Antiaging: Where Are the Data?

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Much of cosmetic dermatology is directed toward maintaining a youthful appearance of the skin. Thus, it behooves cosmetic dermatologists to understand both external and internal drivers of skin aging. Skin-specific drivers of aging such as UV light exposure, cigarette smoking, and overall health status have been illuminated in the literature. Human and animal studies have identified several drivers of systemic or organism-wide aging, as well as potential interventions to slow the rate of aging. These include calorie restriction, reduction of carbohydrate intake, modulation of insulinlike growth factor-I, use of antioxidants, adequate exercise and sleep, and reduction of stress. There are some data to recommend lifestyle changes to slow aging; however, much remains to be studied.

Much of cosmetic dermatology is directed toward maintaining a youthful appearance of the skin. During the past decade, there has been significant publicity surrounding both cutaneous and systemic "antiaging" treatments and the science behind them. Some antiaging approaches are legitimate and data driven, but many are not. Cosmetic patients are increasingly interested in this work, so it would benefit cosmetic dermatologists to understand both external and internal drivers of skin aging and which legitimate data are available.

In the skin, the changes associated with aging include thinned stratum corneum, increased transepidermal fluid loss, loss of elasticity, decreased height of retia, and dermal thinning. Apart from the skin, aging-associated changes include decreased glucose tolerance, decreased levels of hormones such as dehydroepiandrosterone, sarcopenia, osteoporosis, and declines in neural, cardiac, renal, and pulmonary function. Some animal studies have demonstrated interventions that significantly extend life, the clearest marker of antiaging efficacy.

Some drivers of cutaneous aging are skin specific, such as UV light–induced photoaging. Other drivers of aging have been shown to have skin-specific effects, such as tobacco-associated rhytides. In addition to these, recent work has shown that systemic aging may impact cutaneous aging. In this article, we examine the data surrounding skin-specific mechanisms of aging and antiaging interventions, systemic antiaging data from animal studies, and suggestive aging data and potential interventions from human studies.

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SKIN-SPECIFIC DRIVERS OF AGING

UV exposure directly affects the skin but only indirectly affects other organs. UV photoaging is thus specific to the skin. Other drivers of aging, such as exposure to tobacco smoke or emotional stress, affect many organs but have been shown to have skin-specific effects. A few interventions have demonstrated the ability to slow or even reverse the signs of skin aging. Retinoids have decades of data that show some reversal of photoaging. Topical antioxidants, including those found in green tea extract as well as vitamins C and E, have shown similar but more limited efficacy. Data are discussed in the following sections and are summarized in Table 1.[1-22]

UV Light

UV light exposure from the sun or tanning beds produces damage similar to that seen with advanced age. The changes include telomere shortening, nontelomeric DNA damage, elastolysis, inflammation-induced collagen destruction, and increased wrinkling.[4] UVA rays produce reactive oxygen species that damage DNA, lipids, and proteins. UVB rays induce pyrimidine dimers in DNA. Photoaged skin shows a "common deletion" of 4977 base pairs in the mitochondrial DNA of dermal fibroblasts.[1] UVB irradiation of hairless mice increases wrinkle volume and decreases

TABLE 1

Skin-Specific Drivers of Aging and Interventions*

Category	Effects
Drivers	
UV light exposure	UVA damages DNA, lipids, and proteins[1] UVB induces DNA pyrimidine dimers UV induces mitochondrial DNA deletion in dermal fibroblasts UV decreases collagen by activating inflammatory pathways[2] UV decreases dermal collagen, leading to increased rhytides[3] Photoaging and chronologic aging share final common pathway involving telomere disruption and p53 activation[4]
Cigarette smoking	Heavy smoking is equivalent to 10 y chronologic skin aging[5] Smoking decreases blood flow, increases MMP-1, damages connective tissue[6] Tobacco and UV light synergistically upregulate MMP-1
Stress	Physical, environmental, and psychological stressors age skin by activating microinflammatory pathways[7] Skin has its own HPA-like neuroendocrine system and appears to respond to systemic stress[8]
Poor health status	Healthier elderly show less wrinkling in photoprotected sites[9]
Interventions	
Topical antioxidants	Topical green tea extracts reduce oxidative stress and UV light–induced erythema and increase elastic tissue content[10,11] Topical vitamins C and E reduce UV light–induced photodamage[12] Ferulic acid plus vitamins C and E doubles antioxidant photoprotection, reduces thymine dimers, and prevents caspase activation and UV light–induced apoptosis[13]
Topical retinoids	Topical retinoids (tretinoin, tazarotene) clinically proven for treatment and prevention of signs of photoaging[14-22]

*MMP-1 indicates matrix metalloproteinase-1; HPA, hypothalamus-pituitary-adrenal axis.

dermal collagen fiber bundles in a dose-dependent and time-dependent fashion.[23] UV light exposure activates the nuclear factor-κB cascade, including the inflammatory downstream molecules interleukin (IL)-1, IL-6, vascular endothelial growth factor, and tumor necrosis factor-α.[2,3] These molecules activate neutrophils, keratinocytes, and fibroblasts to produce elastase and matrix metalloproteinases, which degrade collagen, thus promoting wrinkles.

Cigarette Smoking

Cigarette smoking causes widespread oxidative stress and tissue damage, which have been shown to decrease capillary and arteriolar blood flow, which in turn degrades connective tissue by increasing matrix metalloproteinase-1 synergistically with UV light exposure.[6,24] Smoking accelerates facial wrinkling and contributes to premature aging and poor wound healing.[25,26] A UK study found that smoking 1 or more packs of cigarettes per day (lifetime smoking history was not reported) had an effect similar to 10 years of chronologic aging; both increased the odds of having macroscopic skin wrinkling greater than the median on a 10-point scale (0=absence of wrinkling; 10=severe wrinkling of the face, neck, and dorsum of the hands) (odds ratio, 3.87 and 4.05, respectively).[5]

Stress

Emotional stress has been shown to accelerate systemic aging, as discussed below. Furthermore, environmental

and psychological stressors have been proposed to accelerate skin aging.[7] The postulated mechanism involves activation of microinflammatory cycles that induce reactive oxygen species, collagenase, and myeloperoxidase, which in turn damage the extracellular matrix. Stress hormones common to both the hypothalamic-pituitary-adrenal axis and the skin neuroendocrine system can incite cutaneous stress responses.[8] The shared hormones include cortisol, corticotropin-releasing hormone, prolactin, melatonin, and catecholamines. Along these lines, it is established that acute and chronic psychological stress can impact progression of cutaneous diseases such as pruritus, prurigo, atopic dermatitis, psoriasis, urticaria, lichen planus, alopecia areata, and telogen effluvium.[27] It remains to be shown whether emotional stress causes defined aging-associated changes in skin.

AGING INTERVENTIONS

Topical Antioxidants

Green tea (*Camellia sinensis*) extract, which contains (-)-epigallocatechin-3-gallate, can reverse in vitro extracellular matrix degradation induced by UV light exposure with a topical application of a practical concentration.[28] An 8-week placebo-controlled trial showed histologic improvement in elastic tissue content with a topical and systemic green tea extract regimen.[10] On a histologic scale for elastic tissue of −2 to +2 (−2/−1=less elastic tissue; 0=unchanged; +1/+2=more elastic tissue), placebo samples had a grade of −0.55 versus treatment samples with a grade of 0.20 (P=.021). Clinically visible improvements in photoaged human facial skin, however, were not apparent in this study. In another in vivo human skin study with implications for prevention of photoaging, topical green tea polyphenol treatment inhibited UVB-induced erythema, oxidative stress, and leukocyte infiltration in skin.[11] Green tea extract also suppressed UVB-induced cyclobutane pyrimidine dimer formation.

Other topical antioxidants, such as vitamins C and E, have also been studied for their antiaging effects. Topical application of vitamin C for 4 weeks increased dermal papillary height in aging skin compared with vehicle cream.[29] Vitamins C and E have been shown to decrease UV light–induced erythema.[30] Applied together topically prior to sun exposure, these antioxidants provided significant resistance to photodamage.[12] A porcine skin study showed that the combination of vitamins C and E is stabilized by the addition of ferulic acid, which synergistically doubled (from 4× to 8× at 4 times the minimal erythema dose) the degree of antioxidant photoprotection measured by erythema and sunburn cell formation.[13] The ferulic acid combination also further reduced UV light–induced thymine dimer formation and prevented caspase activation, thus preventing UV light–induced apoptosis. The exact mechanism has been postulated to involve the endogenous antioxidant system in the stratum corneum. More placebo-controlled clinical trials are needed to define the roles antioxidants may play in mitigating the cutaneous effects of time and environment.

Topical Retinoids

Topical retinoids such as tretinoin and tazarotene offer clinically proven medical therapy for treatment and prevention of photoaging.[14] Multiple trials have shown that tretinoin in various concentrations improves fine and coarse wrinkles, mottled hyperpigmentation, roughness, and actinic lentigines.[15-18] Associated histologic changes include a more compact stratum corneum, reduced spongiosis, a thickened granular layer, increased mucin deposition, and increased basal keratinocyte mitoses.[19] Application of tazarotene, a third-generation retinoid, has been shown to reverse effects of photoaging in a dose-dependent manner.[20] Multiple regimens have shown benefit in improving fine and coarse wrinkles and hyperpigmentation.[21,22]

Cosmeceuticals such as retinol, retinaldehyde, and retinyl esters may also offer some benefit.[31] Retinaldehyde 0.05% cream clinically improved the profilometric parameters of baseline fine and deep wrinkles and roughness when compared with vehicle (arbitrary units, P<.05); some improvement was maintained for 44 weeks.[32] Similarly, topical retinol has been shown in several randomized controlled trials to improve the appearance of fine lines.[33-35]

Hydration

Skin hydration via moisturizers with occlusives and humectants may improve the aesthetic appearance of the skin; however, at this time there are no data demonstrating antiaging effects of hydration.[36]

ANTIAGING DATA FROM ANIMAL STUDIES

Animal studies have identified several aging-associated pathways and antiaging interventions. These include calorie restriction (CR), administration of sirtuin gene 1 activators such as resveratrol, and antioxidant supplementation. Data are discussed below and are summarized in Table 2.[37-44]

Calorie Restriction

CR involves feeding animals a nutritionally complete but calorie-deficient diet, generally 70% to 80% of what animals not undergoing CR eat. Newer protocols involve intermittent fasting, which involves less overall CR since animals eat more during nonfasting periods. CR in rodents increases the maximum lifespan by 20% to 50%

TABLE 2

Aging Interventions in Animal Models*

Intervention	Effects
Calorie restriction	Rodent lifespans increase by 20% to 50%[37] Decreased age-associated changes (body weight, body fat, blood glucose, diabetes risk) in rhesus monkeys[38]
Insulinlike growth factor modulation	Resveratrol increases longevity and improves murine glucose homeostasis by SIRT1-mediated and other complex pathways[39,40] Resveratrol prolongs lifespan by up to 59%, retards expression of age-dependent traits in short-lived vertebrate fish[41] Resveratrol mimics the protective and longevity-promoting effects of calorie restriction in mice fed a high-fat diet[39]
Dietary antioxidants	9%–16% increase in rodent lifespan with dietary antioxidants[42] Blueberry polyphenols reverse age-related neuronal decline in mice[43] Green tea extract suppresses age-related increase in collagen cross-linking in mice[44]

*SIRT1 indicates sirtuin gene 1.

and can increase the median lifespan by 40% if initiated by 3 months of age.[37,45] Although CR can still prolong maximum survival by 6.8% to 13.7% in some strains of mice if begun in adulthood, in other strains it has no effect or may even shorten mean lifespan.[46] Another study employing a different strain of mice showed increases of 10% to 20% in both mean and maximum survival when CR was initiated in adulthood.[47] CR studies on primates, most notably rhesus monkeys, have demonstrated decreased aging-associated changes in body weight, body fat, blood glucose, and diabetes mellitus risk.[38] Many proposed mechanisms for CR involve improved cellular stress resistance.[48]

Insulinlike Growth Factor Modifier and Resveratrol

The insulin and insulinlike growth factor-I (IGF-I) pathways are conserved in organisms ranging from yeast to mice to humans and have been shown to play key roles in the rate of aging. Resveratrol, a polyphenolic compound found in red grapes and wine, produces changes associated with a longer lifespan, including increased insulin sensitivity and reduced IGF-I levels, acting as a dietary restriction mimetic.[39] Most recently, studies in mice and lower animals have shown that resveratrol promotes longevity and improves glucose homeostasis by stimulating the sirtuin gene 1–mediated deacetylation of peroxisome proliferator–activated receptor-γ coactivator 1α (also known as PGC-1α) and increasing adenosine monophosphate–activated protein kinase.[39,40] Other authors have demonstrated that food supplementation with resveratrol prolongs lifespan and retards the expression of age-dependent traits such as decline of locomotor activity and cognitive performance in a short-lived vertebrate fish.[41]

Dietary Antioxidants

Oxidative stress is thought to be involved in aging and age-related diseases,[49] and antioxidant supplementation has been shown to slow aging in experimental animal models. Blueberry supplementation reversed age-related declines in neuronal signal transduction, decreasing cognitive and motor deficits and preventing behavioral deficits in Alzheimer disease mouse models.[43,50] In fact, blueberry-supplemented mice show no deficits in maze performance despite excessive amyloid-β burden. Oral green tea extract supplementation blocked age-related increases in collagen cross-linking in 10-month-old mice ($P<.05$) and fluorescent products due to long-term protein modification mediated by oxidation and glycation reactions at 385 and 440 nm ($P=.052$ and $P<.05$, respectively).[44] Antioxidant-rich pomegranate juice decreased activation of oxidation-sensitive genes in vitro.[51] Polyphenolic antioxidants found in blueberries, pomegranate juice, and green tea extract have been shown to have significant beneficial effects on neurologic,

vascular, and connective tissue functioning and repair abilities, all of which decline with age.[43,44,51] Furthermore, (-)-epigallocatechin-3-gallate has been shown to have some protective effects against ionizing radiation and may have potentially ameliorating effects on many aging-associated changes, including cardiovascular mortality, some cancers, and increased body weight in humans and animals.[52-54] Interestingly, mice fed an antioxidant mixture experienced a 9.5% to 16% increase in lifespan compared with controls.[42]

DRIVERS OF AGING AND POTENTIAL INTERVENTIONS SUGGESTED BY HUMAN STUDIES

Selection of identical cohorts and lifelong observation are virtually impossible in human studies. Nevertheless, human studies have identified several interesting drivers of aging, summarized in Table 3.[55-62] Stress, sleep deprivation, a sedentary lifestyle, and a carbohydrate-rich diet contribute to disease states that result in accelerated aging and early mortality. Although these have not been shown to directly affect skin, there are data that suggest that systemic age may have an impact on skin age. An Australian study that examined general health and skin wrinkling in elderly participants from 4 ethnic groups found that subjects with less skin wrinkling in sun-protected sites had better general health and daily functioning when age, body mass index, and tobacco use were controlled.[9] This effect was more pronounced in women, where the correlation coefficients between skin wrinkling and activities of daily living and general health were -0.14 ($P<.05$) and -0.19 ($P<.01$), respectively. In men, the associations were weak and nonsignificant. Elderly subjects with less skin wrinkling also tended to have an increased dehydroepiandrosterone level, another marker of delayed systemic aging ($r=-0.14$, $P=.06$).[63]

Exercise

Epidemiologic studies have shown links between increased activity and slowed aging. Elderly subjects who had the highest free-living activity energy expenditure incurred a survival advantage over their sedentary peers (absolute

TABLE 3

Suggestive Aging Data and Potential Interventions in Humans*

Intervention	Effect
Regular exercise	Regular exercise is correlated with longer life[55] Resistance training attenuates age-related sarcopenia and decreased insulinlike growth factor-1 action[56] Exercise improves aerobic capacity and glucose tolerance, which reverse age-related decline in skeletal muscle mitochondrial function[57]
Adequate sleep	Sleep-deprivation hormonal changes parallel those seen with aging[58]: Decreased glucose tolerance Increased evening cortisol Increased sympathetic activity Associated with obesity, diabetes, hypertension <6 h sleep/night increases mortality in elderly Japanese women[59]
Stress management	Physical, emotional, and financial stress decrease longevity[59] Stress shortens telomeres and accelerates aging[60]
Low-carbohydrate diets	AGEs increase with age; in persons with diabetes, the AGE hemoglobin A_{1c} is reduced with a low-carbohydrate diet[61] Low-carbohydrate diets induced weight loss and improved lipids in a study of obese persons with type 2 diabetes who showed continued weight loss and maintenance of lower hemoglobin A_{1c} at 22 weeks[61]
Calorie restriction	Calorie restriction may benefit humans (suggestive only)[62]

*AGE indicates advanced glycation end product.

risk of death, 12.1% in the highest tertile vs 24.7% in the lowest tertile).[64] Longevity increased with regular exercise ($P=.002$) in the Jerusalem Longitudinal Study.[55] Aging results in sarcopenia (decreased muscle mass), especially in the type II muscle fiber cross-sectional area,[56] and resistance training attenuates this loss by increasing the cross-sectional area. However, such exercise does not increase the amount of muscle fiber to a level equivalent to that of younger subjects. As people age, levels of IGF-I decrease, reducing myoblast proliferation, differentiation, and protein accretion[56]; exercise can induce IGF-I and IGF-I receptors and pathways, and this overexpression helps prevent age-related sarcopenia. Regular aerobic exercise and resistance training can improve cardiovascular, musculoskeletal, and metabolic status, all of which decline with age.[65,66]

A study of healthy men and women aged 18 to 89 years showed impaired skeletal muscle mitochondrial function, increased cumulative mitochondrial DNA damage, and decreased mitochondrial adenosine triphosphate production at a rate of 5% per decade ($P<.001$).[57] Exercise-related increases in aerobic capacity and glucose tolerance improved mitochondrial function, including mitochondrial adenosine triphosphate production, which was related to an abundance of mitochondrial DNA. Older muscles showed signs of increased oxidative damage compared with younger muscles. Regular aerobic exercise and resistance training slow the aging-related declines in muscle mass and endurance and prolong functional longevity.[55,56,64,65]

Sleep

A study found that elderly Japanese women who slept fewer than 6 hours per night had increased mortality compared with their peers with more rest.[59] This is supported by data on flies and mice.[67,68] Sleep deprivation has been shown to decrease glucose tolerance, increase evening cortisol levels, and increase sympathetic activity, all of which are associated with normal aging.[58] Habitual sleep debt raises the incidence of the aging-associated diseases diabetes and hypertension.[58] This may be related to sleep-dependent changes in growth hormone and IGF release patterns.[69] In the United States, obesity rates rise with age, and adequate sleep may help prevent obesity by modulating appetite via ghrelin and leptin.[70-72] Although neither ghrelin nor leptin are proven factors in obesity in the elderly, leptin has a suggested but undefined role in the onset of insulin resistance and obesity in some aged populations.[73,74] As for the benefits sleep has on the skin, sleep deprivation in a small study of 11 women hindered skin barrier function recovery and increased plasma IL-1β and tumor necrosis factor-α levels and natural killer cell activity.[75] Adequate sleep may decrease obesity, diabetes, and hypertension, and ultimately lead to a longer and healthier life.

Stress Management

Chronic stress, whether physical, emotional, financial, or social, impairs longevity.[55,72] A recent study demonstrated that chronic stress accelerates cellular aging as measured by telomere length. Stress levels and telomeres of 39 mothers of chronically ill children were compared with those of 19 mothers of healthy children.[60] White blood cells from high-stress mothers (the mothers of the ill children) showed 9 to 17 years of increased age based on their telomere clocks. It was postulated that the chronic activation of stress hormones generates oxidative stress, thereby shortening telomeres. Stress management may therefore slow the aging process. Along the same lines, telomere length is substantially shorter in patients with mood disorders, which, according to one study, may accelerate cellular aging by as much as 10 years.[76] Stress in the forms of physical disease and insulin resistance coupled with oxidative stress plays a role in the onset of age-related disorders, such as hypertension.[77] As demonstrated in the offspring cohort of the Framingham Heart Study, hypertension, increased insulin resistance, and oxidative stress are correlated with shorter leukocyte telomere length ($P=.025$, $P=.007$, $P=.005$, respectively).

Low-Carbohydrate Diets

Advanced glycation end products (AGEs) increase with age. AGEs result from the "browning" or Maillard reaction, which occurs when sugar attaches to other molecules via nonenzymatic glycosylation[78]; hemoglobin A_{1c} is a well-known AGE. So-called "low-carbohydrate" diets limit high–glycemic-index foods such as baked goods, pasta, potatoes, rice, and refined sugars. A 22-month study of obese subjects with type 2 diabetes on low-carbohydrate diets showed a sustained reduction in hemoglobin A_{1c} levels from 8.0% to 6.9%.[61] Similar benefits for patients without diabetes have not been demonstrated to date.

Calorie Restriction

Although CR clearly increases longevity in animal models, strong human data are not available at this time. However, epidemiologic data suggest that chronic CR may have extended the average and maximum lifespans in elderly Okinawans.[62]

COMMENT

Although data are spotty, several antiaging interventions may be reasonably deemed to be scientifically based. These include smoking cessation, daily photoprotection, adequate sleep, stress management, regular exercise, and dietary modification. Dietary changes can include

moderate CR, increased antioxidant consumption, and reduced carbohydrate consumption. The use of topical retinoids and some topical antioxidants (vitamins C and E and ferulic acid) can also be of benefit. Interest in anti-aging among cosmetic patients can be expected to grow as new data emerge. Cosmetic dermatologists can help inform their patients about healthy choices that complement the cosmetic interventions they seek.

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