skin is characterized by inelasticity, atrophy, fragility, and fine wrinkling (Figure 1).<sup>2,4,5</sup> Benign growths such as cherry hemangiomas and seborrheic keratoses may also be present.<sup>2</sup> Histologically, thinning of the epidermis with flattening of the dermoepidermal junction and a marked decrease in dermal thickness and vascularity are observed.<sup>5,6</sup> The number of fibroblasts decreases, and those present have a reduced capacity for collagen production, which leads to delayed wound healing.<sup>2,4</sup> There is also loss of dermal elastic fibers (Figure 1).<sup>6</sup>

The irregular pigmentation that is characteristic of photoaging is caused by reactive hyperplasia of melanocytes and includes signs such as freckles and lentigines.<sup>2</sup> Melanocytes are found in sun-exposed skin with a density



**Figure 1.** Intrinsic and extrinsic skin aging.

twice that observed in nonexposed areas.<sup>7</sup> Skin coarsening and yellow discoloration with degeneration of collagen and abnormal deposition of elastotic material (solar elastosis) are key features of photodamage and are most often observed as a copper-beaten appearance over the temples of fair skinned persons.<sup>2</sup> The coarse wrinkles of photoaging are easily distinguished from the fine wrinkles of intrinsic aging by stretching the skin between 2 fingers: fine wrinkles will smooth out completely, whereas coarse wrinkles will not.<sup>2</sup>

Although the effects of photodamage are manifested to a greater extent in white individuals than in darker skins, more darkly pigmented individuals also experience photodamage, albeit of lower severity.<sup>3</sup> Asian patients develop wrinkles less commonly<sup>3</sup> but often display the photoaggravated pigmentation disorder melasma, which is characterized by the appearance of discrete hyperpigmented lesions.<sup>2</sup>

### MECHANISMS OF PHOTODAMAGE: UVA, UVB, AND FREE RADICALS

The most important causal factor in extrinsic aging is exposure to UV radiation. Both UVB (290–320 nm) and UVA (320–400 nm) are responsible.<sup>8</sup> Of the two, UVB is the most acutely damaging, inducing changes predominantly at the epidermal level that include erythema, sunburn, DNA damage, and, ultimately, premalignant and malignant changes such as actinic keratoses, lentigines, carcinomas, and melanomas.<sup>4</sup> UVA penetrates more deeply into the dermis, does not show seasonal variation in sunlight, and is generally considered to be a major contributor to photoaging. Chronic UVA exposure causes marked collagen damage and moderate elastosis in animal models.<sup>9</sup> The effects of UVA on collagen include reduction in the amount of type I collagen in the skin and induction of the enzymes responsible for matrix degradation.<sup>10</sup> In addition, even relatively short but regular exposures can induce a low-grade dermal inflammatory response,<sup>11</sup> thereby contributing to long-term damage to the skin and photoaging. There is also evidence that skin-barrier function is negatively affected, with a change to epidermal lipid content and an increase in permeability.<sup>12</sup>

The precise mechanisms behind the damage invoked by UV exposure are not fully understood, but UV radiation increases the production of matrix metalloproteinases (MMPs), the enzymes that break down collagen. UV light also reduces collagen production, thus resulting in a net decrease in dermal collagen.<sup>13</sup> Even at levels of UV radiation that do not cause sunburn, the expression of MMPs is induced in keratinocytes and fibroblasts, leading to collagen degradation in the dermal matrix. The activity

of the MMPs is partially attenuated by endogenous inhibitors, which limit the extent of the damage. In the aftermath of the collagen breakdown, during synthesis and repair, subtle and undetectable defects can develop in the organization and composition of the matrix. Eventually, successive events of damage followed by imperfect repair accumulate, resulting in observable signs of photodamage such as wrinkles.<sup>13</sup>

Exposure to UVB accelerates MMP activity within minutes.<sup>14</sup> UVA exposure, on the other hand, can generate reactive oxygen species that affect lipid peroxidation and may generate DNA strand breaks.<sup>15</sup> UV exposure may also have harmful angiogenic effects over the long term,<sup>16</sup> and blood vessels in severely photodamaged skin are dilated and twisted.<sup>17</sup>

The idea that aging results from reactions induced by free radicals was proposed by Harman<sup>18</sup> in 1956 when he suggested that organisms age because of the accumulation of free radical damage (which is closely associated in biological systems with oxidative damage) over time. This process is referred to as the free radical theory of aging. Both chronologic aging and photoaging are associated with excessive free radical production, which, when left unchecked, can damage cell membranes and potentially DNA.<sup>15</sup>

### TREATMENT OPTIONS

The adage “prevention is better than cure” is particularly true for skin photodamage, and sun avoidance and use of effective protection (eg, good clothing and sunscreen) are important measures. Current sun safety tips are exemplified by the recommendations of the American Academy of Dermatology, which encourage reduction of outdoor exposure or use of shade, especially during the hours of peak daytime sunshine, and the use of appropriate hats and clothing together with regular use of sunscreens containing both UVA-blocking and UVB-blocking agents.<sup>19</sup>

Options for the reduction of photodamage can be divided into 2 categories: topical treatments and facial rejuvenation or resurfacing procedures (Table).<sup>2,17</sup> Topical therapies are easy to use, noninvasive, readily available, and relatively inexpensive. Current options include over-the-counter cosmeceuticals and prescription retinoids. Cosmeceuticals contain a variety of actives, including  $\alpha$ -hydroxy acids, vitamins and botanical antioxidants, growth factors, and peptides. Although cosmeceuticals are readily available to consumers without a prescription, there is little scientific evidence to support the use of these products in many cases.<sup>20</sup> In contrast, the efficacy of prescription retinoids for treating the signs of photoaging has been confirmed by rigorous scientific studies and multiple clinical trials.

Disadvantages of topical treatments (prescription or nonprescription) include: (1) delay of up to some months before measurable improvements can be noted, (2) the need for very high levels of adherence to maintain improvement, and (3) the potential for problems caused by contact irritancy or hypersensitivity.<sup>2</sup>

In-office treatments for facial rejuvenation include laser resurfacing, intense pulsed light treatments, and chemical peels that are often used in combination with injectables such as botulinum toxin type A, abo botulinum toxin A, and facial fillers (Table).<sup>2</sup> This combination approach improves skin's appearance and facial contour, resulting

in an overall rejuvenated look. This type of nonsurgical facial rejuvenation yields best results when effective topical therapy is included as part of the overall skin care regimen.<sup>21</sup> Of all topical agents currently marketed, the retinoids have been the most consistently effective in clinical studies. This has been clearly demonstrated most recently by a comprehensive meta-analysis of 30 studies comparing a variety of topical and other interventions.<sup>3</sup> In this analysis, the weight of evidence was far greater for tretinoin at concentrations of 0.02% or 0.05% than for isotretinoin or tazarotene.<sup>3</sup> In the United States, tretinoin 0.02% cream is the only tretinoin formulation approved for use in the mitigation of fine wrinkles associated with photodamage on the basis of significant benefit in randomized, double-blind, placebo-controlled trials.<sup>22</sup>

### Treatment Options for Photoaging<sup>2,17</sup>

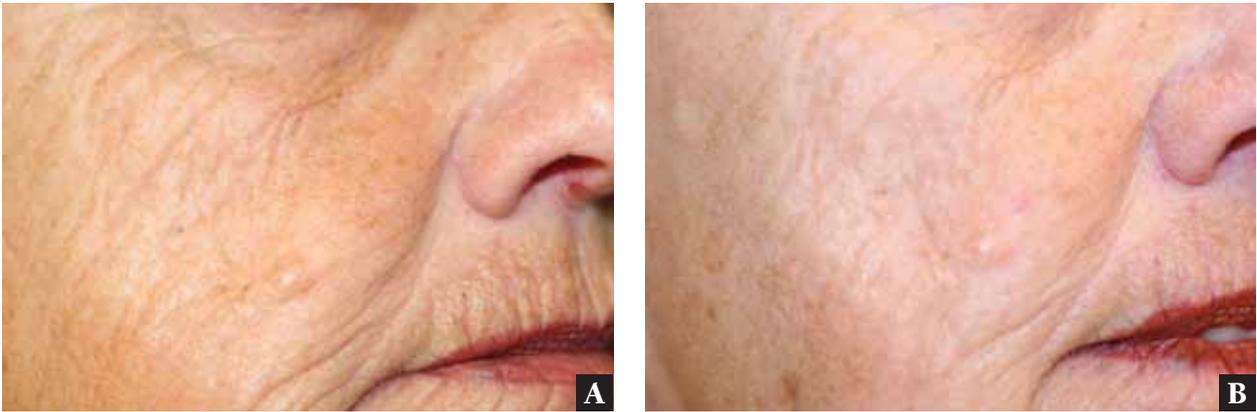
| Type                                  | Agents/Procedures   |
|---------------------------------------|---|
| Topical therapies                     | α-Hydroxy acids   |
|                                       | • Glycolic acid   |
|                                       | • Lactic acid   |
|                                       | • Malic acid  |
|                                       | Antioxidants  |
|                                       | • Vitamin C   |
|                                       | • Vitamin E   |
|                                       | Retinoids   |
|                                       | • Isotretinoin  |
|                                       | • Retinaldehyde   |
| • Tazarotene                          |   |
| • Tretinoin                           |   |
| Injectable facial rejuvenation agents | Botulinum toxin   |
|                                       | Soft tissue augmentation  |
|                                       | • Autologous fat  |
|                                       | • Calcium hydroxylapatite   |
|                                       | • Collagen  |
|                                       | • Hyaluronic acid   |
| • Poly-L-lactic acid                  |   |
| Resurfacing                           | Chemical peels  |
|                                       | • Combinations (trichloroacetic acid + Jessner solution, trichloroacetic acid + glycolic acid, trichloroacetic acid + solid CO <sub>2</sub> ) |
|                                       | • Glycolic acid   |
|                                       | • Jessner solution  |
|                                       | • Phenol  |
|                                       | • Trichloroacetic acid  |
|                                       | Dermabrasion  |
|                                       | Laser resurfacing   |
|                                       | • CO <sub>2</sub> lasers  |
|                                       | • Erbium:YAG lasers   |

### CASE STUDY

The use of retinoids in clinical practice is illustrated by the following case study, typical of white women in midlife or later who seek treatment for characteristic signs of photodamage.

A 66-year-old white woman presented asking for treatment options for facial wrinkles and sun-induced skin discoloration. She had lived in the Caribbean for 9 years, where she experienced intense sun exposure while engaging in outdoor activities. The patient was an outdoor enthusiast and competitive tennis and croquet player. She was not using cosmeceutical skin care products and denied having had any cosmetic procedures in the past. As an outdoor enthusiast and sportsperson, she knew that she would not be able to stay out of the sun and felt that this would preclude use of any type of topical retinoid.

After a lengthy discussion of treatment options, the patient indicated a preference for topical treatments over in-office procedures. The benefits of topical retinoids were reviewed, and tretinoin 0.02% cream was prescribed to be used every other night for the first month, after which the dosage would be increased to every night as tolerated. She was also advised to use sun protection with broad-spectrum coverage that was to be applied every morning and reapplied every 2 hours during outdoor sporting activities. At the 1-month follow-up, the patient was tolerating the treatment well. She reported no redness or peeling and was therefore instructed to begin using tretinoin 0.02% cream each night as planned. She was seen for follow-up at 2 and 3 months (Figure 2). At the 2-month follow-up visit, the patient expressed satisfaction with the treatment and noted visible improvement in wrinkling and skin discoloration. She also reported that her skin was smoother and brighter overall.



**Figure 2.** Appearance of the skin and severity of photodamage before (A) and after 3 months of treatment with tretinoin 0.02% cream in a 66-year-old white female patient (B).

### MECHANISM OF ACTION

Although the retinoids have been in clinical use for many years, their mechanism of action in reversing the effects of photodamage is still not fully understood. These agents are known to influence a variety of processes involved in cellular growth and differentiation however, and to cause cell-surface alterations and immune changes. Many effects are believed to be modulated through interaction with cellular and nucleic acid receptors, such as cellular retinoic acid-binding protein type II,<sup>23</sup> the nuclear retinoic acid receptor family,<sup>24</sup> and the retinoid X receptors (RXR- $\alpha$ , RXR- $\beta$ , and RXR- $\gamma$ ).<sup>25</sup> The retinoic acid and RXRs and their heterodimers are present in normal skin, where they are thought to modulate the action of topically applied retinoids.<sup>17</sup>

Although the exact mechanism for how topical retinoids mitigate skin wrinkling is not fully understood,<sup>26</sup> these agents have been shown to mitigate sun-induced changes in the dermal matrix. It is thought that wrinkles arise in chronically sun-exposed skin from a reduction in collagens I, II, and VII, and of fibrillin in the papillary dermis, secondary to reduced production and increased breakdown by MMPs.<sup>26</sup> Pretreatment with topical retinoids inhibits the upregulation of MMP activity seen during exposure to UVB.<sup>14</sup> In addition, retinoids increase type I and II procollagen gene expression in photoaged skin.<sup>27</sup> This was demonstrated by Griffiths and colleagues,<sup>27</sup> who studied the effects of creams formulated with and without tretinoin 0.1% (retinoic acid) on the photodamaged forearm areas versus the sun-protected buttock areas of 29 white participants. They found that collagen I formation was reduced by 56% in photodamaged skin compared with skin protected from the sun ( $P < .001$ ) and that the extent of collagen reduction correlated with the severity of photodamage ( $r = -0.58$ ,  $P = .002$ ). In addition, treatment of photodamaged skin with tretinoin produced an 80% increase in collagen I formation, which was

contrasted with a 14% decrease in skin treated with inactive cream ( $P = .006$ ).<sup>27</sup> This retinoid effect is presumed to be due to an upregulation of transforming growth factor  $\beta$ .<sup>28</sup>

Skin smoothing, the first sign of improvement during topical retinoid administration, is seen within the first month and is probably attributable to increased epidermal proliferation and epidermal thickening, compaction of the stratum corneum, and the deposition of glycosaminoglycans.<sup>17</sup> The lightening of hyperpigmentation and lentigines takes place by way of inhibition of melanogenesis, transfer of melanin from melanocytes to keratinocytes, or via shedding of melanin-laden keratinocytes during epidermal proliferation.<sup>17</sup>

### ADVANTAGES OF RETINOIDS

A major advantage of the retinoids in clinical practice relates to the confidence with which they may be used. No other group of topical agents has been as extensively tested in patients with photodamaged skin, and the evidence for significant and lasting clinical benefit of  $\alpha$ -hydroxy acids and other cosmeceutical actives is considerably less compelling.<sup>3</sup> Most information on vitamin C has been derived from in vitro experiments or animal models, although there are some data from small double-blind studies in humans to suggest beneficial effects of topical vitamin C complex (10% as water-soluble ascorbic acid and 7% as lipid-soluble tetrahexyldecyl ascorbate) on periorbital, perioral, and cheek wrinkles,<sup>29</sup> hydration, small wrinkles, glare, and brown spots after treatment with topical ascorbic acid 5% for 6 months.<sup>30</sup> Controlled clinical studies in persons using  $\alpha$ -hydroxy acids for photodamage are very few in number. Improved skin thickness has been reported in 1 placebo-controlled study in 17 individuals using 25% glycolic, lactic, or citric acid on the forearms.<sup>31</sup>

Topical retinoid therapy also has advantages over facial-rejuvenation procedures, despite the speed with which

results may be achieved with the latter. Chief among these is the avoidance of the periprocedural morbidity and discomfort, follow-up clinic visits, and costs that inevitably accompany facial-resurfacing procedures. Availability of the topical route of application also contributes to the ease of use of the retinoids and minimizes the risk for systemic toxicity.<sup>32</sup>

### SUMMARY

Many topical therapies are now available for the treatment of photodamaged skin, but many remain unproven or are supported by only limited clinical evidence. Topical retinoids have been shown in an extensive range of controlled clinical studies to be effective in alleviating the effects of photoaging and are currently the most effective noninvasive treatment for photodamaged skin. The greatest evidence of benefit is with tretinoin at concentrations of 0.02% and higher. Although a number of topical retinoids are available in the United States, few are indicated for photodamage; tretinoin 0.02% cream is the only tretinoin formulation approved for use in mitigating the signs of photodamage in the United States. Research is continuing to explore the molecular and cellular mechanisms behind the beneficial effects of these agents and their potential role in intrinsic aging is also of interest.

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