EMPIRICAL STUDIES

A Review of Skin and the Effects of Aging on Skin Structure and Function

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Skin, the largest and most visible organ of the body, undergoes an aging process that presents multiple clinical manifestations and problems. Comorbidities that frequently increase as the body ages cause further deterioration in this important organ. Organ aging and failure, not usually visible processes, become evident when the skin is affected. In the failing individual, skin deterioration is the outward manifestation of faltering physiology. Even in the healthy aged population, normal and expected changes occur, leading to problems.

Functional skin changes over time produce many problems, but in the case of this visible organ, the physical changes also have significant psychological impact, affecting interpersonal interactions, body image, and the overall image of a person's health.[1] Understanding the changes in the skin associated with aging will aid the practitioner caring for the older individual. With the shift in the demographics of aging, understanding chronological skin changes is of increasing importance. By the year 2030, one in five Americans is expected to be 65 years or older; according to the 2000 US census, approximately one in eight people are over 65, an 11-fold increase since 1900.[2,3]

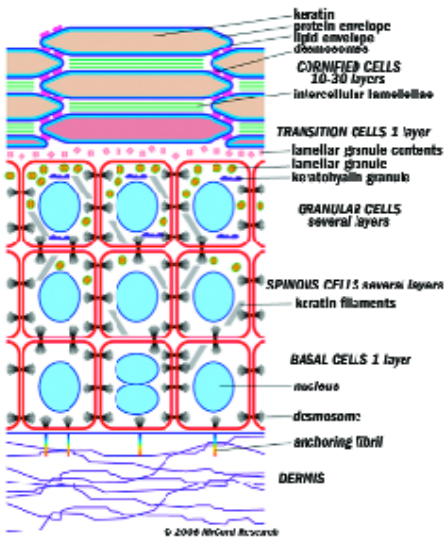
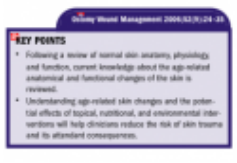
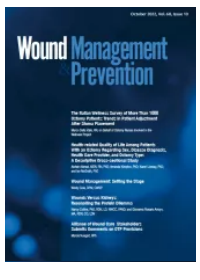


Figure 3. Schematic drawing of the anatomic cellular development of the skin. Note the cornified cells that are the bricks of the stratum corneum surrounded by the intercellular lipid lamellae of the mortar. Used with permission from McCord Research, Coeur d'Alene, Idaho.



The changes associated with the aging process are best understood when compared with normal, young skin.[4] Aging is a complex process leading to biologic attrition at the cellular level that is manifested in many ways. Senescence and apoptosis play a role in the aging processes of all cells — review articles affirm they are influenced by cumulative DNA damage from external and internal insults.[5-8] These accumulated cellular changes likely contribute to the anatomical, functional, and physiologic changes of aging skin[6,9] and likely account for much of the slowing of wound healing observed with aging.

Skin aging involves chronological or intrinsically aged skin and photoaged skin



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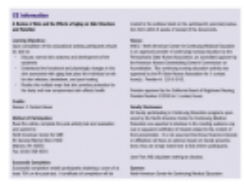
proteins resulting in reduced function, and oxidation of membrane lipids, resulting in abnormal transmembrane signaling and reduced transport efficiency. Incomplete repair of this damage over time leads to abnormal structure and function.[5,6] Ultraviolet exposure will speed up chronological skin changes, suggesting similar molecular mediators and some similar outcomes of damage. With increasing age, the impact of photoaging increases and the effect of the underlying genetic tendencies decreases.[12]

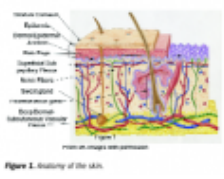


The skin is a dynamic, regenerating organ. It comprises about 15% of the total body weight and is the body's primary defense structure. Development and maintenance of healthy skin with a fully functional skin barrier/stratum corneum is the ultimate role of normally developed and mature skin.[14] Any compromise of the skin barrier is significant. The defense functions of the skin reside in the stratum corneum and depend on interactions of all of its components to be effective.[15] Skin maintenance is the primary therapy for wound prevention —a wound is defined as the absence of healthy, normally developed and intact skin. Healthy skin should look and function well, so it serves two purposes. All of the functions of the skin change with age.[9,12]

The purpose of this review is to help clinicians appreciate the myriad of changes that accompany the process of aging in the skin to better understand and anticipate challenges in treating and maintaining this important organ.

Anatomy and Development of Skin and Its Functions

Discussion of the anatomy of the skin includes both the dermis and the epidermis (see Figure 1). The composition and thickness of the epidermis and dermis vary depending on the location on the body. In general, the thickness of the epidermis varies from 0.04 mm on the eyelids to 1.6 mm on the palms and soles of the feet. The primary cell in the epidermis is the keratinocyte. Additional cells include the melanocytes (cells of neural crest origin that produce pigment), the Langerhans cells (mobile, dendritic antigen-presenting cells), and the Merkel cells (cells with both neuroendocrine and epithelial features that synapse with the dermal sensory axons and adjacent epithelial cells and are sensitive to mechanical stimuli, especially pressure). There are three epidermal appendages: the sweat glands, the pilosebaceous follicles that produce the hair and sebaceous excretions, and the nails that cover the distal phalanges.[4] Sweat glands function as thermoregulators; recent findings also indicate they secrete antimicrobial peptides.[16] The normal turnover rate for the epidermis is about 28 days.



The dermis, located between the subcutaneous and dermal-epidermal junction, measures from 0.3 mm on the eyelids to 3.0 mm on the back. The dermis and its blood supply are responsible for delivering nutrients and circulatory support (the epidermis has no blood supply of its own). Communication is ongoing between the dermis and epidermis. The junction between the epidermis and dermis undulates; the epidermis protrudes more deeply into the dermis, alternating with a more shallow protrusion into the epidermis. The final outcome causes the epidermis and dermis to interdigitate like fingers coming in-between each other to form, via invagination, the rete pegs. Nutritive capillaries and venules circulate close to the dermal-epidermal junction at the top of the rete pegs.[17]

Terminal nerve endings of the afferent and efferent nervous system — the small diameter unmyelinated C-fibers and the thinly myelinated A-δ fibers — are located in and near the basement membrane and even penetrate into the epidermis. At the dermal-epidermal junction, they lose all myelin. As described in the a recent review article,[18] the neurites go into the epidermis and connect with all of the cell types in the

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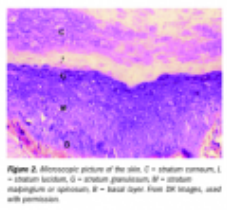
differentiation notes that nerve function has a trophic effect — the release of neural molecules affects the normal function of non-neuronal cells.

The epidermis is separated into layers anatomically as the skin develops and matures from the basement membrane to the outer layer, the stratum corneum (see Figure 2). The epidermal regenerative layer contains the basal keratinocyte where mitosis (regeneration of cells) occurs. The developing keratinocytes mature, becoming the stratum spinosum, the stratum granulosum, and finally the stratum corneum. The stratum corneum is responsible for the skin barrier that protects the skin, preventing water loss, maintaining satisfactory hydration of the skin, and preventing overhydration in addition to many other protective functions. Reviews in the literature[20-22] state that the purpose of the epidermis is to create a fully functional and well-formed stratum corneum.



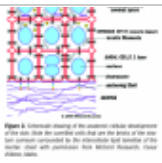
The dermal cellular components include the fibrocyte, monocyte, histiocyte, Langerhans cells, lymphocytes, and eosinophils, along with the vascular- and lymphatic-associated cells. These comprise approximately 10% of the dermal content. The dermis is primarily a connective tissue matrix made up of approximately 90% collagen (mostly Type I) along with elastic fibers, blood vessels, and lymph vessels, with some muscle fibers and pilosebaceous and sweat glands — structures that originated in the deep dermis and subcutaneous layer. There are two blood vessels plexuses: one at the deeper area of the dermis where it meets the subcutaneous tissue and another (the superficial subpapillary plexus) in the more superficial aspect of the reticular dermis below the rete pegs. From this superficial plexus, the capillaries project into the rete pegs up near the dermal epidermal junction.[17,23]

As the keratinocytes leave the basal layer, many cellular changes occur. The cells take basic building blocks such as carbohydrates and amino acids that diffuse through the dermal epidermal junction and some essential products such as glycerol, linoleic acid, and other fatty acids and create all of the chemicals necessary to build the stratum corneum skin barrier. The numerous synthetic processes involved with development of skin and the lifelong process of repair and regeneration require ongoing cellular activity throughout life.[21,24,25]

The stratum corneum and the skin in general have biosensor activity. Any disruption of the skin barrier/stratum corneum or deeper layers initiates reparative mechanisms that turn on synthetic and inflammatory responses in the skin.[26] This barrier disruption signal turns on mitotic activity in the basal layer, stimulates the stratum granulosum to secrete lamellar granules into the intercellular space (forming more stratum corneum), and initiates a cytokine response to upregulate immune defense responses.[27,28]

The cells mature as they move toward the surface. Internal processing of keratohyalin filaments and the proteins *involucrin* and *filaggrin* leads to development of the mature corneocytes, which have natural moisturizing factors and the strong corneocyte envelope that bonds to the intercellular lipid complex. Phospholipids, cholesterol, and glucosylceremides are the synthesized precursor lipids stored in the lamellar granules of the stratum granulosum cells along with the enzymes and proteases needed for the development of the intercellular lipid complex. At the transition layer of the granulosum to the stratum corneum, the lamellar granule contents are extruded from the cells and chemically processed to form the intercellular structure. The final lipids in the stratum corneum intercellular complex are equimolar amounts of cholesterol and cholesterol esters, ceramides, and long-chain fatty acids.[29]

The stratum corneum is structurally like a brick-and-mortar complex (see Figure 3). The bricks are the mature corneocytes (matured keratinocytes of the stratum corneum)



It is exposed and responds to environmental challenges. Classically, the skin has been viewed as a barrier and sensory organ. Current research[20] shows the skin to be a highly active biological factory for protein synthesis and metabolism, signaling molecules and lipids, and an integral part of the immune, nervous, and endocrine systems.

All cell types of the epidermis contribute to an integument-related innate and acquired immune system. The skin signals the body when it is disrupted through sensory, chemical, and cellular mechanisms. The skin provides mechanical integrity and resilience, protection against harmful foreign chemicals, antioxidant protection, selective absorption of many substances including oxygen, protection against dehydration and overhydration (water repellency), ultraviolet protection, and regenerative and restorative mechanisms when injured. The epidermis and dermis are responsible for afferent and efferent sensation and thermoregulation through changes in the cutaneous blood supply and sweating.[30] Topical cellular respiration (ie, the diffusion of oxygen from the environment) provides a source of oxygen for the skin, diffusing through the epidermis and even the superficial dermis at a depth of 0.25 to 0.40mm.[31,32] Senescent skin changes affect all of these functions.

Anatomic and Developmental Changes Associated With Aging

Epidermal anatomical changes associated with aging remain somewhat controversial.[32] Because of the described skin thickness variations from one part of the body to another, making generalizations about senile skin thickness changes is difficult. The epidermis becomes thinner with aging, primarily due to a retraction of the rete pegs. The vertical height of the keratinocytes decreases, corneocyte surface area enlarges, keratinocyte adherence decreases, and epidermal turnover rate generally slows.[12,33,34] The overall thickness of the skin decreases with a decline in the thickness of the stratum spinosum and a significant decrease in the maximum thickness of skin.[35] The usual 28-day turnover time for skin increases approximately 30% to 50% by age 80. The mitotic activity in the basal layer is reduced and the transit time from the basal layer to the stratum corneum is increased. The orderly maturation of the skin proceeds in a slower and incomplete or disjointed fashion.[36-38]

Melanocytes, Langerhans cells, and Merkel cells in the epidermis drop out. According to several reviews,[37,39] the senescent keratinocytes become resistant to apoptosis and may survive long enough to accumulate DNA and protein damage — cancerous changes. By age 80, the Langerhans cells decrease in number as much as 50%.[40] This is exaggerated in sun-exposed areas. These dendritic cells are the most important part of the innate immune system. Changes of aging Langerhans (dendritic) cells include fewer dendrite projections infiltrating the skin, reduced antigen trapping capacity, and atrophic morphology.[41] The melanocytes decrease 8% to 20% percent each decade after age 30.[42] Melanocyte dropout is less in sun-exposed areas but these cells are functionally impaired and irregularly spaced, producing an irregular pigmentation on sun exposure. The dropout of melanocyte number and function leads to graying of hair.[43] Changes in the cutaneous nerves lead to an impaired early warning function of pain with an increase in pain threshold and widespread change with fallout of nerve endings of the central nervous system nociceptive pathways. Resolution of post-injury hyperalgesia is slower.[44,45] Dropout of nerve function stunts the ability to thermoregulate through vasodilation and sweating and reduces trophic effects on the skin by the nerves.[46,47]

The epidermal rete pegs flatten and the underlying dermal papillae smooth out, producing a flattening of the dermal-epidermal junction. The basal cells also normally display numerous villous cytoplasmic projections into the dermis at the dermal-

Dermal changes are significant in the cellular and cell matrix components. The dermis thins. Senescent fibroblast changes include an increase in matrix metalloproteinase expression and a decrease in its inhibitors.[52] The number of fibroblasts and their functional capacity decreases.[52] New collagen production decreases and the matrix of the dermis declines. The dermis loses turgor, due in part to a reduction of glycosaminoglycans, especially hyaluronic acid and dermatan sulfate.[53] Collagen fiber disorganization and random orientation, thickening, and collagen fragmentation lead to overall dermal disorganization.[48] Elastic fibers undergo irreversible structural and compositional changes that progress with age, leading to a substitution of the fibers with amorphous elastin with poor functional activity.[54]

The number of sebaceous glands remains the same but sebum production decreases and the sebaceous glands become hypertrophic.[55] The eccrine and apocrine sweat glands reduce in number and show cellular degeneration and the response to thermal stimulation and acetylcholine is reduced.[56,57] Cutaneous blood flow through the capillaries decreases with the decline in rete pegs.[58] Skin capillary blood flow in response to heat is decreased partly due to a decline in sensory nerve function.[47] The endothelial-dependent response to vasodilator chemicals is reduced.[59]

The cellular epidermal changes lead to developmental changes in the stratum corneum, which maintains the same thickness but takes longer to develop. The surface area of each corneocyte is larger and decreased in height. The intercellular lipid structure is normal but focally decreased. The total lipid component is decreased but has the normal distribution of cholesterol, ceramides, and free fatty acids. Cholesterol synthesis is profoundly reduced.[60] The ability of the stratum corneum to regenerate after barrier disturbance is slowed, likely influenced by a decrease is cytokine response in the senescent epidermal cells.[61] The amino acid content of the corneocytes is reduced with a decrease of the natural moisturizing factors, water-binding, and strength and flexibility of the corneocytes.[62] The pH of the skin is constant until about age 70; then it increases, especially in the lower limbs.[63] Vitamin D synthesis, an endocrine function of the skin, declines with age along with the general trend of reduced sun exposure, leading to a lack of vitamin D production.[64] The inadequate supply of active vitamin D also has an adverse effect on the differentiation and development of the skin.[65]

In the epidermal and dermal compartments, the proliferative and regenerative response to skin disruption is reduced as well as the degree of injury necessary to induce barrier disruption. The overall water content of the skin is decreased.[36] Transepidermal water loss under basal, ideal conditions is similar in aged and young skin, suggesting a good skin barrier, but any disturbance in aged skin increases the loss of water and the ability to restore the barrier is slow and incomplete. The overall susceptibility of intrinsically aged skin to any internal or external insults is increased.

Dermal regeneration and repair are impaired due to matrix, cellular, and vascular aging changes. The connections between the dermis and epidermis weaken due to the flattening of the rete pegs and the basal cell layer connections to the dermis at the dermal-epidermal junction. The supportive role of the dermis to the epidermis as far as nourishment, structural, vascular support, and repair when injured is impaired. Innate and acquired immune function is less effective due to the identified changes in the skin. Recognition of and response to possible pathogens is blunted and the skin is not able to defend itself as effectively. Cell signaling is also blunted and the secondary inflammatory response to injury, harmful chemicals, and pathogens is not as efficient. The tendency for dermatitis may be enhanced due to exposure of the body to allergens from disruption of the skin barrier—eg, from Candida antigen and nummular eczema.[66] Irritation from chemicals or other potential irritants is also more likely.

Clinical Skin Changes Associated With Aging

Skin problems related to chronological aging changes become obvious once the changes of aging are compared with normal young skin. The general anatomical changes of the skin associated with aging result in atrophy, laxity, wrinkling, sagging, dryness, pigment and blemish development, neoplasms, and nail and hair changes. The skin is paler. The clinical changes associated with aging affect all skin functions. Categories of clinical aging changes include decreased strength, impaired skin barrier, altered immunity, skin senescence, skin appendage and vascular changes, and decrease in skin protective functions (see Figure 4).

list of stressors that can disrupt the stratum corneum is extensive — each is of greater clinical significance in the elderly due to the slower epidermal repair and reserve (see Figure 5). Realizing the increased risk of skin problems associated with these stressors and conditions can trigger the onset of therapy.

The cumulative effects of age are accelerated by photoaging, medication side effects, organ failure in other systems, and comorbidities such as diabetes mellitus, nutritional deficiency, and general vascular decline.

Treatment

Preventive and active treatment of aging skin includes several strategies. Recognizing the age-induced skin impairment is the first step. The clinician should identify correctable, treatable internal and external factors that compromise the skin, especially regarding the stratum corneum (see Figure 5). Comorbidities should be addressed, including adverse effects of medications. Nutritional issues should be assessed and supplements provided to help correct deficiencies — eg, essential fatty acids are important to the proper development of skin. Clinicians should understand and implement practices that will enhance skin moisturization and conditioning. Topical nourishment should be provided to enhance maintenance and repair.

Cleansing. Cleansing should not compromise the skin. Several practices help clean the skin in a safe, noncompromising manner. Harsh soaps that strip stratum corneum lipids and proteins can be avoided by using products with fewer or milder surfactants and more phospholipids. Skin cleansers combined with moisturizers help replace and repair the barrier disrupted by cleaning. Minimizing the use of soaps (frequency) and limiting the area where they are used, using liquid and foam soaps rather than bar soaps, and using a soft cloth and cooler water are some strategies to reduce skin disruption.[67] A cleanser that maintains the acidic pH of the skin (about 5.5) is beneficial because pH directly affects the integrity of the stratum corneum.[68] Cleanser surfactants can cause immediate after-wash tightness due to stripping of the lipids and protein alteration in the stratum corneum, leading to barrier damage, loss of water from the skin, erythema, irritation, and itch.[69] The goal of a mild moisturizing cleanser is to provide cleansing benefits without negatively altering the hydration and viscoelastic properties of skin. Current cleanser technology can mitigate damage by depositing oils, lipids, and humectants during washing. Products used on the skin should be evaluated because of their potential damaging effect on compromised and aged skin.

Moisturizing. Moisturizing is important. The softness of skin correlates with its hydration status. The stratum corneum skin barrier prevents water loss, but with age the ability to limit transepidermal water loss is impaired. The most important factor for healthy skin is adequate moisture. The optimum environmental humidity level to prevent excessive loss of water from the skin is 40%. Lower humidity will reduce skin

Topical and systemic supplements. Modern approaches to active skin therapy and enhancement include topical and oral vitamins, minerals, fatty acids, cholesterol, alpha-hydroxy acids, glycerol, antioxidants, melatonin, creatine, amino acids, peptides, and hormones.[72-76] These are all topically absorbed (if they do not exceed 500 daltons) through the intact stratum corneum and can enhance and repair skin from the outside in. When the skin barrier is not intact, even larger molecules may pass through into the lower levels of the epidermis and even outer dermis.[77] Topical retinoids treat changes of chronological and photoaging.[78] Topical and oral vitamins that may be of benefit include vitamins A, C, D, niacinamide, panthenol, and pyridoxine.[79,80] Physiologic lipids like fatty acids, cholesterol sphingolipids and phospholipids, and omega-3 fatty acids enhance the development of the skin barrier.[81,82] Urea, glycerin, and hyaluronic acid help restore skin. Reviews of estrogen and dehydroepiandrosterone —hormones that effect skin — discuss their topical and oral use.[83] Oral and topical applications of selenium, calcium, and zinc enhance the skin.[84,85]

Implementing corrective and therapeutic treatments for abnormal ailing skin can help restore function, not just temporarily reduce the loss of transepidermal water. The brick-and-mortar complex of the stratum corneum can be enhanced through these efforts; topical therapy also can affect degenerative dermal changes. Scientific evidence supporting topical therapy of skin is extensive. Topical products, oral dietary supplements, and appropriate treatment have a significant impact on the skin.

Conclusion

The skin, an essential organ that undergoes many changes as the individual ages, is metabolically active and regenerative throughout life. Understanding the aging process of skin helps predict the problems that will be encountered in taking care of the aged person. Identifying and treating these problems can make a big difference in the physical and psychological state of the patient as well as treatment outcomes — the treatment and maintenance of skin is the first essential step in preventive wound care. The future holds new understanding of aged skin and ways to correct and prevent the associated problems.

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