doi:10.36849/JDD.SF378083

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Sugar Sag: What Is Skin Glycation and How Do You Combat It?

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ABSTRACT

Skin aging is influenced by various exogenous and endogenous factors, ranging from ultraviolet (UV) light exposure and environmental toxins to biological sources, such as those that arise from normal metabolic processes (eg, free radicals). Glycation is the normal process by which glucose and other reducing sugars react with proteins to form an array of heterogeneous biomolecular structures known as advanced glycation end-products (AGEs) over time. However, AGEs are toxic to human cells and are implicated in the acceleration of inflammatory and oxidative processes, with their accumulation in the skin being associated with increased skin dulling and yellowing, fine lines, wrinkles, and skin laxity. Clinicians should become cognizant of how AGEs develop, what their biological consequences are, and familiarize themselves with available strategies to mitigate their formation.

J Drugs Dermatol. 2024;23:4(Suppl 1):s5-10.

A Biological Definition of Advanced Glycation End-Products (AGEs)

As time goes on and our bodies change, alterations in the texture and color of our skin serve as a constant reminder of aging. Skin aging is a multifactorial process, reflecting the sum effects of genetic, endogenous, and environmental factors.[1] Exogenous sources include exposure to ultraviolet (UV) light and environmental toxins, such as tobacco products and heavy metals, while endogenous sources derived from normal cellular metabolism can also contribute to aging. This includes processes such as glycation, which significantly promotes unwanted changes in human skin.[1-3]

Factors and Sources Contributing to the Development of AGEs

Skin glycation is the biological process by which glucose and other reducing sugars react with and modify biomolecular entities, such as lipids, nucleic acids, and proteins, to form many complex heterogeneous molecules potentially toxic to cells and tissues. These products of nonenzymatic sugar reactivity with other biological molecules are collectively known as advanced glycation end-products (AGEs).[1-3] To date, more than 20 species of AGEs have been identified in human skin and are primarily classified based on differences in their biochemical properties.[2,3] The principal mechanism by which these AGEs are created endogenously is known as the Maillard reaction. This nonenzymatic reaction was discovered initially in the 1900s and was shown to give rise to yellowish-to-brown–colored products that develop following the heating of a mixture of amino acids with reducing sugars.[2,4] Other mechanisms that can form AGEs and their associated intermediates include sugar autoxidation, lipid peroxidation, and the polyol pathway. Along with the formation of AGEs, these pathways can produce additional reactive compounds (eg, Amadori products, dicarbonyls, Schiff bases, and oxidized compounds) that can disrupt normal cellular physiology (Figure 1).[1-3,5]

Exogenous sources linked to the production and accumulation of AGEs include eating refined and simple carbohydrates, as well as foods that are cooked at high temperatures (eg, grilling, frying, and baking) that have a brown/crunchy consistency (eg, cookies, chicken), which acquires its characteristic color and texture from the Maillard reaction.[1-3,6] Excessive alcohol consumption, smoking, and living a sedentary lifestyle can also contribute to the production of AGEs. Other external factors that can increase the content of AGEs in the skin include exposure to pollution, metabolites in tobacco smoke, and UV light.[1-3] Individuals should also be aware that self-tanning products contain compounds

(eg, dihydroxyacetone [DHA], the active browning ingredient in sunless tanning lotions) capable of increasing levels of AGEs in the skin.[7,8] While most AGEs appear to arise from Maillard reactions occurring at the stratum corneum of the skin, studies suggest that self-tanning components (from sunless/chemical tanners) such as DHA (~12%, according to a US Food and Drug Administration [FDA] investigator-led study) may also slightly penetrate the epidermis and dermis layers where they can then promote some glycation.[9-11] However, the use of self-tanners is generally considered a safe alternative to UV-induced tanning.

Consequences of Skin Glycation

Due to their ability to negatively alter skin biology, the accumulation of AGEs is tied to several adverse effects in both the extracellular and intracellular compartments (Figure 1). One particularly problematic effect of AGEs is their ability to diminish protein function by altering their structure through cross-linking mechanisms.[1-3] This impacts several protein factors that comprise the architectural framework of the extracellular matrix (ECM). For example, ECM proteins, such as collagen and elastin, can be captured and cross-linked by various AGEs, resulting in the loss of their native conformation (ie, normal structure). This compromises the integrity and biomechanical properties of the skin, ultimately causing reduced skin elasticity and increased stiffness.[1-3] These processes are further exacerbated by the fact that, as humans age, skin fibroblasts exhibit a reduced capacity to secrete elastin and collagen fibers, further decreasing the quality of the ECM in the dermis.[1,12] In addition to the deepening and lengthening of skin wrinkles, these molecular events contribute to several manifestations of skin aging, such as yellowing, pigmentation changes (browning), and autofluorescence.[1,3]

Another important biological effect of AGEs and their intermediates is their capacity to independently react with molecular oxygen and metals to generate reactive oxygen species (ROS), furthering their toxic potential.[1-3] Additionally, AGEs can promote an inflammatory phenotype in cells by stimulating the production and release of pro-inflammatory cytokines and ROS.[1-3] The ROS and cytokine-inducing phenotypes observed in cells with elevated levels of AGEs may also be partly mediated by the binding of AGEs to the receptor for advanced glycation end-products (RAGE), the activation of which results in oxidative stress and upregulation of pro-inflammatory cytokines.[13,14] Lastly, AGEs can impair the signal transduction properties of cell growth and survival pathways, impinging upon important cellular cascades, including those required for normal proliferation, differentiation, motility, and cell death.[2,3,15]

Given the pleiotropic effects of AGEs in the cell, it is no surprise that their presence and persistence are linked to several disease pathologies (Figure 1).[1-3,5] The role of AGEs in patients with chronic metabolic disorders, such as diabetes, has garnered much attention, being a condition marked by a hyperglycemic state where patients may eventually suffer from skin complications (eg, ulcers, wound healing issues).[2,3,16,17] The high glucose levels in patients with diabetes can serve as a reservoir for accelerating AGE-related metabolism.[2,3,18] Indeed, patients with diabetes display higher levels of AGEs in their skin than healthy individuals.[19,20] Studies have also shown a correlation between high sugar levels and skin aging among patients with diabetes, and it has been revealed that patients with diabetes have impaired structural and mechanical properties in dermal collagen.[2,3,21,22] These observations point to a possible role of AGEs in mediating some aspects of diabetic disease. However, the exact mechanisms are poorly understood and likely involve other biological factors.

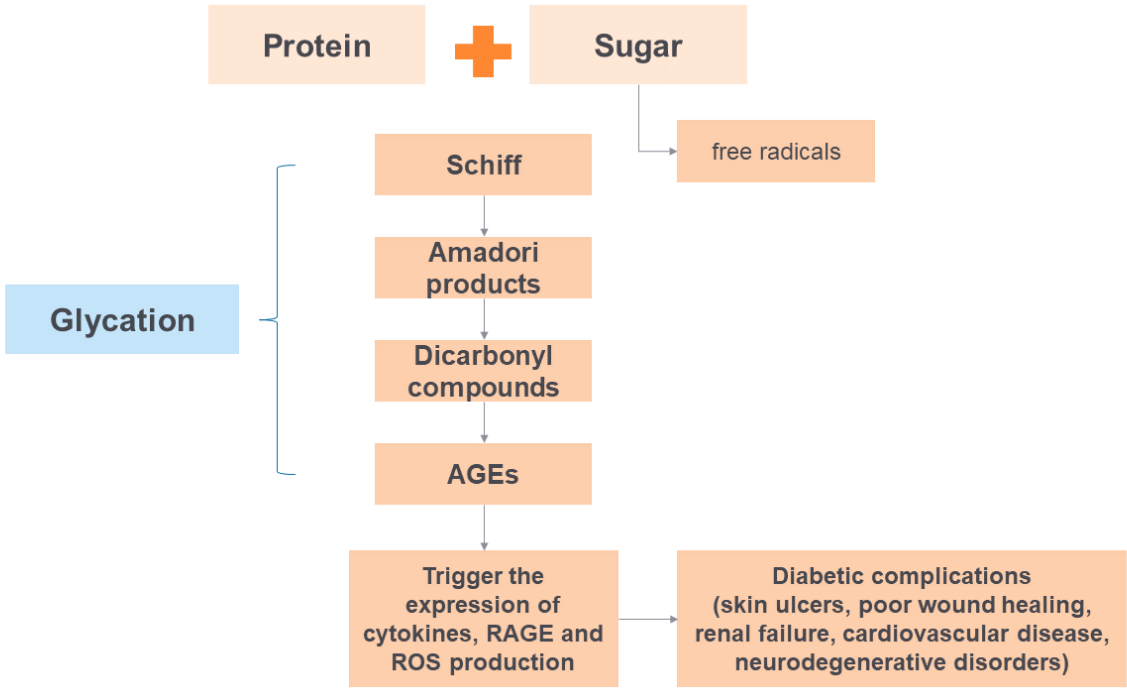
The formation of AGEs and activation of AGE pathways are also implicated in other chronic illnesses and conditions marked by an underlying inflammatory element, such as cardiovascular disease, neurodegenerative processes, and kidney disorders (Figure 1).[1-5,23] Whether AGEs are involved in initiating or driving the progression of such diseases remains unclear. Still, research scholars theorize that AGEs may help elicit cellular responses and pathways that involve pro-inflammatory signals and promote oxidative stress, leading to age-related disease and metabolic disorders (see Figure 1 for a summary of key biological effects and consequences of AGEs in humans).[2]

Recommendations for Preventing Skin Glycation and Reducing AGEs

Lifestyle Modification

Clinicians should emphasize to their patients that the most direct strategy to mitigate the accumulation of AGEs is to restrict the intake of exogenous sources of sugar and heat-treated foods (eg, fried and baked foods) (Figure 2). This aligns with the observation that patients with diabetes and renal failure who receive a diet low in AGEs have reduced circulating levels of AGEs and inflammatory biomarkers.[15,24,25] Therefore, it is recommended that patients are educated on how to modify their lifestyle by regularly exercising and changing their diet to consume healthier foods. Consuming fruits and vegetables may be beneficial since they contain antioxidants, such as phytochemicals, phenolic acids, and polyphenols, that can contend with AGE-related free radical stress.[1-5] Additional lifestyle modifications include limiting the use of cigarettes,

FIGURE 1. AGEs: Biological effects and involvement in human disease.[5]



reducing consumption of alcoholic beverages, and lessening exposure to environmental pollutants and UV light, as these are all exogenous sources of AGEs.[1-5]

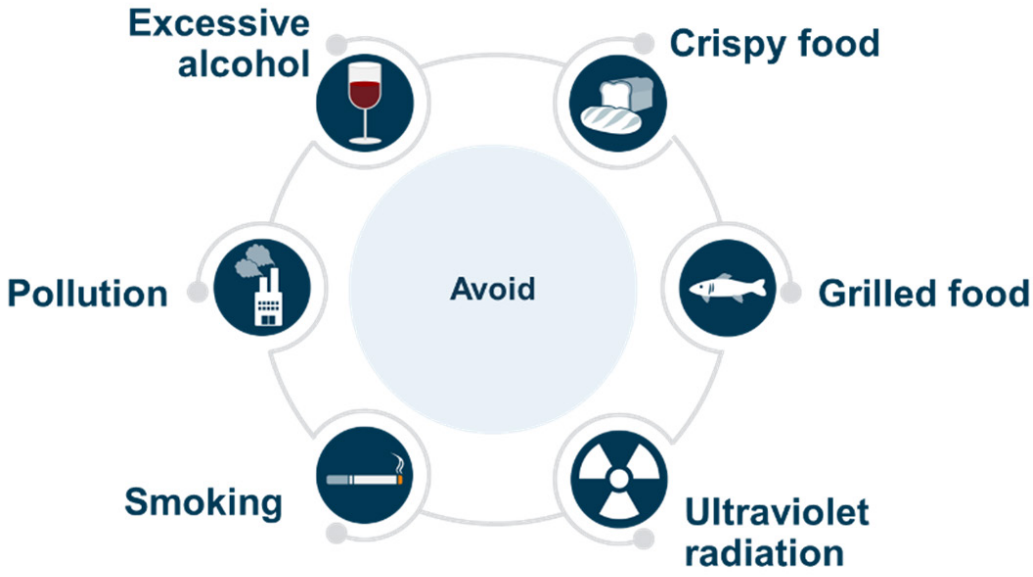
Emerging Investigative Agents and the Role of Nutraceuticals

Several promising pharmacologic approaches are being studied, all aimed at processes that target AGEs and the chemical steps that lead to their formation. Current classes of agents under study include carbonyl-trapping agents, which aim to reduce carbonyl stress; metal ion chelators or free radical scavengers, which work to block sugar oxidation; crosslinking reversal agents, which undo cross-linked AGEs; and the use of RAGE antagonists (eg, anti-RAGE antibodies, soluble decoy RAGE, and small molecule inhibitors) to lessen the effects of free radical–mediated stress and inflammation in tissues.[1-5] However, these approaches are still in their early development phases, and much work remains to establish their place as emerging treatments to target AGEs.

Topical formulations containing plant-based compounds have been studied for their antioxidant and antiglycation properties in the skin.[1-3,5] Such compounds may be derived from licorice root (eg, glycyrrhetinic acid) and wild fruits (eg, anthocyanins, flavonoids).[26,27] Blueberry extract is another organic source rich in antioxidants and has been studied for its potential beneficial role in several diseases, including type 2 diabetes (T2D).[28] In one small study of 20 female patients with T2D, a topical formulation containing blueberry extract and C-xyloside (a glycosaminoglycan stimulator) significantly improved several parameters of skin aesthetics including fine lines (P=.01), firmness (P=.0011), radiance (P<.001), tone (P=.014), smoothness (P<.001), creping (P<.004), and overall appearance (P<.001).[29] However, researchers were unable to measure changes in AGEs due to the short duration of the study (12 weeks).[29] Further trials are needed to analyze this topical formulation over extended periods and capture potential meaningful changes in skin AGEs.

Another emerging strategy to prevent excessive skin glycation due to AGEs includes the use of exogenous collagen. In a recent study of 31 Japanese patients aged 47 to 87 years old,

FIGURE 2. Strategies for reducing AGEs: Lifestyle recommendations.[33-36]



the investigators showed that consumption of exogenous collagen (5 g, derived from fish) containing high concentrations of prolyl-hydroxyproline and hydroxyprolyl-glycine or placebo for 12 weeks resulted in significantly lower levels of skin AGEs (P<.05) and a slightly lower insulin resistance index (correlation between the rate of change in levels of AGEs and the rate of change in the homeostasis model assessment ratio, [HOMA-R values, an indicator of insulin resistance]).The study formulation was well tolerated, with no significant safety signals reported.[30] Although larger trials in a broader study population are needed, these data suggest that consumable collagen peptides should be further studied as a possible intervention to manage illnesses related to the accumulation of AGEs.

Lastly, vitamin supplements (eg, vitamins B_6, C, D, E) can also target the process of glycation since they can scavenge free radicals, preventing the generation of reactive intermediates involved in forming AGEs.[1,15,31,32]

Clinical Pearls From the Physician

Remember, it is important to counsel your patients on how to make their skin look healthier and protect it from external factors that may enhance the metabolism of AGEs and their toxic accumulation. Important lifestyle modifications include increasing the consumption of fruits and vegetables that are enriched with antioxidants and refraining from eating foods that are high in sugar, baked, fried, or roasted.[37] Patients should also refrain from smoking and excess alcohol consumption.[36,37] Incorporating a daily supplement that contains vitamins C, D, and E into one's daily regimen may also help maintain skin health, as these nutrients can aid in building a line of defense against AGEs and associated oxidative stress.[32] Patients may also consider applying a daily moisturizer cream, sunscreen, or facial foundation to shield them from the unwanted effects of UV rays and pollutants (eg, aerosolized nanoparticles).[38] Lastly, for patients who use makeup, using colored cosmetics that contain talc, kaolin, or oxide-based compounds (eg, titanium oxide, iron oxide) is advised.[39,40] This is important as it can provide an additional layer of skin protection against the effects of environmental insults that cause glycation and speed up the aging process.

DISCLOSURES

Zoe Diana Draelos MD has the following relevant financial relationships: Contracted researcher and consultant for: Aclaris Therapeutics, Inc.; Aesthetics Biomedical; Allergan, Almirall; Amderma; Amgen, Inc.; AOBiome; Arcutis Biotherapeutics, Inc.; Bausch Heath; Bayer AG; Biopelle; Boehringer Ingelheim Pharmaceuticals, Inc.; Boots; Botanix Pharmaceuticals; Brickell Biotech, Inc.; Burt's Bees; Carpe; Chattem Chemicals Inc.; The Chlorox Company; Clarke Pharmaceuticals, Inc.; Colgate-Palmolive Company; Coloplast Corp.; Combe; DelArrivo, Inc.; Dermavant Sciences, Inc.; Dermira, Inc.; Dial; Dr. Reddy's Laboratories Ltd.; Estée Lauder Inc.; E.T. Browne Drug Co., Inc.; Evolus, Inc.; Ferndale Laboratories, Inc.; Foamix Pharmaceuticals Ltd.; Galderma Laboratories, LP; Genentech, Inc.; General Mills, Inc.; GlaxoSmithKline; Helix Biomedix, Inc.; Henkel; International Specialty Products, Inc.; Johnson & Johnson Services, Inc.; Kamedis; Kao Corporation; La Roche-Posay; LEO Pharma Inc.; Lilly; L'Oréal; Maruho Co., Ltd.; Merck; Nice-Pak Products, Inc.; Novartis; Nu Skin; Perricone MD; Perrigo Company plc; Pfizer Inc.; PharmaNet, Inc.; Proctor & Gamble; Reckitt Benckiser Group plc; Revance Therapeutics, Inc.; Rodan & Fields, LLC; Roivant Sciences Ltd; Sanofi; SkinCeuticals; Symrise; Taro Pharmaceuticals Industries Ltd.; Teoxane; TEVA Pharmaceuticals USA, Inc.; Topix Pharmaceuticals, Inc.; Vanda Pharmaceuticals Inc.; Verrica Pharmaceuticals; Warner-Chilcott; WellSpring Pharmaceutical Corporation; YA-MAN Ltd; ZO Skin Health, Inc.

Compensation: Zoe Diana Draelos MD received an honorarium from Medscape Education for authorship of this manuscript.

Commercial Supporter: Supported by an independent educational grant from SkinCeuticals.

ACKNOWLEDGMENT

The author would like to thank Briana Betz PhD and Jason Luis Quiñones PhD for their assistance in drafting the manuscript, Joel Vega for his editorial assistance, and Trudy Grenon Stoddert ELS for her editorial assistance and for preparing the manuscript for submission.

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