

Overview of Skin Aging and Photoaging

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Aging skin is an issue of concern to many patients. In this review aging and photoaging are defined, mechanisms which underlie these processes explored, and available treatment options discussed.

One of the more common dermatologic concerns in patients is aging skin. In a culture that is often called "youth-obsessed," patients increasingly look for creams and procedures that can improve the appearance of their skin. In 2004, U.S. retail sales of cosmeceuticals, cosmetic products purported to have medicinal or drug-like benefits, accounted for over \$12.4 billion. By 2010, the anti-aging market is expected to account for over \$16.5 billion in sales (Choi & Berson, 2006). Research into skin aging has also advanced considerably in the past 2 decades. Clinical manifestations of skin aging, mechanisms which underlie these clinical changes, and approaches to treatment will be explored.

Clinical Signs of Aging and Photoaging

Many of the skin changes commonly associated with aging, changes in pigmentation, sallowness,

OBJECTIVES

This continuing nursing educational (CNE) activity is designed for nurses and other health care providers who care for and educate patients and their families regarding skin aging and photoaging. For those wishing to obtain CNE credit, an evaluation follows. After studying the information presented in this article, the nurse will be able to:

1. Define the clinical signs of aging and photoaging.
2. Describe the mechanisms of aging and photoaging.
3. Discuss treatments for aging skin.

and deep wrinkling, are actually the result of sun exposure. Sun-exposed areas of the skin, such as the face, neck, upper chest, hands, and forearms, are the sites where these changes occur most often. As early as the 19th century, researchers noted profound differences in the facial skin of farmers and sailors as compared to that of indoor workers (Urbach, Forbes, Davies, & Berger, 1976). Outdoor laborers were noted to have thickening and brownish discoloration on light-exposed skin; these changes were also associated with an increased number of skin cancers (Urbach et al., 1976).

The term "photoaging" was first coined in 1986 and describes the effects of chronic ultraviolet (UV) light exposure on skin (Kligman & Kligman, 1986). Clinical signs of photoaging include dryness; irregular, dark/light pigmentation; sallowness; either deep furrows or severe atrophy; telangiectases; premalignant lesions; laxity; and a leathery appearance (see Table 1) (Yaar, Eller, & Gilchrist, 2002). Other signs include elastosis (a coarse, yellow, cobblestoned effect of the skin) and actinic purpura (easy bruising related to vascular wall fragility in the dermis) (Gilchrist, 1990). Chronologic skin

aging, in contrast, is characterized by laxity and fine wrinkling, as well as development of benign growths such as seborrheic keratoses and angiomas, but is not associated with increased pigmentation or the deep wrinkles that characterize photoaging (Yaar et al., 2002).

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Table 1.
Comparison of Changes Seen in Photoaging and Chronologic Aging of Skin

Photoaging	Chronologic Aging
Deep, coarse wrinkles	Fine wrinkles
Mottled pigmentation	Laxity
Sallowness	Benign neoplasms
Dryness	
Telangiectasia	
Premalignant lesions	
Laxity	
Atrophy	
Leathery appearance	
Elastosis	
Actinic purpura	

Microscopic Findings in Aging and Photoaging

There are microscopic differences in the two aging processes as well. In chronologically aged skin, the epidermis is atrophic, with flattening of the dermal-epidermal junction and loss of rete pegs (Kurban & Bhawan, 1990). The dermis also becomes thinner, with decreased numbers of fibroblasts and decreased levels of collagen (Varani et al., 2000). Photoaged skin, in contrast, can be associated with either increased epidermal thickness or pronounced epidermal atrophy. The most pronounced histologic change is the accumulation of elastin-containing material just below the dermal-epidermal junction, known as solar elastosis (Lavker, 1995). Collagen, which composes over 90% of the skin's total proteins, becomes disorganized (Bernstein et al., 1996).

Mechanism of Photoaging

Collagen is one of the main building blocks of human skin, providing much of the skin's strength. Dermal fibroblasts make precursor molecules called procollagen, which is converted into collagen. There are

two important regulators of collagen production: transforming growth factor (TGF- β) and activator protein (AP)-1. TGF- β is a cytokine that promotes collagen production (Massagué, 1998). AP-1 is a transcription factor that inhibits collagen production and up-regulates collagen breakdown (Kang, Fisher, & Voorhees, 1997). Collagen in skin undergoes continuous skin remodeling and turnover, with TGF- β and AP-1 playing important roles. TGF- β promotes collagen formation, while AP-1 promotes collagen breakdown by up-regulating enzymes called matrix metalloproteinases (MMPs).

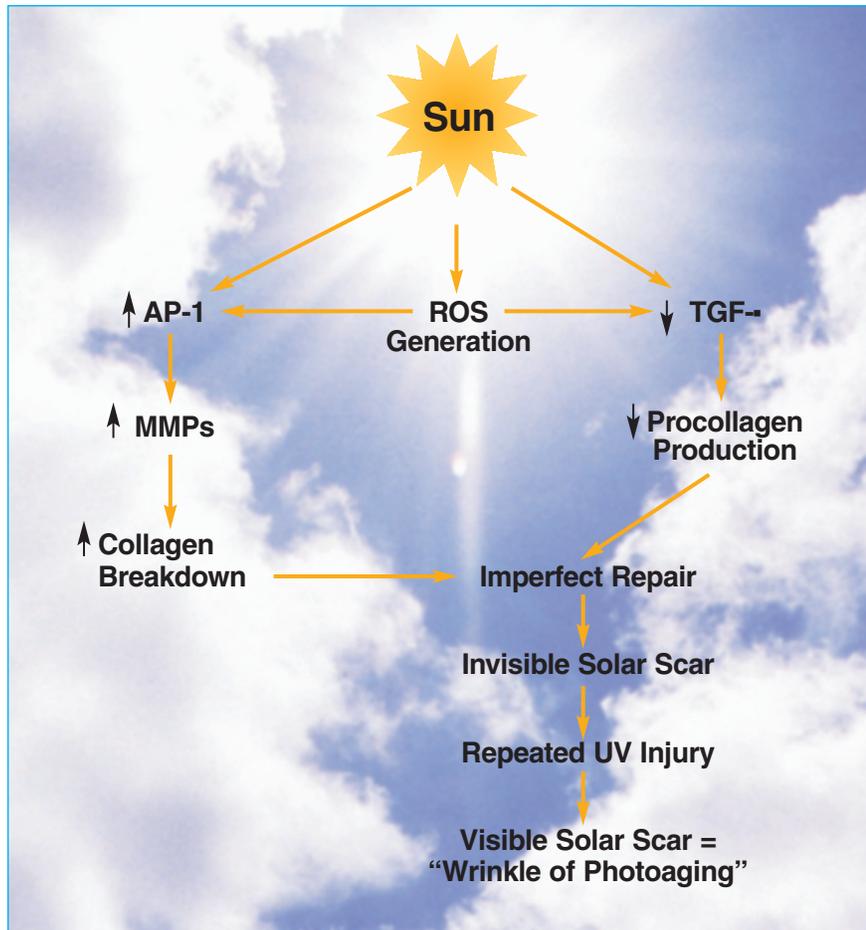
When skin is exposed to sunlight, UV radiation is absorbed by skin molecules that can generate harmful compounds, called reactive oxygen species (ROS), which then cause "oxidative damage" to cellular components like cell walls, lipid membranes, mitochondria, and DNA. These ROS also play an important role in molecular pathways. Irradiation of human buttock skin with 2 MED (two times the dose of UVA/UVB that causes barely perceptible skin reddening, the minimal erythema dose) causes increased

generation of hydrogen peroxide, an ROS, within 15 minutes (Kang et al., 2003). Within the same time frame, AP-1, which leads to increased collagen breakdown, becomes elevated and remains elevated for at least 24 hours following UV irradiation (Fisher et al., 1996). Collagen-degrading MMPs, which are up-regulated by AP-1, are also markedly elevated within 24 hours of UV irradiation (Fisher et al., 1996). Within 24 hours of a single dose of UV irradiation, increased collagen breakdown can be demonstrated (Fisher et al., 1997).

To summarize, UV irradiation leads to generation of ROS and induction of AP-1, which causes increased MMP production, with subsequent increased breakdown of collagen. In addition, UV irradiation leads to decreased expression of TGF- β , a member of the TGF- β family. As noted previously, TGF- β promotes collagen formation; therefore, decreased expression of TGF- β causes decreased collagen production. Researchers have demonstrated decreased procollagen synthesis within 8 hours of UV irradiation (Quan, He, Kang, Voorhees, & Fisher, 2002). Increased breakdown and decreased production of collagen are the cornerstones of photoaging. Each UV insult induces a wound response with subsequent imperfect repair, leaving an invisible "solar scar." Repetitive UV insults over a lifetime eventually lead to development of a visible "solar scar," manifesting as a visible wrinkle (Kang, Fisher, & Voorhees, 2001) (see Figure 1).

It is commonly accepted that increased innate pigmentation (darker skin tone) is associated with protection from sun damage. Darker-skinned people are less likely to develop a sunburn after intense sun exposure, and have a lower incidence of skin cancer. In addition, darkly pigmented subjects have significantly less induction of collagen

Figure 1.
Model Depicting the Effect of Ultraviolet Radiation on Skin



Acute ultraviolet irradiation leads to generation of ROS, upregulation of AP-1, and downregulation of TGF- β . AP-1 leads to collagen breakdown, while decreased TGF- β activity is associated with decreased collagen production. No damage to the skin is repaired perfectly; acute solar damage leads to an invisible solar scar. Repeated ultraviolet irradiation and injury eventually leads to accumulation of damage, eventually manifesting as a visible solar scar, or a wrinkle associated with photoaging.

breakdown and less DNA damage than lightly pigmented subjects (Fisher et al., 2002). These molecular findings support the clinical observation that darker-skin pigmentation protects against photoaging.

Mechanism of Skin Aging

Generally, the molecular changes of photoaging are considered to be an augmentation and amplification of the molecular changes associated with chronologic skin aging (Fisher et

al., 2002). In aged skin, there is elevation of AP-1 as compared to young skin (Chung et al., 2000). MMP activity is also increased in aged human skin, and is associated with increased levels of degraded collagen (4-fold higher in aged vs. young subjects) (Fisher et al., 2002). In addition, synthesis of types I and III procollagen is reduced in aged human skin (Varani et al., 2000). The combination of increased breakdown of collagen and decreased synthesis of new collagen

results in an overall decrease in collagen levels in the dermis. These molecular changes in chronologically aged skin resemble the changes associated with photoaging. This supports the notion that photoaging is superimposed upon and amplifies the changes associated with chronologic skin aging.

Chronologic aging is thought to result from a combination of forces. Generation of ROS is thought to play a major role. The free radical theory of aging proposes that aging results from accumulation of oxidative damage over a lifetime due to excess ROS, which result from aerobic metabolism (Hensley & Floyd, 2002). ROS generation is increased in aged skin. As discussed previously, ROS generation is a key step in molecular pathways which eventually lead to increased collagen breakdown. This free radical theory of aging gives a good explanation of the molecular changes associated with chronologic aging.

Treatment of Aging Skin

Treatment of aging skin includes (a) measures to prevent against UV damage and (b) medications and procedures to reverse existing damage.

Photoprotection. Photoprotection refers to measures that can be taken to protect the skin from UV damage and is achieved by sunscreens, sun-protective clothing, and sun avoidance. Sunscreens are broadly defined as agents that protect against UV damage and protect against sunburn, wrinkles, and pigmentary changes (Gilchrest, 1996). Sun-protection factor (SPF) refers to the degree of protection from ultraviolet B and does not account for protection against ultraviolet A. Patients should be advised to choose a sunscreen with an SPF of 15 or higher and to apply liberally and frequently to all exposed body sites, especially the face and neck. Sunscreens should be applied every 2 to 3 hours, especially if patients are engaged in outdoor activities. Because

the SPF rating only confers protection against ultraviolet B, patients should be educated to look for ultraviolet A protection features in a sunscreen. Chemical blockers of UVA include oxybenzone and avobenzone (Parsol 1789). Some newer UVA blockers have become available in the United States including ecamsule, which is the most photostable UVA blocker available and sold under the trade name Mexoryl™ (Anthelios, La Roche Posay/L'Oreal), and Helioplex™, a stabilized form of avobenzone (Neutrogena). Sunscreens that contain physical blockers such as titanium dioxide and zinc oxide confer protection against both UVB and UVA. Newer technologies such as micronization have been developed over recent years to make these physical blockers more cosmetically acceptable. A complete list of sunscreens with the Skin Cancer Foundation's Seal of Recommendation can be found at www.skin-cancer.org.

Sun-protective clothing lines exist and are widely available in sporting goods stores and on the Internet. These clothing lines provide hats, long-sleeved clothing, etc. and are geared towards patients who work outdoors and are avid outdoor enthusiasts for whom sunscreens might be less practical to use. The fabrics used in these lines are highly engineered and sophisticated materials that confer high levels of sun protection and protect against both UVA and UVB. Solumbra, manufactured by Sun Precautions, offers an SPF 30+ and reportedly blocks 97% of UVA and UVB. Coolibar is another brand of sun-protective clothing and hats and offers an ultraviolet protection factor (UPF) of 50+ and reportedly blocks 98% of ultraviolet A and B. UPFs are similar to SPFs but are typically used for devices such as clothing and fabrics rather than for sunscreen. Clothing lines and other sun-protective devices endorsed by the Skin Cancer Foundation are listed on their Web site.

Finally, sun-protective behavior is achieved through patient education. Patients should be discouraged from using tanning beds, which accelerate photoaging. Patients should be educated to avoid midday sun exposure when ultraviolet radiation is most intense, to participate in outdoor activities early or late in the day, to avoid sunbathing (even with sunscreens), and to seek shady, covered areas rather than direct sunlight.

Topical retinoids. Available topical retinoids include prescription tretinoin (Retin-A®), adapalene (Differen®), and tazarotene (Tazorac®) and over-the-counter Retinol® and Retinol-A®. These drugs are derivatives of vitamin A which have anti-aging properties. Topical tretinoin was first observed to ameliorate the clinical signs of photoaging by Cordero (1983) and Kligman, Grove, Hirose, and Leyden (1986). The first double-blinded, randomized, vehicle-controlled clinical trials investigating the use of tretinoin for photoaged skin were performed in the late 1980s. In these studies, investigators found that surface roughness, dyspigmentation, and fine wrinkles demonstrated the most improvement with topical tretinoin therapy in the first 4 to 10 months of therapy (Weiss et al., 1988). Because epidermal changes seen early in therapy reverted to baseline, the wrinkle-improving effect of tretinoin was presumed to be due to effects on the dermis. In studies, topical tretinoin increased collagen type I in photoaged skin (Griffiths et al., 1993; Talwar, Griffiths, Fisher, Hamilton, & Voorhees, 1995). It is common and predictable for patients to develop a retinoid dermatitis characterized by erythema and scaling after starting a retinoid. With time and continued use, this dermatitis improves. A patient may use topical tretinoin as part of a daily and ongoing program to reverse the signs of clinical photoaging. Topical tretinoin is typically prescribed as a 0.05% or 0.1% cream, and for patients more sensitive to the effects, lower strengths can

be used (0.02%, 0.025%). Tretinoin can be used indefinitely. There are no true contraindications to its use, though some patients are not able to tolerate the accompanying retinoid dermatitis.

Cosmeceuticals. Cosmeceuticals are agents that are marketed as cosmetic products, contain biologically active ingredients, and are available without a prescription. Drugs exert a biologic effect, are dispensed by prescription, and are regulated by the U.S. Food and Drug Administration. Cosmeceuticals do not undergo the rigorous testing required for drug approval, and there are few clinical controlled trials of these products. In fact, most of the work supporting their use is *in vitro* or small, open-label, industry-sponsored trials. The cosmeceutical industry is huge and future projections estimate that it will exceed \$16 billion by 2010 (Choi & Berson, 2006). Cosmetic products containing peptides, antioxidants, and botanicals are examples of cosmeceuticals. A complete review of cosmeceuticals is beyond the scope of this article, so only select ones will be mentioned.

Peptides are amino acid chains that are fragments of large proteins such as collagen. Pal-KTTS is a collagen peptide fragment, and there is evidence in wound healing that it may penetrate into the dermis and stimulate collagen production (Katayama, Armendariz-Borunda, Raghov, Kang, & Seyer, 1993). Pal-KTTS is marketed as Matrixyl™ (Sederna, France) and is an ingredient in a number of cosmeceuticals. A tripeptide-copper complex can increase collagen in wounds and is an ingredient in a number of cosmeceuticals such as Procyte GHK-copper peptide (Maquart et al., 1993).

Antioxidants are molecules that work in the skin to reduce ROS, which are generated by UV damage and lead to breakdown of collagen. There is much interest in the use of antioxidants both orally and topically to combat aging skin, but there are

few published studies on the efficacy of these agents. There is reason to be optimistic, as preliminary studies demonstrate that certain antioxidants may exert an anti-aging effect by preventing and even reversing sun damage. Idebenone is a synthetic analog of Coenzyme Q 10 with potent antioxidant activity; it reduces skin roughness, increases skin hydration, reduces fine lines, and was associated with an improvement in overall global assessment of photoaged skin (McDaniel, Neudecker, DiNardo, Lewis, & Maibach, 2005). Topical vitamin C 5% cream applied for 6 months led to clinical improvement in the appearance of photoaged skin with regard to firmness, smoothness, and dryness compared to vehicle (Humbert et al., 2003). Topical vitamin C stimulates the collagen-producing activity of the dermis (Nusgens, Humbert, Rougier, Richard, & Lapière, 2002).

Botulinum toxin and soft tissue fillers. Purified botulinum toxin type A (Botox[®], Allergan Inc., Irvine, CA) is a neurotoxin used to paralyze various muscle groups of the face for cosmetic improvement of wrinkles. Injection of Botox[®] is easily one of the most popular procedures for aesthetic enhancement. Botox[®] is most commonly used to treat wrinkles of the glabella, forehead, and periocular regions. Paralysis of these small muscle groups of the face results in a more youthful appearance. With time and repeated injections, many patients will note softening or disappearance of particular facial lines. Botox[®] works by neuromuscular inhibition of acetylcholine and the effects last from 3 to 6 months. Side effects of Botox[®] injections include pain, bruising, and paralysis of the nerves that control eyelid function.

Of the 9.7 million nonsurgical procedures performed in the United States in 2004, nearly 10% were soft tissue augmentation procedures, as reported by the American Society for Aesthetic Plastic Surgery (Matarasso,

Carruthers, Jewell, & The Restylane Consensus Group, 2006). First approved in 1981, bovine collagen was the gold standard for soft tissue augmentation, but in recent years, non-animal stabilized hyaluronic acid gel marketed as Restylane[®] (Medicis Pharmaceuticals, Scottsdale, AZ) has gained tremendous popularity among patients and physicians, and is currently the most widely used filler in the United States and Canada (Coleman & Carruthers, 2006). Other available fillers include calcium hydroxylapatite (Radiesse[®], BioForm Medical, Inc., San Mateo, CA), poly-L-lactic acid (Sculptra[™], Dermik Laboratories, Bridgewater, NJ), and human-based collagen (Cosmoderm[®] and Cosmoplast[®], both made by Allergan Inc., Irvine, CA). Soft tissue fillers are most commonly used to improve the appearance of the nasolabial folds, which become more pronounced as a result of photoaging and chronological aging. They are also injected into cheeks, periocular areas, and glabellar lines, and are often used in combination with Botox[®] for maximal effect, since they address different aspects of aging skin (Coleman & Carruthers, 2006). Soft tissue fillers have been thought to exert their effect by volume expansion, but recent work investigating the mechanism of action of Restylane[®] suggests the filler stretches fibroblasts, leading to new collagen formation (Wang et al., 2007).

Laser procedures. Laser procedures for the aging face are numerous and emerging rapidly. A complete discussion of these is outside the realm of this article.

Ablative laser resurfacing is considered to be the gold standard to improve clinical features of the aging face and generally refers to treatment with a carbon dioxide laser (10,600 nm). It improves fine and some coarse wrinkles and overall dyspigmentation, lightens dark under-eye circles, and generally improves the texture of skin; it can also be used to

ameliorate old acne scarring. This procedure works by vaporizing the epidermis and portions of the papillary dermis so that neocollagenesis can occur (Railan & Kilmer, 2005).

The biochemical changes associated with the carbon dioxide laser have been studied; a well-organized wound healing response occurs, resulting in quantitatively significant increases in production of types I and III procollagen (Orringer et al., 2004). Due to the depth of penetration of this laser, anesthesia is required and can be achieved by IV sedation, endotracheal sedation, or a combination of oral anxiolytics, topical EMLA, and regional nerve blocks. Carbon dioxide laser resurfacing is performed as a single treatment, and it takes 2 weeks for the skin to re-epithelialize following the procedure. Antiviral prophylaxis is started 1 day prior to the procedure and continued for 14 days, and anti-staphylococcal antibiotics are started 1 day prior and continued for 7 days. During this time, wound care is frequent and time consuming, and patients must be monitored closely for viral and bacterial skin infections. Patients with Fitzpatrick skin types I and II are the ideal candidates, as the procedure is associated with skin lightening. Additionally, patients may retain a pink or erythematous tone to their skin that may last for weeks to months following the procedure.

At our institution, an occlusive protective dressing is left in place for 48 hours. Once the dressing is removed, the skin is cleansed with a diluted vinegar solution and a copious layer of Aquaphor[®] Healing Ointment or Vaseline[®] is used to cover the resurfaced skin. Patients need to perform dilute vinegar soaks for 7 to 14 days every 2 to 3 hours during the day and through the night followed by Aquaphor or Vaseline application until the skin is completely re-epithelialized.

Non-ablative laser resurfacing procedures are much less invasive

than ablative lasers. There is much interest in these techniques because of the intense wound care, high cost, and recovery time immediately associated with ablative laser resurfacing. Select non-ablative lasers include the long-pulsed neodymium YAG (1064 nm), 1320 nm (CoolTouch[®], Roseville, CA), radiofrequency (Thermage[®], Thermage, Inc, Hayward, CA), and Fraxel[®] (Reliant Technologies, Mountainview, CA). Each of these treatments is performed on multiple occasions, usually several weeks apart. It is important to bear in mind that none of the non-ablative lasers can replace the ablative procedures.

Intense pulsed light is another light-based treatment but is not a true laser as it is composed of several different wavelengths. It is popular for facial rejuvenation and is used to lighten lentigines and reduce telangiectases to achieve an overall blending effect. When used with a photosensitizer (photodynamic therapy), intense pulsed light and other light-based therapies may have a greater effect than the light source alone (Dover, Bhatia, Stewart, & Arndt, 2005). Q-switched lasers are lasers that target pigment in skin and are useful for removing benign pigmented lesions seen in photoaged and aged skin. Careful clinical assessment is required prior to proceeding with treatment to avoid laser treatment of potentially malignant skin lesions such as lentigo maligna or melanoma. Pulsed-dye lasers and KTP lasers are used in photoaging to target the dilated blood vessels which produce a ruddy and uneven appearance. Treatment with either of these vascular lasers usually requires several treatments. Side effects include increased erythema immediately following the treatment, slight discomfort, swelling, and potential bruising.

Pre-treatment clinical assessment and consultation are critical before prescribing or performing the previously described treatments and procedures to review the risks and com-

plications. Patient expectations must be gauged so that optimal improvement is achieved. It is of utmost importance that patients follow wound care instructions after ablative resurfacing in order to achieve optimal healing. It is also crucial that patients understand that textural irregularities and dyspigmentation of skin can be improved, and that there will be a tightening effect, but that the results will not simulate a surgical facelift.

Summary

It is important to distinguish between natural skin aging and photoaging. Knowledge about the mechanisms underlying these processes can be utilized for developing future therapies. Educating patients is essential, as sunscreens and sun protection can prevent many of the changes associated with photoaging. Many treatments are available to treat photoaged skin; however, the best treatment is prevention. ◆

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