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NEWS, VIEWS, & REVIEWS

Antihyperglycemic Medication to Combat Skin AGE-ing

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INTRODUCTION

A multifactorial and complex process, aging is defined as the culmination over time of damage in cells and tissues resulting in altered function of an organism. Intrinsic and inevitable, the aging process impacts every organ of the human body, including the skin, leading to age-related diseases and ultimately death. Oxidative stress, cellular senescence, chronic inflammation, and the accumulation of metabolic waste products are major contributing factors to aging.[1] Skin aging affects not only its protective mechanical and immunological functions but also its aesthetic appearance. Two antihyperglycemic drugs, metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have garnered interest for their geroprotective properties.[2,3] The review herein will summarize the mechanisms underlying how these drugs may be protective specifically against skin aging.

Pathogenesis of Skin Aging

Defining features of aged skin are decreased elasticity, epidermal atrophy, dyschromia, and xerosis.[4] A main intrinsic factor of skin aging is the decline of estrogen and androgen levels over time, while the primary extrinsic factor is exposure to ultraviolet radiation (UVR).[5] Common to both intrinsic (chronological) and UVR-induced skin aging is the increased generation of reactive oxygen species (ROS) and DNA damage. Both products lead to increased induction of matrix metalloproteinases (MMPs), thereby increasing degradation of collagen and other extracellular matrix components and inhibiting neocollagenesis.[5]

Advanced glycation end products (AGEs) are increasingly implicated in age-related diseases.[6] AGEs are free amino acids of nucleic acids, proteins, or lipids covalently bonded together under high-glucose conditions.[7] Accumulating in the skin throughout aging and during high-glycemic states, AGEs lead to the transcription of proinflammatory genes through activation of the nuclear factor kappa B (NFkB), induce oxidative stress, and impair the biomechanical properties of skin through deleterious modification of collagen, elastin, and fibronectin.[6,8] Reducing the accumulation of AGEs and thus activation of the receptor for AGE (RAGE) through anti-hyperglycemic medications therefore may protect against skin aging. A summary of putative anti-aging mechanisms can be found in the Table.

Antihyperglycemic Medications and Skin Aging

Metformin

Metformin is a synthetic biguanide used as a first-line treatment for type 2 diabetes. By enhancing insulin sensitivity, decreasing glucose production in the liver, increasing GLP-1, and reducing intestinal absorption of glucose, metformin effectively lowers basal and post-prandial blood glucose levels.[9,10] Metformin has been associated with a reduction in early mortality due to age-related diseases and this effect is theorized to be a result of its antihyperglycemic actions.[2] Studies specifically investigating the impact of metformin on skin aging have been conducted in vitro and using animal models. Treatment of human foreskin fibroblasts with 100 μM metformin attenuated photoaging

Table 1. Putative Anti-Skin Aging Mechanisms of Antihyperglycemic Drugs

Drug	Anti-aging Mechanisms
Metformin	Decreased activation of RAGE/NFkB pathway[22] Decreased ROS accumulation[11] Reduced mitochondrial autophagy (mitophagy)[11] Inhibits activation of PI3K/AKT/mTOR signaling pathways[11] Reduced photoaging by UVA and UVB radiation[11,12] Decreased collagen degradation[13,14] Reduced MMP expression[11] Decreased fibroblast apoptosis[13,14]
GLP-1 Receptor Agonists	Reduces expression of inflammatory factors IL-17, IL-22, IL-23, and TNF alpha[17] Reduces influx of invariant natural killer T cells[16] Reduces C-reactive proteins[19] Reduces MMP-9 and MMP-9/TIMP ratios[19] Induces oxidative defense genes HO-1 and NQO1[20] Inhibits NAD(P)H oxidases[21]
Both	Decreased AGEs[22,23]

Abbreviations: interleukin (IL), tumor necrosis factor (TNF), matrix metalloproteinase (MMP), tissue inhibitor of matrix metalloproteinases (TIMP), heme oxygenase 1 (HO-1), quinone oxidoreductase 1 (NQO1), nicotinamide adenine dinucleotide phosphate (NADPH), advanced glycation end products (AGEs), receptor of advances glycation end products (RAGE), reactive oxygen species (ROS), phosphatidylinositol 3-kinases (PI3K), mammalian target of rapamycin (mTOR)

due to UVA irradiation through reduced ROS accumulation and mitophagy, and the attenuation of the DNA-repairing phosphatidylinositol 3-kinases (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways[11]; in vivo, UVA-irradiated mice treated with 10 mg/kg/day of metformin showed decreased signs of skin photoaging grossly and histologically and had significantly decreased expression of MMP1 and the mitophagy protein Parkin.[11] Similarly, signs of UVB-induced photoaging were attenuated following the topical application of 0.6% metformin cream to mice skin.[12] Furthermore, in vitro studies exploring the effects of 50 μM and 500 μM metformin on the viability of fibroblasts under high-glucose conditions (50 μM) found both doses of metformin significantly downregulated NFkB (p65) activity, inhibited apoptosis of fibroblasts, and increased production of collagen I-III compared to control.[13,14] Altogether, metformin appears to have protective properties against two major sources of skin aging, UVR-damage and AGEs.

Glucagon-Like Peptide-1 Receptor Agonists

Indicated for type 2 diabetes and weight management, GLP-1 RAs increase incretin hormones and glucose-dependent insulin release, decrease glucagon secretion, and reduce gastric emptying.[15] Given the similar antihyperglycemic effect of metformin, it is logical to suspect GLP-1 RAs may also have similar anti-aging effects. Indeed, multiple clinical trials demonstrated that GLP-1 RAs delay and treat age-related diseases, including osteoporosis, Parkinson's disease, atherosclerosis, kidney diseases, and non-alcoholic fatty liver disease.[3] GLP-1 RAs also ameliorate psoriasis by inhibiting generation of inflammatory cytokines.[16,17] Though GLP-1 RAs have not been studied within the context of skin aging, chronic inflammation is a known driver of skin aging as discussed above[18]; thus the anti-inflammatory benefits of GLP-1 RAs may curtail skin aging, namely through reduction of deleterious AGEs. Notably, GLP-1 RAs have demonstrated efficacy in diabetic rat wounds, significantly reducing C-reactive protein concentrations and MMP-9/tissue matrix metalloproteinase inhibitor-1 ratios in fibroblast cultures, reflecting increased expression of anti-inflammatory and pro-healing markers.[19] Purposeful studies on the effects of GLP-1 RAs and their impact on skin aging specifically are necessary to fully establish a relationship.

CONCLUSION

While the role of antihyperglycemic drugs such as metformin and GLP-1 RAs in combatting skin aging have yet to be fully described, dermatologists should be aware of the underlying mechanisms of these drugs and anticipate their potential inclusion in future armamentariums.

DISCLOSURE

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