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Prevention and Treatment of Skin Aging

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ABSTRACT: Skin aging is a complex biological process that is a consequence of both intrinsic or genetically programmed aging that occurs with time, and extrinsic aging caused by environmental factors. The dramatic increase in the aging population and the psychosocial impact of skin aging has created a demand for effective interventions. The advances that have been made in the past 25 years in our understanding of the clinical, biochemical, and molecular changes associated with aging have led to the development of many different approaches to reduce, postpone, and in some cases, repair the untoward effects of intrinsic programmed aging and extrinsic environmental injury.

KEYWORDS: skin aging; anti-aging; photoaging; skin rejuvenation; photoprotection; sunscreen; antioxidant; cytokinin; cosmeceutical

INTRODUCTION

The skin is a unique organ that reflects the inevitable changes that occur in the body's aging process. In the 21st century, we now have an understanding of the factors that contribute to the pathogenesis of skin aging and consequently we can develop rational approaches to both prevent and treat the effects of this process.

Intrinsic Aging

Genetically programmed intrinsic aging (or chronological aging) causes structural and functional changes in all layers of the skin.[1] In the epidermis, there is a progressive decrease in the renewal rate of epidermal cells. Epidermal turnover, which in young adult skin takes about 28 days, requires 40–60 days in the elderly.[2] Slower turnover causes thinning of the epidermis that gives aged skin a translucent appearance. Diminished epidermal renewal also adversely affects skin barrier function and repair and cell exfoliation. In aged skin, the corneocytes tend to clump together on the surface, giving a

rough, scaly appearance, and texture. Histologically, one of the most prominent changes with intrinsic aging is a flattening of the dermal–epidermal junction, which increases skin fragility and decreases transfer of nutrients between the two layers. In aged skin, there are fewer melanocytes populating the epidermis and decreased functional activity of the remaining melanocytes, resulting in dyschromic changes, such as mottled pigmentation, freckles, and lentigines. Because the skin is thinner and has fewer melanocytes, it is more susceptible to sunburn. Aging also affects the Langerhans cells, the immunocompetent cells in the epidermis. There is nearly a 50% decrease in the Langerhans cells in late adulthood.[3] This compromises the skin's level of immune surveillance and leads to a higher risk of skin cancer.

In the dermis, there is a decrease in the number of fibroblasts as well as synthesis of the fibroblast products collagen and elastin, resulting in skin wrinkling and loss of elasticity. Aging also results in considerable loss of dermal microvasculature, reducing blood supply to the skin and contributing to atrophy of the skin and its appendages. Loss of sebaceous glands in the dermis makes the skin dry due to reduced oil production.

Further, intrinsic aging causes a decrease in subdermal fat tissue. This loss of support contributes to wrinkling and sagging (laxity) of the skin. With less padding, skin is more susceptible to trauma and bruising. Decreased insulation also affects the body's ability to conserve heat.

Although intrinsic aging causes all the above-described structural changes, effects are mostly functional, with only minor impact on skin appearance, which can be summarized as generalized fine wrinkling, dryness, and thinning. It is also important to note that the genetic program of intrinsic aging differs per individual in terms of rate and severity of effect.

Extrinsic Aging

Extrinsic aging is superimposed on intrinsic aging and is caused by environmental factors such as ultraviolet damage, pollution, harsh weather, and cigarette smoke. Chronic sun exposure is the principal environmental cause of extrinsic skin aging and is responsible for the majority of age-related changes, including fine wrinkles, roughness, mottled hyperpigmentation, dilated blood vessels, and loss of skin tone. Acute effects of ultraviolet irradiation are inflammation, sunburn, pigmentation, epidermal hyperproliferation, and immune suppression.[4] Chronic effects are photoaging and photocarcinogenesis.[5] Shorter UVB (290–320 nm) wavelengths only penetrate to the epidermis. Longer UVA wavelengths penetrate deeper into the skin and are primarily responsible for clinical changes seen with photoaging. The UVA wavelength is split up into UVA1 (340–400 nm) and UVA2 (320–340 nm). It is the longer wavelength (UVA1) that causes the most photoaging.[6] The primary cause of skin damage by UVA light is oxidative stress. UVA is absorbed by

chromophores present in skin (e.g., trans-urocanic acid), generating various reactive oxygen species (ROS)[7] that cause oxidative damage to nucleic acids, cellular proteins, and lipids. The ROS trigger a host of cytokine cascades that result in photoaging and photocarcinogenesis. One of the primary effects of UVA oxidative damage is ROS-induced synthesis of a series of matrix metal-loproteinases[8] that cause collagen degradation resulting in wrinkles.

PREVENTION OF SKIN AGING

While it is currently impossible to halt or reverse the genetic processes responsible for intrinsic aging, skin changes associated with extrinsic aging are largely preventable.

Photoprotection

Protection from ultraviolet light at any age reduces photoaging and decreases the risks of age-related skin diseases. Various photoprotective measures, including sun avoidance, wearing protective clothing, and use of sunscreen, retard the onset and slow the progression of photoaging.[9] Since approximately 80% of the skin's sun damage is thought to occur by the age of 18 years[10] (although it does not become apparent until years later), preventive measures should begin in early childhood. The use of sunscreens is the "gold standard" for protecting the skin from ultraviolet light. Clinical studies have well documented that regular use of a broad spectrum sunscreen can prevent not only sunburn, but also many skin-aging effects (e.g., wrinkles, pigmentary changes).[11] Sunscreens have also been shown to reduce actinic keratoses, solar elastosis, and squamous cell carcinoma.[12] The use of sunscreens and sun protection is important in association with implementation of skin-aging treatments, as the beneficial effects of skin rejuvenation measures will be minimized, or even cancelled if unprotected sun exposure continues to induce skin damage.

Sunscreen technology includes chemical or physical blockers that filter various UV wavelengths.[13] Early sunscreens used *para*-aminobenzoic acid (PABA) or PABA derivatives to protect from UVB. However, there was no protection against harmful UVA wavelengths and a significant incidence of contact sensitivity. Newer chemical sunscreen formulations use UVB protectors with lower allergenicity (aminobenzoates, cinnamates, salicylates, and benzophenones) in combination with chemicals such as oxybenzone that extend protection to UVA wavelengths. Physical sunscreens containing titanium dioxide or zinc oxide provide broad spectrum coverage that blocks or reflects UVA and UVB.

The sun protection factor (SPF) is the international standard for rating the effectiveness of sunscreens and is based solely on prevention of erythema (sunburn) induced by UVB.[14] There is no similar universal standard for UVA

protection. The inadequacy of rating UVA protection has raised the concern that the use of a high SPF product may provide a false sense of protection (prevent sunburn), allowing individuals to spend greater time in the sun, without adequate UVA protection, particularly UVA-1.[15] Some manufacturers have introduced a star rating system, which defines the ratio of UVA relative to UVB protection.[16] When used in combination with the SPF rating, this gives a more complete picture of a sunscreen's overall performance for protecting the skin and preventing aging.

Antioxidants

Antioxidants provide yet another approach for the prevention and treatment of intrinsic and extrinsic skin aging. Free radicals play a pivotal role in the biological events that lead to the clinical manifestations of skin aging. Skin has an integrated endogenous antioxidant defense mechanism that scavenges free radicals and protects cells from damage.[17] Naturally occurring antioxidants are reduced in chronically aged skin and further reduced in photodamaged skin.[18] Various approaches have been used to supplement the levels of these antioxidants in the skin to enhance defense mechanisms. Oral supplementation has not been successful in augmenting skin antioxidant levels due to physiological processes including absorption, transport, and metabolism.[19] Studies have shown that antioxidants can be delivered percutaneously to directly supplement the skin's antioxidant reservoir. Topical vitamin C, when properly formulated, effectively penetrates the skin and enhances 20-fold endogenous cutaneous levels vitamin C.[20] Most studies evaluating antiaging effects of topical antioxidants have been done *in vitro* or in animal skin. Studies in pig skin demonstrated that the combination of topical vitamins C and E synergistically provide protection against UV-induced erythema and formation of sunburn cells and thymine dimers.[21,22] Although there are countless commercially available antiaging products that contain "antioxidants," only a few studies have been done to establish the efficacy of topical antioxidants in *in vivo* human skin for skin protection and rejuvenation.[23,24] Clinical studies with long-term follow-up are needed to establish the protective and therapeutic effects of topical antioxidants in skin aging.

REJUVENATION OF AGING SKIN

Topical Medications

The topical retinoid, tretinoin (all-*trans*-retinoic acid), was the first medically approved product for the treatment of photodamaged skin. Now, over a decade of basic and clinical studies document the beneficial clinical and histological

effects of retinoids for the treatment of photodamaged[25,26] and intrinsically aged skin.[27] Clinically, topical retinoids are effective in minimizing fine lines and wrinkles and improving skin texture and mottled hyperpigmentation.[28] Tretinoin decreases fine wrinkles by increasing dermal collagen production via stimulation of synthesis,[29] reducing collagen degradation by inhibiting UV-induced matrix metalloproteinases,[30] and stimulating epidermal turnover, resulting in a thicker epidermis. Clinical changes are dose-dependent, with progressive improvement over a 6- to 12-month period, and slow regression once treatment is discontinued. The greatest obstacle to topical retinoid use is the high incidence of skin irritation, dryness, and the potential for increased photosensitivity.[31] New topical retinoids (e.g., tazarotene, adapalene) and novel formulations (e.g., microsponge) available in the last few years have fewer adverse effects and improved tolerance.[32,33]

Cosmetics and Cosmeceuticals

More than US$ 230 billion is spent annually worldwide on over-the-counter cosmetics and cosmeceuticals to improve the appearance of aging skin.[34] Antiaging cosmetics are touted to erase wrinkles and rejuvenate the skin. Most of these products serve only to camouflage wrinkles and moisturize the skin. Cosmeceuticals, a new category of antiaging products introduced in the 1990s, represent the fastest growing segment of the skin care market.[35] These antiaging products are not classified as prescription drugs or regulated by the Food and Drug Administration, but produce changes in skin structure or function. Examples include the alpha and beta hydroxy acids, which are generally found in over-the-counter preparations at relatively low concentrations (3–15%) and may be used to exfoliate the skin, increase cell turnover, and reduce fine wrinkles and mottled hyperpigmentation.[36]

Kinetin (N6-furfuryladenine) is a cosmeceutical used for the prevention and treatment of skin aging. It is a naturally occurring plant growth factor that retards senescence in plants[37] and has anti-aging effects on human adult skin fibroblasts *in vitro*.[38] Kinetin appears to be both a direct anti-oxidant[39] and a signaling molecule that stimulates pathways of the maintenance and repair in cells.[40] In a 52-week clinical study in 96 subjects with photodamaged facial skin, twice-daily application of kinetin lessened skin roughness (63%), mottled hyperpigmentation (32%), and fine wrinkles (17%), and also improved skin barrier function as measured by a decrease in transepidermal water loss.[41] Extended treatment with kinetin was well tolerated and did not cause irritation. Other cytokinins may also provide benefit for aging prevention, intervention, and therapy.[42]

The list of cosmeceuticals continues to grow and claims proliferate. It is important that scientific efforts be devoted to the rational development of anti-aging products and that clinical testing be done to substantiate claims.

Cosmetic Skin Rejuvenation Procedures

Topical agents alone provide some skin-aging prevention and treatment. However, combining use of topical compounds with one or several of the wide array of available cosmetic procedures can help maximize antiaging effects. Botulinum toxin, a purified neurotoxin, is one of the most popular procedures for temporary paralysis of select facial muscles and resultant diminution or elimination of unwanted lines in areas such as the glabella, periorbital, and perioral regions.[43,44] A multitude of injectable dermal fillers is available for diminishing skin atrophy and fine and deep rhytides.[45] Nonablative light-based procedures can be used to improve fine lines, and possibly skin tone.[46] Various skin resurfacing methods, including chemical peels,[47] dermabrasion,[48] and laser resurfacing[49] can been used to improve wrinkles, skin texture, and dyspigmentation. Cosmetic surgery produces the greatest improvement in wrinkles and skin laxity, but also has the highest associated risk and longest recovery period.

The current trend is to address skin aging before cosmetic surgery is required.[50] This is accomplished by combining available aging prevention and treatment options including daily sun protection and use of topical products, such as retinoids, kinetin, and moisturizers; regular-interval treatments (e.g., botulinum toxin, fillers, and nonablative light-based treatments); and only occasional major surgical procedures, as necessary. Youthful skin appearance can be preserved to some degree with less-invasive options, mitigating the need for cosmetic surgery. Implementation of skin protection and anti-aging treatment regimens should begin as early as possible and continue throughout life to counteract the effects of intrinsic and extrinsic skin aging. The future in the treatment of skin aging is bright and promises more effective preventive and therapeutic strategies.

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