Skin Aging: An Inevitable Physiological Process

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ABSTRACT Aging is a continuous and irreversible process which affects the skin. Skin aging, which is the result of changes in the function and structure of the dermis, is characterized by thinning, drying, and loss of elasticity. It significantly adversely influences the role of the skin as a barrier against all aggressive exogenous factors. Herein, skin aging is reviewed in terms of clinical, pathological, etiopathogenic, and molecular aspects.

KEY WORDS: skin, aging, pathogenesis

INTRODUCTION

The skin makes up about 17% of the human body weight and acts as a protective-defensive line against water loss, physical stressors, and aggressive environmental factors such as sun exposure and pollution (1). It also has a role in controlling body temperature and the perception of temperature, pressure, and pain (2). The epidermis, particularly its outermost layer, the stratum corneum, plays an important role as a barrier against exogenous factors and water loss, while the mechanical properties effective against physical stressors are mainly dependent on the structural composition of the dermis, although the stratum corneum can also significantly influence mechanical properties of the skin. In the dermis, elastic fibers form a network that allows the skin to return it to its initial position after deformation, while collagen fibers make up the main tensile power of the skin (1).

Aging is a continuous and irreversible process which affects the skin and the other organs (3). The human body, which is composed of a highly complex network of tissues, organs, proteins, and genes, loses its homeostatic balance due to the aging process (4). Skin aging, which is the result of changes in the function and structure of the dermis, is characterized by thinning, drying, and loss of elasticity (5). It significantly adversely influences the role of the skin as a barrier against all aggressive exogenous factors (1). Skin aging-related disorders result in significant morbidity in the elderly, particularly if associated with other comorbid systemic diseases (3).

Given the fact that the human skin is the largest organ of the body, it offers an optimal model for investigating biological pathways and alterations which are common to many aging-related disorders in the other organs (4).

EPIDEMIOLOGY

During the past few decades, there has been an increase in the elderly population across the world as a result of changes in socio-economic development. It is estimated that the number of people aged 65 or older will increase from 524 million in 2010 to approximately 1.5 billion in 2050, with more of an increase in developing countries (3). These changes in worldwide demographics are accompanied by the increasing risk of aging-related disorders such as diabetes mellitus, cardiovascular diseases, dementia, cancer, chronic inflammatory disorders, and degenerative alterations (4).

In comparison with young skin, geriatric skin is more prone to different dermatoses, and thus 13.3% of skin disorders have been observed in elderly persons over 60 years of age. Furthermore, there is an association between systemic disorders and skin problems in the general population. Therefore, in geriatric people with more prevalent systemic disorders, skin conditions due to these systemic disorders are common. In a study by Nair and Vora, eczema was the most common dermatosis reported in elderly patients with hypertension, while generalized pruritus was the most common in patients with diabetes (3).

CLINICAL MANIFESTATION

The most important features associated with skin aging are summarized below.

Photo-aging: This is a dermatosis caused by prolonged exposure of the skin to solar ultraviolet (UV) radiation. It is characterized by fine and coarse wrinkles, roughness, erythema, lentigines, and dyspigmentation (6).

Skin laxity, sagging, wrinkling, and fragility: The intrinsic skin aging process results in reduced numbers of dermal fibroblasts, decreased synthesis of collagen and elastin in the extra cellular matrix (ECM), particularly collagen types I and III, and thinning of the dermis, all of which induce laxity, wrinkling, and loss of elasticity, as well as increased fragility in the skin (7).

Insufficient sweating: Decreased sweat gland function and reduced sensitivity of these glands to cholinergic stimuli are the most important factors that play a role in insufficient sweating caused by the aging process (8).

Increased sensitivity to temperature: Thermoregulation, as a vital function of the skin, is also impaired by the aging process (8). Catecholamine-induced lipolysis, which is the first step for generation of energy substrates via triglyceride hydrolysis, decreases with aging. Mobilization impairment of free fatty acids due to the aging process results in increased visceral adiposity and lower exercise capacity. All these factors are responsible for failure to maintain core body temperature during cold stress in the elderly (9). On the other hand, there is an association between ageing and decreased heat tolerance as well as impaired response of thermoregulatory effectors (10). Additionally, decreased cutaneous vascular function and reduced sweating rate leads to reduced sweat function during the aging process (8). All of these factors lead to a high risk of developing life-threatening manifestations of heat stress such as heat stroke, which progressively increases with aging (10).

Xerosis (dry skin): In spite of unaltered thickness of the stratum corneum and modestly decreased or unchanged hydration of this skin layer, synthesis of surface lipids significantly decreases with aging, which results in increased risk of xerosis, pruritus, and skin irritation in the elderly (8).

Pruritus: Aging results in changes in the skin structure and function such as hydration loss, impaired blood circulation, impaired function of the skin as a barrier to pathogens, impaired immune system responses, loss of collagen, etc. These changes play a large role in the increased risk of pruritic disorders in the elderly. In this population, the presence of comorbid conditions, the lack of mobility, and the increased use of medications also increase the risk of pruritus (3). Furthermore, the loss of age-related Merkel cells has been suggested as another cause of chronic pruritus in the elderly, as it results in converting the sense of touch to an itching sensation (7).

Altered skin pigmentation: Senescence-related skin pigmentation such as mottled pigmentation (senile lentigo) and melasma are typical features of the photoaging process. The cellular senescence, which is a state of permanent arrest of the cell cycle, contributes to the skin pigmentation observed in the aging process. Different types of skin cells such as melanocytes, keratinocytes, fibroblasts, and endothelial cells, as well as the crosstalk between them, contribute to impaired melanogenesis and subsequent aging-related pigmentation during this process (11).

Impaired wound healing: In the elderly, the risk of chronic wounds is high, with a rise in the prevalence rate of chronically-afflicting conditions such as diabetes mellitus (12). Impaired wound healing is a noticeable clinical manifestation in the process of aging. This problem is associated with prolonged inflammatory response and defects in fibroblast-dependent ECM formation, neovascularization, and re-epithelialization (13).

Increased risk of skin malignancy: Long-term exposure to UV radiation impairs the normal skin structure, which results in increased risk of skin cancer (photocarcinogenesis) (14).

Skin problems due to systemic disorders: In the elderly population, the risk of skin conditions is increased because of a high prevalence rate of chronic systemic diseases. Additionally, systemic diseases often decrease the itch threshold, resulting in a mild stimulus being able to trigger an exaggerated pruritus in this setting. Moreover, comorbidity with decreased skin hydration in geriatric skin exacerbates pruritus in older patients with systemic diseases (3).

The prevalence of pressure ulcers is high in the elderly population, particularly in persons suffering from chronic diseases. Due to aging, several chronic conditions impairing mobility, with cumulative vascular, inflammatory, hormonal, and degenerative changes, play important roles in the development and treatment of pressure ulcers. Increased prevalence of some conditions and comorbidities resulting from the aging process is associated with increased pressure ulcers, among which cardiovascular diseases, diabetes mellitus, chronic pulmonary diseases, renal diseases, musculoskeletal disorders, neurodegenerative disorders, malnutrition, anemia, infectious diseases, incontinence, and hospitalization are the most important ones (15).

The relationship between some of the most important chronic systemic diseases prevalent in elderly persons with skin problems is summarized below:

Cardiovascular diseases: Advanced cardiac diseases with low cardiac output and decreased oxygenation lead to hypotension, decreased blood perfusion, and peripheral ischemia in the elderly, which can increase the risk of pressure ulcers. Atherosclerosis as a primary physiological process involving the vascular system in the elderly can result in local ischemia in the skin, with increased risk of pressure ulcers (15). Hypertension results in impaired blood flow, which predisposes the skin to eczema, infection, xerosis, and delayed wound healing. Additionally, vascular atrophy, impaired supporting dermis, and loss of collagen and elastin fibers enhance the risk of vascular diseases such as stasis dermatosis (3).

Hyperlipidemia: This condition increases the risk of cutaneous infection, xerosis, and impaired wound healing by disturbing the blood flow (16).

Diabetes mellitus: Because of impaired glycemic control, poor vascular and microvascular circulation, peripheral neuropathy, and decreased immune response in elderly diabetic patients, the risk of skin and soft tissue infection is high (17).

Thyroid disorders: In elderly people with thyroid disorders, the risk of xerosis, pruritus, and lichen planus is high (3).

Renal failure: As a chronic inflammatory process, it results in increased level of pro-inflammatory cytokines and histamine in the skin, which enhance the prevalence rate of xerosis and pruritus in the elderly (18, 19).

Chronic obstructive pulmonary disease: Geriatric patients with chronic obstructive pulmonary disease have a high prevalence of herpes zoster due to systemic inflammation and dysregulated immune function underlying this disorder, as well as corticosteroid administration in these cases (20).

Neurodegenerative disorders: Prevalence of neurodegenerative disorders such as dementia, Alzheimer's disease, and Parkinson's disease increases with age. Increased tendency towards bed confinement, immobility, and flexion contractures in cases with advanced stages of these diseases also increases the risk of pressure ulcers due to the aging process (15).

Malnutrition: Because of the high prevalence rate of chronic conditions in the elderly, the risk of dysphagia, anorexia, and malnutrition is high. Secondary to reduced tissue thickness of the skin and subcutaneous tissues and impaired immune and hormonal function due to these conditions, the prevalence of pressure ulcer increases in the elderly (15).

Anemia: With age, anemia secondary to chronic diseases such as chronic renal failure, inflammatory diseases, and cancers can adversely influence the healing process. Additionally, consequent changes in the oxygen dissociation-curve increase the risk of tissue ischemia and the development of pressure ulcers (15).

Incontinence: Secondary to increased prevalence of urinary and/or fecal incontinence in the elderly, compression and shear in the aged skin accompanies the highest skin surface load due to wetness. This increases the risk of pressure ulcers in the elderly (15).

HISTOPATHOLOGY

The skin demonstrates many histologic changes with progressive age, most of which can be attributed to chronic UV exposure. The changes are more pronounced in the epidermis and dermis than in the subcutis.

Epidermal changes

With advanced age, the epidermis becomes progressively thinner. While keratinocyte maturation is preserved, basal keratinocytes give rise to fewer spinous layers before developing a granular layer and ultimately, the stratum corneum. In some cases, rete ridges become less pronounced. A tendency towards xerosis with thickening of the stratum corneum is present in the elderly population. These changes are markedly accentuated in areas subject to chronic lifelong UV exposure but occur to some degree in all non-acral surfaces (21).

With prolonged UV exposure, the effective transfer of melanin pigment from melanocytes to keratinocytes becomes disrupted. This results in uneven distribution of the pigment. Darker areas, known as "age spots", "liver spots", lentigo senilis, senile lentigines, or actinic lentigines are a frequent manifestation of aging skin. Histologic changes include increased basilar melanin, largely present within the keratinocytes. The basilar melanocytes may be slightly increased in number, but lack significant cytologic atypia, any tendency towards nest formation, or upward pagetoid migration through the epidermis. The keratinocytes demonstrate irregular numbers and distribution of melanosomes on electron microscopic examination, further suggesting impaired pigment transfer between the keratinocytes and melanocytes (21).

Likely due to diminished blood supply, there is a progressive loss of hair follicles occurs with age. This finding is most pronounced on the skin from the lower extremities. The pilosebaceous units are gradually replaced by fibrotic dermal collagen (21).

Another secondary change is an increase in the presence of sebaceous units in areas of the skin that generally contain many sebaceous glands. This histologic alteration is believed to be secondary to increased levels of circulating estrogens that are observed in the elderly population (21).

Dermal changes

Dermal changes observed in aging skin largely center around UV-induced damage to dermal supporting connective tissue. These changes are readily observed with routine microscopic evaluation. The normal dermis is comprised of predominantly collagen types I and III, with more of the former in the reticular dermis and more of the latter in the papillary dermis. Type III collagen fibers are thinner and have a wispy appearance on routine hematoxylin and eosin staining. Within the papillary dermis, these fibers may be vertically oriented. In the reticular dermis, it is difficult to identify the type III collagen with routine microscopy, as the type I collagen fibers tend to be much larger, thicker, more eosinophilic, and predominant. Type VII collagen is reduced in the elderly, and this is believed to play a role in the clinical appearance of wrinkling (22).

Another component of the dermal connective tissue are elastic tissue fibers, which are composed of two components: oxytalin and elaunin. These elastic fibrils are only 1-3 μ in thickness. Those found in the deeper reticular dermis are somewhat thicker and are arranged in bundles that run parallel to the surface of the skin. In young, healthy skin, the elastic tissue fibers are relatively inconspicuous on routine histologic sections, as the collagen fibers comprise the vast majority of the eosinophilic dermis. However, the elastic tissue fiber infrastructure is a vital component of the dermis, as evidenced in conditions of elastolysis (i.e., anetoderma, wrinkling due to mid-dermal elastolysis) that result in loss or destruction of such fibers (23).

In skin that is not subject to long-term UV exposure, there is a progressive loss of the elastic tissue fibers within the skin, a finding demonstrated only with the use of elastic tissue stains. By middle age, there is a reduction in the amount of the vertically-oriented oxytalin component of the elastic tissue fibers, ultimately resulting in near absence in the skin of the elderly (23).

In sun-exposed skin, the histologic changes are much more obvious and do not require special stains to be detected. The collagen present in the superficial dermis loses its eosinophilia and fibrillar appearance and is replaced by globular, more basophilic material. This material is highlighted with use of elastic tissue stains. This is known as elastotic change. This material retains the antigenic properties of elastin, but has lost the microfibrillar features of young, healthy elastic tissue. Some authors believe that this elastotic material is not the result of degenerating healthy elastic tissue fibers but is rather a newly-formed material produced by sun-damaged fibroblasts within the aging dermis. It has also been postulated that increased transcriptional activity by the elastin gene may account for this elastotic material (23). The material consists of elastin, fibronectin, fibrillin, and various glycosaminoglycans (24). This elastotic material has a different ultrastructural appearance than normal, healthy elastic tissue. The thick fibers show a fine, granular matrix admixed with electron-dense inclusions. Microfibrils are largely absent (25).

Many of the other histologic changes present in the dermis are the result of disruption of the connective tissue infrastructure. Aging skin presents vascular ectasia, vascular fragility, and dermal hemorrhage. These changes can largely be attributed to lack of structural support of the vascular walls. With diminished extravascular support, long-standing intraluminal pressure caused by the blood flow results in progressive vascular ectasia, thinning of the vessel walls, and ultimately in fragility and hemorrhage (25).

Subcutaneous changes

Over time, progressive loss of subcutaneous fat occurs in many body sites. This is primarily due to loss of adipocytes through apoptosis. In the abdomen of men and the thighs of women, subcutaneous fat may actually increase with aging (25). The exact factor(s) contributing to this shift of the fat distribution are not well-known. It seems that hormonal alteration due to aging may play role in this shift (26).

ETIOLOGY

Skin aging is a complex process resulting from intrinsic factors (chronologic aging with a genetic basis) and extrinsic factors (such as detrimental influences from the environment, mainly UV radiation) (5). Intrinsic skin aging is defined as an inevitable physiological process resulting in thin, fine wrinkles, dry skin, and progressive dermal atrophy. Extrinsic skin aging is induced by external environmental factors leading to coarse wrinkles, a rough appearance of the skin, loss of skin elasticity, and skin laxity (27).

Intrinsic factors

Impaired fibroblast function characterized by abnormality in proliferation, differentiation, and synthesis of collagen plays the main role in inducing skin aging. These changes result in structural, functional, and mechanical abnormalities in the skin. Additionally, fibroblast interaction with the surrounding fibrous matrix is decreased due to aging, which results in a vicious cycle of decreased procollagen synthesis, disorganization of the collagen bundles, and more loss of mechanical stimulation of the fibroblasts (5).

Extrinsic factors

The structural and molecular composition of the epidermal stratum corneum can be altered by extrinsic factors associated with its role as skin barrier (1). The most important environmental factors implicated in the aging process are listed below.

Ultraviolet radiation: UV radiation has a large role in the photoaging process through direct destruction of tissue and indirect effects due to the induction of inflammation and reactive oxygen species (ROS) production (7, 28). UV radiation is responsible for approximately 80% of facial aging. The severity of photoaging is dependent on a variety of factors such as the season, altitude, skin phototype, and frequency, duration, and intensity of the solar radiation (7).

With regard to the different wavelengths of UV, although UVC has the strongest mutagenicity, it is blocked by the ozone layer. UVB also has strong mutagenicity and directly interacts with the DNA for the production of thymine dimer photoproducts, leading to DNA damage. Although UVA mutagenicity is weak, its penetration to the skin is high, and it can thus affect the dermis and even the subcutaneous tissue (7).

UVB can break down the extracellular matrix (ECM) and create an imbalance between production and degradation of the ECM components in the dermis. It acts by increasing the expression level of proteinases, such as the matrix metalloproteinases (MMP) and elastase, and subsequently results in decreased expression of ECM components such as type I collagen, fibrillin 1, elastin, and dystroglycan 1 (28).

Furthermore, UV radiation can induce production of ROS, resulting in destructive oxidative stress, activation of the arachidonic acid pathway, and mediation of inflammatory responses. Acute UV radiation can cause sunburn and exaggerated pigmentation, while long-term exposure can induce malignancy (7).

Dietary factors: Calorie restriction without malnutrition can extend the lifespan and prevent age-related diseases through induction of sirtuin mediation by upregulation of AMPK and increase of NAD^+ levels (29).

Air pollution: Air pollution is defined as contamination of either the indoor or outdoor environment by physical, chemical, or biological agents. It is currently considered the largest single environmental risk factor for global health with carcinogenic properties. Traffic-related air pollution plays a well-documented role in the skin aging process. Air pollution is comprised of a mixture of components including particulate matter of various sizes (such as PM10, PM2.5, or smaller) and gases (such as O3, NOx, NO2, and CO). The association of PM exposure and skin aging has been demonstrated in cohort studies and has been confirmed by mechanistic investigations. The effect of NO2 exposure in the induction of pigment or age spots (lentigo senilis) has been demonstrated in different epidemiological studies. Ozone exposure can promote the appearance of wrinkles (30). The role of polyaromatic hydrocarbons has been demonstrated in the induction of extrinsic skin aging, skin pigmentation, acneiform eruptions, and cutaneous cancers. Volatile organic compounds can induce atopic dermatitis in sensitive patients (31).

Smoking: Long-term exposure to cigarette smoke is considered an independent cause of skin aging. It can promote the intrinsic aging process (7). In addition to its contributing role in premature aging, smoking increases the incidence rate of acne vulgaris, psoriasis, allergic skin conditions such as atopic dermatitis and eczema, and cutaneous cancers (31).

PATHOGENESIS AND PATHOPHYSIOLOGY

The cellular level

Cellular senescence is a physiological process resulting in permanent arrest of the cell cycle that manifests as flattening and increased size of the nuclei and nucleoli and the appearance of vacuoles in the cytoplasm (32). In the process of cellular senescence, the capacity of normal dividing cells for replication decreases over time (7). Although this process is beneficial in young organisms under stress as it removes aberrant cells, it is detrimental in old organisms and induces of the aging phenotype. With age, the percentage of senescent cells increases (32). Cellular changes due to skin aging at different levels of the skin are described below.

Epidermal level

Generally, all structural elements of the stratum corneum have their own characteristics and their own role in mechanical properties of the skin that can be altered in the aging process. The process of aging alters the physiological parameters of the stratum corneum, including the thickness, intercellular lipid content, and structure, subsequently leading to dysfunction of the epidermis in its role as a barrier against aggressive environmental factors. The keratin (α-helix form) from the corneocytes, and the protein, lipid, and water content of the epidermis, all affect stratum corneum fatigability (1).

In the intrinsic aging process, the most significant pathological alterations involve the basal cell layer. In this physiological process, the proliferation of cells in this layer decreases, resulting in epidermal thinning, a decreased contact surface between the epidermis and dermis, and a subsequent decrease in the nutrition supply to the epidermis. Consequently, the proliferative ability of the cells, including keratinocytes, fibroblasts, and melanocytes, is reduced (27).

By contrast, the epidermis in extrinsically aged skin is thicker and the stratum corneum is more affected than the basal cell layer. The stratum corneum increases secondary to failure in degradation of the corneocyte desmosomes. The differentiation process of the epidermal keratinocytes is altered by UV radiation, resulting in increased expression of involucrin as a differentiation marker. In the basal cell layer, the expression of β1-integrin as a cell-surface protein interacting with ECM proteins and as one of the epidermal stem-cell markers is significantly reduced, demonstrating the impaired proliferation of the basal keratinocytes. The expression of collagen type I and VII decreases in photoaged skin (27). As part of the photoaging process, UV radiation stimulates melanocytes to increase synthesis and transfer of melanin to the neighboring cells, forming age-related pigmented spots (7).

Dermal level

The number of mast cells and fibroblasts decreases due to intrinsic skin aging (27). The degradation of collagen and elastic fibers is associated with the aging process (1). A remarkable characteristic of extrinsic skin aging is the accumulation of abnormal elastic tissue deep in the dermis, also known as solar elastosis. UV radiation increases the expression level of elastin by 4 times, which leads to elastolysis by proteases through the elastic fiber cleavage and consequently severe deposition of the truncated elastic fiber. Additionally, the function of the microvasculature declines in the skin aging process due to endothelial cell dysfunction, resulting in decreased angiogenic capacity, aberrant expression of the adhesion molecules, and altered vasodilatory function (27). Additionally, reflex vasoconstriction during cold exposure is significantly altered in the elderly, resulting in relative inability to maintain core temperature during mild cold stresses. This is due to functional impairment at multiple levels along the efferent sympathetic reflex axis, including a defect in the sympathetic outflow directed to the skin vasculature, decreased presynaptic neurotransmitter synthesis and release, and a deficit in end-organ responsiveness at several loci, as well as potential impairments of the afferent thermoreceptor function (33).

Subcutaneous level: The occurrence of mutations in the mitochondrial (mt)DNA plays a role in the aging process. Studies have shown that these mutations, along with ROS, are two important factors contributing to the aging process of the subcutaneous fatty tissue through induction of apoptosis, leading to reduction of subcutaneous fatty tissue and loss of adipocytes. Hunger signals contribute to the aging process by playing a role in reduction of the fat content in the adipocytes due to a decrease in their intensity (34).

Cockayne syndrome (CS) A and B proteins are two factors that play a role in repairing oxidatively-induced DNA damage through nucleotide excision repair in the nucleus. These two proteins, which are found in very large amounts in mitochondria upon oxidative stress, can protect mtDNA from deletions through direct interaction with the mtDNA and two repair-associated proteins, namely mtSSBP-1 and mtOGG-1. Due to a lack of CSA or CSB, accumulation of mtDNA mutations, particularly in the cells of subcutaneous tissue, can mediate loss of adipocytes via apoptosis (34).

Skin appendages

With aging, skin appendages also show significant changes, such as atrophy of the sebaceous glands, decreased sweating, and insufficient secretion of oily compounds on the surface of the skin (7).

The molecular level

In the process of cellular senescence, some biomarkers target the senescence-associated β-galactosidase and heterochromatic foci, telomerase attrition, cell cycle arrest in the G1 phase, and accumulation of damaged DNA with increased expression of ATM, p16, p21, and p53 (29). Some of the most important factors contributing to the aging process at the molecular level are listed below.

Water content: The skin requires large amounts of water to retain its health. The water content of the skin is dependent on the evaporation rate through the skin and on epidermal hydration. The presence of glycosaminoglycans in the dermis, especially heparan sulfate and versican, are essential for skin hydration. As the amount of glycosaminoglycans decreases with aging, the hygroscopicity of the skin also subsequently decreases (35). The water molecules have a role in the mechanical properties of the epidermis, particularly the stratum corneum. It appears that moderate hydration has a significant role in achieving optimal biomechanical characteristics, including strong elasticity and low fatigability of the stratum corneum (1).

Protein content: Alteration of the α-helix form of keratin due to aging plays a role in the fatigability of the outermost, but not the innermost, layers of the stratum corneum. It seems that the unfolding process of the proteins, which increases with the depth of skin, results in protein conformational changes; this process may explain why the α-helix form of the keratin does not play more of a role in skin fatigability in the deeper layers (1).

Lipid content: Skin aging is promoted by increased in-situ production of ROS as results of disturbed mitochondrial function and acute stress responses to the environmental insults. ROS can disturb the ECM and the structure of DNA, proteins, and lipids (35). The lipid content of the outermost, but not the innermost, layers of the stratum corneum has a key role in skin fatigability due to the aging process (1).

Collagen: Procollagens are sensitized as individual chains with a central triple helix domain flanked by amino and carboxy propeptides. Before formation of the homo- and hetero-trimers from the procollagens, leading to the synthesis of the collagen fibril and fiber, these propeptides are proteolytically cleaved by the procollagen N-proteinases belonging to the family of disintegrin and metalloproteinase with thrombospondin type I domain proteases (ADAMTS), including ADAMTS2, 3, and 14, and C-proteinases from the tolloid family, respectively. These cleavages decrease the solubility of the collagens and induce their spontaneous assembly into long and cylindrical collagens (36).

Type I collagen is the major component of the ECM in the dermis and is progressively destroyed in the process of UVB-induced aging (28). In intrinsically aged skin, the production of type I procollagen decreases due to downregulation of the transforming growth factor-β (TGF-β)/Smad signaling and its downstream connective tissue growth factor that has been identified as a regulator of the collagen expression (27). Although the function of minor collagens present in the dermis, such as types VI, XXVII, and XV, has not been defined, their role in the aging process along with collagen I has been hypothesized (28).

Elastic and fibrillin fiber: Elastic fibers are the essential component of the ECM in the human body and are present in several tissues and organs with elastic and resilient properties such as the skin, lungs, and blood vessels. Due to aging, these fibers are influenced by a variety of enzymatic, chemical, and biophysical factors, resulting in the accumulation of damage in them due to their low turnover. Aging induces changes in elastin and elastic fibers, which include enzymatic destruction, oxidative degradation, glycation, calcification, aspartic acid racemization, binding of lipids and lipid peroxidation products, carbamylation, and mechanical fatigue, leading to their functional impairment (37). Furthermore, expression of elastin and fibrillin 1 is seriously affected by UVB irradiation (28).

Fibroblast growth factor (FGF): FGF is an important growth factor in dermatology, as it promotes the production of type 1 collagen. Hence, it plays a role in governing the process of skin aging. This growth factor increases the proliferation and activation of fibroblasts and promotes collagen accumulation. It also stimulates endothelial cell division, through which it induces angiogenesis, which plays an important role in the cell repair process. In aged skin, collagen synthesis by fibroblasts is decreased, along with an increased function of the enzymes degrading the collagens. FGF has a role in controlling the skin aging process, acting by inducing repair and remodeling of the dermis, as it is a regulatory protein that mediates important signaling pathways and acts on cell regeneration and repair. Studies have shown that FGF plays an important role in anti-aging therapy through stimulation of the collagen and elastin synthesis contributing to skin resistance and elasticity (38).

Vascular endothelial growth factor (VEGF): Epidermis-derived VEGF is a homodimeric, heparin-binding glycoprotein which has a role as a potent angiogenic factor. It binds to specific receptors, mainly present on endothelial cells (39). VEGF is necessary for skin rejuvenation at both the clinical and molecular levels. This requirement has confirmed the "angiogenesis hypothesis of aging". Cutaneous vascular networks undergo noticeable alterations with age. Thus, a reduction in microvasculature can be observed in the skin of elderly persons. On the other hand, studies have shown that a single exposure to the UVB irradiation results in vascular hyperpermeability, dilation of the dermal blood vessels, and angiogenic switch, while acute UV irradiation can promote the process of angiogenesis in the human skin. All of this indicates the significance of alterations in vascularization that take place intrinsically aged and photo-aged human skin (40).

TGF-β: TGF-β is one of the most important regulators of ECM biosynthesis. It manages homeostasis of the collagens in the fibroblasts through regulation of collagen production and its degradation via the Smad pathway. The genes associated with ECM, including collagens, fibronectin, decorin, and versican, are directly upregulated by TGF-β/Smad signaling. Thus, impairment of the TGF-β signaling pathway results in decreased neocollagenesis in the dermis, leading to reduction of the net amount of collagen. Generation of ROS as part of the skin aging process stimulates the expression of the MMPs and inhibits TGF-β signaling, which consequently results in the degradation and decreased biosynthesis of collagens. Studies have shown that dermal hyaluronic acid fillers stimulate the production of type I collagen through promoting the TGF-β signaling pathway in dermal fibroblasts and increasing the proliferation of these cells (41).

Dystroglycan: Dystroglycan 1 is one of the cell surface components that is converted to α-dystroglycan and β-dystroglycan by a post-translational modification. It is involved in biological functions such as cell-ECM interaction, the process of laminin assembly, and formation of the basement membrane. This protein is shed in keratinocytes under influence of IL-1β-promoted proteinases. It appears that UVB radiation can stimulate dystroglycan shedding via activation of IL-1β signaling (28).

ROS: ROS is synthesized as a byproduct of mitochondrial aerobic metabolism electron transport. In the skin, about 1.5% to 5.0% of oxygen is converted to ROS through an intrinsic process. Although ROS promotes the aging process in different organs including the skin, its presence in small amounts plays important roles in managing the health of the body or cells, among which activating cyclooxygenase and lipoxygenase and regulation of the inflammatory process are the most important (7). Free radicals consist of highly reactive molecules of oxygen, which, by participating in a cross-linking process with the collagen fibers, can result in decreased elasticity (2).

The leukocyte NADPH oxidase is one of the main sources of ROS (13). Studies have shown that ROS is involved in the following processes which are necessary for the body health:

A: Pathogen killing: Studies in vertebrates have shown that mitochondrial ROS (mROS) contributes to anti-bacterial activity in macrophages (13).

B: Vascular endothelial growth factor (VEGF) signaling: VEGF-induced signaling can promote endothelial cell migration through mROS (13).

C: TNF response: TNF can promote the production of mROS in endothelial cells that play a great role in the inflammatory responses (13).

D: Wound healing: Although the effectiveness of mROS has been observed at various phases of the wound healing process, its excess can result in decreased endothelial cell motility and inhibition of the angiogenesis, which imitates the aging skin phenotype (13).

In the skin, ROS reduces collagen synthesis, production and activation of MMPs, and secretion of the senescence-associated secretory phenotype (SASP) by activating a set of signaling pathways which result in skin aging (7). Summarily, deteriorative effects of the ROS in the skin include:

Inflammation: ROS induces skin erythema through production of the prostaglandin E2. Studies have shown upregulated expression of COX-2 by ROS to be a pivotal enzyme in synthesis of this prostaglandin (42).

Oxidation at the skin surface: Skin conditions are altered by oxidized lipids and proteins. Disrupted barrier function of the skin and skin roughness are complications caused by ROS. Additionally, stimulation of the sebaceous glands results in an increase of sebum secretion through increased levels of the oxidized lipids, triglyceride hydroperoxides, and cholesterol hydroperoxides (42).

Melanogenesis: ROS plays a paradoxical role in melanogenesis. On one hand, it induces depigmentation, as can be observed in vitiligo; on the other hand, it increases pigmentation as observed in skin aging (42).

Collagen content of the dermis: ROS increases the expression of MMP-1 in dermal fibroblasts via production of interleukins (IL)-1a and IL-6. Additionally, oxidized lipids, including linoleic acid hydroperoxide, stimulate the expression of the MMP-1 and MMP-3. On the other hand, the production of new collagens, which is controlled by the activator protein (AP)-1, is attenuated due to decreased collagen synthesis under the impact of ROS and its effects on MMP-1 expression (42).

Autophagy: Autophagy plays a role as a protective process against stressful conditions such as starvation or nutritional deficiencies by removing damaged proteins, lipids, and other cytoplasmic substances. Although activation of autophagy contributes to postponing the aging process, several studies have shown it to have the opposite role. Thus, confirmation of the exact role of autophagy in this process necessitates more robust studies (7).

Senescence-associated β-galactosidase (SA-β-Gal): SA-β-Gal, as one of the earliest biomarkers associated with aging, is used as a gold standard for detecting senescent cells in tissues and *in vitro*. It can accurately detect the aging process at a pH of 6.0; otherwise, false positive may occur. Furthermore, increased activity of this biomarker has also been reported in quiescent cells or in response to various forms of stress. The activity of SA-β-Gal is often lost in fixed or cryopreserved tissues, which leads to false negative results (43).

Renin-angiotensin system: The angiotensin converting enzyme (ACE) contributes to conversion of inactive angiotensin I to its active form, angiotensin II, which plays a key role in the renin-angiotensin system. In addition to the significant role of this system in the pathogenesis of hypertension and atherosclerosis in the cardiovascular system, it contributes to local regulation of cell function and induction of tissue pathologies such as skin disorders. In general, the exact mechanism of this system in the aging induction is not clear, but it seems that this system is involved in the inflammation process and the induction of IL-1β signaling. In a study on hair loss in mice, increased ACE expression and angiotensin II levels were detected after repeated sessions of UVB irradiation. Treatment with enalapril maleate as an ACE inhibitor could reverse the aging process and repair wrinkles (28). Additionally, sirtuins, including SIRT1 and SIRT6, have a protective role in angiotensin II-treated human coronary artery endothelial cells (29).

Matrix metalloproteinase: One of the mechanisms of UVB irradiation in inducing aging is activation of matrix metalloproteinases (MMPs) (28). These molecules play significant roles in the cell communication and cell-matrix signaling processes (7). Regarding their structure and substrate specificity, they are classified into five main subgroups, including: 1- collagenases (MMP-1, MMP-8, and MMP-13), 2- gelatinases (MMP-2 and MMP-9), 3- stromelysins (MMP-3, MMP-10, and MMP-11), 4- matrilysins (MMP-7 and MMP-26), and 5- membrane-type MMPs (MMP-14, MMP-15, and MMP-16) (14). MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12 have various roles in the decomposition of elastin (27).

MMP-1, as a collagenase 1, acts by initiating catalyzation of the α chains of the type I, II, and III collagens. It is effective in achieving destruction of the damaged collagen and replacement of the matrix in processes such as wound healing and skin response to UV irradiation. The increased expression of MMPs after application of an ablative fractional resurfacing CO2 laser and their association with decreased wrinkle severity demonstrates their positive role in preventing aging (44).

MMP-14 acts through ECM degradation, regulation of the cellular function by degrading and releasing cell surface proteins including growth factors, and interaction with the dermal-epidermal crosstalk regulating angiogenesis. Expression of MMP-14 is decreased by UVB irradiation, which affects the aging process (28).

Tissue inhibitor of metalloproteinase (TIMP): While MMP expression is induced in aged fibroblasts in the aging process, the expression of TIMPs is reduced (7). TIMP3 has very wide-spectrum inhibitory properties against MMPs, ADAMs, and ADAMTSs. It prevents aminopropeptide cleavage of the procollagens I, II, and III in the presence of heparin (36). The expression of TIMP is induced by oxidative stress and decreased by antioxidants such as resveratrol, isoorientin, equol, etc.

Elastase: Elastase is a protease enzyme which degrades elastin (45). In UVB-induced photoaging, its expression is increased (28). Inhibition of this enzyme prevent skin aging (47).

The ADAMTS family: The ADAMTS family of enzymes consists of various types of enzymes participating in biological processes such as collagen processing, angiogenesis, immunity, and fertility, as well as the pathogenesis of diseases such as multiple sclerosis, osteoarthritis, some types of Ehlers-Danlos syndrome, and osteogenesis imperfecta. Among the members of the ADAMTS, ADAMTS2 is the most known and best characterized, expressed by fibroblasts and cells of mesenchymal origin. The substrate specificity of ADAMTSs is dictated by their distribution. High expression levels of the ADAMTS2 are detected in type I collagen-rich tissues such as the skin, bone, tendons, and aorta. Its expression is increased by TGF-β *in vitro* and fibrotic lesions *in vivo*. It is secreted as an inactive proenzyme which is cleaved and activated by subtilisins such as furin. ADAMTS14 is co-expressed with ADAMTS2, but in lower amounts. Their activation can be negatively controlled by internalization and co-localization with their substrates. The presence of neutral-to-mildly basic PH, calcium, and zinc are essential for the activity of ADAMTS2 and ADAMTS 14 (36).

ADAMTS2 is a secreted procollagen N-proteinase which plays a role in processing of type I, II, and III procollagens (28). In the absence of this protein, the skin becomes fragile due to excessive accumulation of aminoprocollagen I, which leads to the formation of abnormal collagens. *In vitro*, it has apoptotic effects on endothelial cells through interacting with the nucleolin receptor on these cells, resulting in anti-angiogenic activity. Due to reduced vascularization, it is expected to exhibit anti-tumor activity (36). It seems that the down-regulation of the ADAMTS2 gene plays a role in the process of aging.

Wnt5a: Wnt5a acts as a representative ligand in the activation of β-catenin-independent pathways. It plays a role in biological processes including cell migration, adhesion, differentiation, specification, growth, and apoptosis, induction of MMP-1 and 2 expression, restoration of epidermal tissue patterning, and anti-apoptotic activity in dermal fibroblasts. It is thus involved in the development of various organs, function of the postnatal cells, and the processes of wound healing and dermal remodeling. It appears to have anti-aging properties, as its expression is elevated by application of ablative fractional resurfacing CO2 lasers, which results in wrinkle repair (44).

CYR61: The CYR61 is a secreted, ECM-associated signaling molecule, associated with connective the tissue growth factor cyr61/cef10, which plays role in cell growth, adhesion, and migration, angiogenesis, the regulation of the ECM-production, and the balance between production and degradation of collagen by controlling production of MMP-1. It acts by inhibition of type I collagen production and stimulation of collagen degradation, leading to loss of collagen (44).

HSP90: HSP90 is a widely-distributed chaperone needed for eukaryotic homeostasis. It is involved in promoting endothelial cell migration and angiogenesis in the wound healing process in an ECM-associated pathway (44). It also stimulates the proteolytic activity of MMP-2 and plays a role in dermal remodeling (46). Its increased expression level after application of an ablative fractional resurfacing CO2 laser is associated with decreased wrinkle severity, and its role in preventing aging has been demonstrated (44).

Sirtuin: The sirtuin family consists of nicotinamide dinucleotide (NAD^+)-dependent deacylases, which are effective in preventing diseases and alleviating some aspects of aging. They participate in enzymatic activities including deacetylation, O-ADP-ribosylation, demalonylation, desuccinylation, and depropionylation. They play roles in regulation of fat differentiation, insulin sensitivity, glucose output, fatty acid oxidation, neurogenesis, and inflammation. Their effect in delaying cellular senescence and prolonging organismal lifespan is through regulation of a variety of biological processes, including postponing age-related telomerase attrition, maintaining genome integrity, promoting DNA repair, deacetylation of some signaling molecules such as forkhead box O (FOXO), NFκB, and p53, and interacting with all of the major longevity pathways including AMP-activated protein kinase (AMPK), insulin / insulin-like growth factors (IGF-1) signaling (IIS), target of rapamycin (TOR), and FOXO. In addition to senescence suppression of the mitotic cells, they can delay senescence in stem cells, which is essential for the maintenance of self-renewal in stem cells. In mammals, there are 7 types of the sirtuins, SIRT1-SIRT7, with different enzymatic activities and subcellular localization, among which the role SIRT1 and SIRT6 has been investigated with regard to protection against the senescence process (29).

The nuclear types of the sirtuins, including SIRT1, SIRT6, and SIRT7, have a regulatory role in gene transcription and stabilize chromatin structure by suppressing gene expression (29).

Different studies in animal models have shown that sirtuins act in a dose-dependent manner, so that very large increases in sirtuins can result in decreased lifespan, while milder increases lead to lifespan extension (29).

Insulin/IGF-1: Insulin/IGF-1 signaling is effective in promoting extension of the lifespan and resistance to stress via the FOXO, as its major component, and the effect of prolonging the longevity of sirtuin. The interaction of insulin/IGF-1 signaling and sirtuin has been demonstrated in mammals (29).

FOXO: The FOXO family are classified as multi-functional transcription factors playing roles in the integration of various signaling pathways in the transcriptional networks, governing cell and tissues homeostasis due to aging and in response to environmental impacts. Among the signaling molecules which are transcriptionally regulated by the FOXOs, the ones involving the processes of oxidative stress, apoptosis, cell cycle, energy metabolism, and DNA repair are the most important. Factors such as the oxidative stress, cytokines, insulin, IGFs, and macro- and micro-nutrients have a role in the management of FOXO transcription factors. The roles of the FOXOs in controlling skin homeostasis and health has been confirmed in different studies. The activation or deactivation of some of the FOXO transcription factors has been demonstrated in aging, melanogenesis, wound healing, acne, and melanoma (47).

AMPK: AMPK belongs to a protein kinase family activated through the deacetylation of LKB1, its regulator, and SIRT1. It activates SIRT1 *per se*. This protein kinase has a role in the extension of the lifespan and also contributes to role of insulin/IGF-1 signaling, thus increasing longevity of organisms (29).

Telomere shortening: The telomere is the repetitive nucleotide sequence capping which preserves the ends of the chromosomes from degradation and abnormal recombination. Its shortness can be observed with age resulting in cellular senescence, restriction of cell division, and defective tissue regeneration. The telomerase is an enzyme which prevents the telomeres from shortening by adding repetitions to the end of the telomeres (27).

CONCLUSION

In conclusion, aging is a natural process which continuously and irreversibly involves the skin and other organs. During the aging process, intrinsic progressive degenerative changes in the skin impair its structure, which makes it prone to different dermatoses resulting in impaired quality of life in the elderly. Education and health promotion would be invaluable in order to decrease the risk of skin problems in the elderly (3).

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