Aging Skin and Wound Healing

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KEYWORDS

• Aging • Photoaging • Wound healing • Skin structure • Skin function
• Chronic wounds

KEY POINTS

- Each of the many components of skin undergo changes with age that affect structure and function.
- Wound healing occurs in a highly regulated and evolutionarily conserved manner.
- Wound healing in the elderly is delayed but not defective.
- The higher prevalence of chronic wounds in aged populations is primarily due to comorbidities.

THE SKIN AND AGING

As the human body's largest organ, the skin is responsible for a myriad of essential functions, including immunologic surveillance, thermoregulation, sensation, excretion, and protection from external forces, such as UV radiation and foreign agents. Each of the 3 layers of the skin, the epidermis, the dermis, and the subcutaneous tissue, undergoes significant changes with aging.

The outermost layer of the skin is the epidermis, which gives rise to the cutaneous appendages, including sebaceous glands, sweat glands, hair follicles, and nails. The stratum corneum, the most superficial layer of the epidermis, gives the skin its waterproof barrier properties. The state of hydration of the stratum corneum is governed by 3 factors: water that reaches it from the epidermis, water lost from the skin's surface by evaporation, and the intrinsic ability of the stratum corneum to retain water. The ability of the stratum corneum to hold onto water relies on 2 mechanisms. The first mechanism involves the skin lipids, which consist of ceramides, cholesterol, and fatty acids. It is the ratio of each of these lipids, rather than one particular component, that is key to skin moisturization.[1] The second mechanism is the natural moisturizing factor, a mixture of amino acids, organic acids, urea, and inorganic ions that are extremely

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water soluble and can absorb large amounts of water.[2–4] The elderly have a decreased amount of lipids and amino acids in the stratum corneum, thus contributing to the clinical presentation of dry skin (xerosis).[5–7]

Melanocytes are the pigment-producing cells of the epidermis. The density of melanocytes varies depending on the anatomic location, with more melanocytes concentrated on the face and fewer on the extremities. Aging takes its toll on melanocytes and their activity. Beginning at age 30 years, melanocyte density decreases by 6% to 8% with each decade of life.[8] In addition, melanocytes do not produce melanin pigment as efficiently with age, which explains why the elderly do not tan as easily as when they were young.[8]

Langerhans cells are the antigen-presenting cells within the epidermis. They act as immunologic sentinels by presenting foreign antigens to T lymphocytes. With aging and UV light exposure, the number and function of epidermal Langerhans cells decline, thereby decreasing the incidence of contact allergy in elderly patients.[9–11]

Sebaceous (oil) glands produce lipid-rich sebum, which prevents transepidermal water loss and has antimicrobial properties, inhibiting growth of certain fungi and bacteria. After peaking in adolescence, sebum production decreases about 23% per decade in men and 32% per decade in women.[12] Although sebaceous gland function diminishes with age, sebaceous gland size increases, which explains the yellow skin lesions of sebaceous gland hyperplasia that occur commonly in middle-aged and elderly adults.[13]

Eccrine sweat glands are responsible for thermoregulation, maintenance of electrolyte homeostasis, and excretion of metabolic byproducts. Certain heavy metals, organic molecules, and macromolecules may also be excreted in the sweat.[14] In elderly persons, the number and size of the sweat glands diminish, leading to the decreased sweating capacity of older adults.[14]

Hair follicles develop as downgrowths of the epidermis and function as a secondary sexual characteristic, as touch receptors, and as reservoirs for proliferating cells to help regenerate the epidermis after trauma. With age, the number, the growth rate, and the diameter of the hair shaft decline.[15] Gray hair results from decreased amounts of pigment within the hair shaft. Melanocytes are present in the hair follicles of people with gray hair, but melanin production is diminished in a comparable manner to the epidermis.[15]

Beneath the epidermis lies the dermis, which is composed of a fibrous connective tissue component and ground substance. Because the dermis is the main contributor to the thickness of skin, it is particularly important in the skin's cosmetic appearance. As a person ages, the dermis loses its thickness, elasticity, and water content.

Collagen gives the dermis its structural stability and resilience. Chronic UV light exposure upregulates the production of collagen-degrading enzymes called matrix metalloproteinases, such as collagenase and gelatinase. These degradative enzymes induce collagen damage, resulting in thinner, less-resilient skin with increased wrinkle formation.[16]

The skin's ability to return to its original shape after being stretched is due to the presence of elastic tissue in the dermis. Chronic sun exposure and aging cause a characteristic change in the elastic fibers of the skin, a finding called elastosis, in which elastic fibers appear thickened, coiled, and haphazardly arranged. It is controversial whether elastosis represents an increased breakdown of elastic fibers or an overproduction of abnormal elastic fibers.[17] Regardless of the mechanism, the elastic tissue in aging and photodamaged skin does not function normally, which leads to decreased skin recoil and a wrinkling effect.[18–20]

Collagen and elastin reside in the dermis within a gellike milieu called ground substance composed of glycoproteins and glycosaminoglycans. Glycoproteins are

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involved in cell migration, adhesion, and orientation, which allow for production of granulation tissue, re-epithelialization, and other aspects of wound healing. One of the primary roles of glycosaminoglycans is to bind water and give skin its supple appearance. In aging skin, the predominant glycosaminoglycan in the dermis, hyaluronic acid, is replaced by chondroitin sulfate, which has less effective water-binding capacity, leading to decreased skin suppleness.[21]

Aged skin has fewer dermal blood vessels, resulting in decreased blood flow, diminished nutrient exchange, impaired thermoregulation, lower skin surface temperature, and skin pallor. In addition, pericytes surrounding the cutaneous vessels decrease in number and synthetic activity with aging.[22] This loss of vascular stromal support explains the increased susceptibility to bruising in the elderly.

Beneath the dermis lies the subcutaneous fat, which serves as an energy reservoir, contributes to thermoregulation, and provides mechanical support. During the aging process, certain parts of the body, such as the face and the dorsal hands, lose subcutaneous fat, whereas other body parts, such as the abdomen in men and the thighs in women, gain subcutaneous fat.[23]

Significant structural and functional changes occur in the skin with aging. Two major forces contribute to this process: chronologic aging of the skin related to the intrinsic passage of time and photoaging resulting from cumulative UV light exposure. Many of the functions of skin that decline with age show an accelerated decline in photoaged skin. Photoaging likely causes a decrease in skin thickness in the upper dermis, but chronologic age is associated with an increase in thickness in the lower dermis. No general relationship between skin thickness and age has been observed.[24] Photoaging accounts for many of the cosmetic concerns associated with aging, such as dyspigmentation, yellow hues, enlargement of pores, wrinkling, laxity, telangiectasia, and leathery appearance.[25] Although the accumulation of actinic damage owing to solar injury seems to account for a major portion of observed skin change with aging, it is difficult to separate the degree of photoaging from chronologic aging in humans in vivo.

Delayed wound healing seen in elderly people can be explained by a 50% decrease in epidermal turnover rate between the third and eighth decades and the vascular changes mentioned above.[26] Vascular changes also increase the risk of bruising during activities of daily life and during medical procedures. As the skin becomes less elastic, configurational changes in the skin become irreversible and wrinkles develop. Loss and redistribution of the subcutaneous tissue produce further changes with folds and drooping skin. The impact of these changes on human wound healing is not clear. Reports have been complicated by lack of adjustment for environmental, solar, and comorbid factors as well as for specific skin sites.

NORMAL WOUND HEALING

Wound healing occurs in a carefully regulated and evolutionarily conserved fashion and relies on complex interactions of cells and extracellular matrix components. Acute wound healing progresses temporally through 3 distinct but overlapping phases: inflammatory, proliferative, and remodeling.

Within seconds after injury, the tissue repair process begins, as arriving platelets secrete proinflammatory cytokines and growth factors, including platelet-derived growth factor (PDGF), which facilitate the recruitment of inflammatory cells and fibroblasts into the nascent wound.[27] As the coagulation cascade proceeds, it releases anaphylatoxins C3a and C5a, which attract neutrophils, the predominant inflammatory cell type of the initial portion of the inflammatory phase.[28] Upon activation, neutrophils

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release additional proinflammatory cytokines, including interleukin-8 (IL-8) and tumor necrosis factor (TNF). This leads to the upregulation of cellular adhesion molecules, which are essential for leukocytes to migrate into the wound. Within 24 to 48 hours, macrophages replace neutrophils as the predominant cell type. In addition to cleaning the wound of foreign substances, macrophages synthesize and release growth factors important for the initiation of angiogenesis, such as vascular endothelial growth factor (VEGF), and for the stimulation of fibroblasts, including transforming growth factors (TGF-α, TGF-β), fibroblast growth factor (FGF), and IL-1.[29]

These growth factors usher in the second phase of wound healing, the proliferative phase. Characteristic changes include capillary growth, granulation tissue formation, fibroblast proliferation with collagen synthesis, and increased macrophage and mast cell activity. This stage is responsible for the development of wound tensile strength. Growth factors, especially PDGF and TGF-β, acting in concert with the extracellular matrix molecules, stimulate nearby fibroblasts to proliferate, express integrin receptors, and migrate into the wound space.[30–32] The expression of integrin receptors on epidermal cells allows them to interact with a variety of extracellular matrix proteins (eg, fibronectin and vitronectin) that interact with stromal type I collagen at the margin of the wound and in the fibrin clot in the wound space.[33–35] Plasminogen activator also stimulates collagenase (matrix metalloproteinase 1) and therefore facilitates the degradation of collagen and extracellular matrix proteins.[36] The process of neovascularization in this phase produces a granular appearance of the wound owing to formation of loops of capillaries and migration of macrophages, fibroblasts, and endothelial cells into the wound matrix. FGF sets the stage for angiogenesis during the first 3 days of wound repair, and VEGF is critical for angiogenesis during the formation of granulation tissue.[37] Re-epithelialization begins soon after injury and continues throughout the proliferative phase. In partial-thickness wounds, the stem cells originate from the hair follicles and sweat glands. In full-thickness wounds, epithelial cells migrate from the wound margin. The rate of migration of epithelial cells is dependent on tissue oxygen tension and moisture of the wound.[38,39] Migration is mediated in part by epidermal growth factor (EGF), TGF-α, FGF, heparin-binding EGF, PDGF, insulin-like growth factor 1, and IL-6.[40–47]

The third phase of wound healing is defined by maturation. This long phase of contraction, tissue remodeling, and increasing tensile strength lasts up to a year. Fibroblasts are responsible for the synthesis, deposition, and remodeling of the extracellular matrix. Fibroblast proliferation and collagen remodeling lead to contraction. This contracted tissue, or scar tissue, is functionally inferior to original skin and is a barrier to diffused oxygen and nutrients.[48] At maximum strength, a scar is only 80% as strong as normal skin.[49]

If the inflammatory response persists rather than resolves during the maturation phase, a disturbed healing response may result, leading to a chronic wound. Certain conditions can impair the process of wound healing, allowing an acute wound to progress to a chronic wound. The most common conditions that contribute to poor wound healing are diabetes, atherosclerosis, venous insufficiency, and pressure.[50,51] These conditions impede wound healing by reducing the supply of oxygen, nutrients, and mediators involved in the repair process.

WOUND HEALING IN OLDER ADULTS

Because most chronic wounds occur in aged populations, it has been concluded that aging itself may worsen wound healing. Indeed, many age-related morphologic and structural changes in skin have the potential to negatively influence wound healing.

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Elderly skin demonstrates flattening of the dermal-epidermal junction, leading to increased vulnerability to shearing forces.[52] Older skin has a reduction in nerve endings that increases the risk of injury.[53] It has reduced and disorganized microcirculation, which may result in the development of ischemic ulcers.[54] It has fewer and less-effective Langerhans cells, leading to decreased recognition and elimination of foreign pathogens.[55] Older skin has decreased proliferation of keratinocytes and increased keratinocyte migration time, which may lead to delayed re-epithelialization.[56] In aged skin, fibroblasts decrease in number and produce less extracellular matrix material, which leads to delayed collagen deposition and remodeling.[57] Taking all of these contributing factors together, it seems intuitive that aged skin would demonstrate less efficient and effective wound healing compared with younger skin.

However, this concept has been challenged by recent research, which has shown that wound healing in healthy older people is delayed but not defective.[58–60] Impaired wound healing leading to chronic wounds in the elderly seems to be primarily due to higher prevalence of comorbidities rather than innate deficiencies in the wound healing process. It is important to consider that certain diseases that are associated with poor wound healing, including peripheral arterial disease, venous stasis, and diabetes mellitus, are much more prevalent in aged persons. Older patients are also more likely to receive treatments such as chemotherapy or corticosteroids, which may inhibit proper wound healing. In addition, as aged individuals more often undergo surgery and as their physical abilities and dexterity decline, they are at higher risk of developing more wounds overall.

The effect of age on wound tensile strength has been measured in several animal models, but in few human studies. The basis for the first reports on impaired healing in elderly persons came from a study in 1970 that showed increasing rates of dehiscence with age. Dehiscence occurred in 0.9% of surgical wounds in patients aged 30 to 39 years, in 2.5% in patients aged 50 to 59 years, and in 5.5% in patients over age 80 years.[61] However, adjustment for comorbidity or other potential confounders was not done. In 2015, a retrospective review of 25,967 plastic surgery patients showed that aging was not associated with an increased incidence of wound dehiscence.[62]

The visual quality of scarring and microscopic evaluation of scarring have been shown to be superior in older subjects.[63] A trial of experimental forearm wounding demonstrated that persons greater than 80 years of age had a nonsignificant decrease in tensile strength compared with persons less than 70 years of age.[64] Collagen deposition is similar in both young and elderly wounded subjects. No difference in hydroxyproline accumulation in polytetrafluoroethylene tubes was seen in young healthy volunteers compared with elderly healthy volunteers.[65] Age has no effect on collagen synthesis 2 weeks after wounding.[65] In fact, aging may be associated with increased amounts of fibrillin and elastin during acute wound healing and may lead to an improved quality of scarring, particularly in women. The messenger RNA (mRNA) expression of elastin was greatest in the wounds of older persons.[66]

The rate of epithelialization does seem to differ with age. Complete epithelialization of partial-thickness wounds occurs approximately 2 days faster in young healthy patients compared with elderly healthy patients.[65] A difference in in vitro growth of epidermal cells has been shown among newborns, young adults, and older adults. Although there was large interdonor variability, growth of keratinocytes obtained from upper arm biopsies of young adult (ages 22–27 years) and elderly adult (ages 60–82 years) donors significantly decreased with age. Cell yields at 7 days showed an 8-fold increase for young adults but only a 4-fold increase for elderly adults.[67]

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Fibroblasts have a significant role in the synthesis and reorganization of the extracellular matrix during wound repair. An impaired functional response of these cells to stimulation by growth factors might contribute to the delayed wound healing reputed in aging. Cultures of dermal fibroblasts from young and elderly individuals exposed to TGF-β demonstrated a 1.6-fold to a 5.5-fold increase in the levels of secreted type I collagen and extracellular matrix proteins and exhibited a 2.0-fold to a 6.2-fold increase in the amounts of the corresponding mRNAs.[68] The dose-response to TGF-β was as vigorous in contractile properties in cells from aged donors as in cells from a young donor.[68] The response of cultured fibroblasts to cytokines does not seem to change with age. In fibroblast cell lines derived from persons aged 3 days to 84 years, synthesis of collagen in response to EGF, TNF-α, PDGF, and TGF-β did not vary with the age of the donor.[69]

Studies have suggested that microscopic structure of wounds in older persons is better than in younger persons and that the formation and quality of scarring may improve with age. This lack of inferior wound healing with aging is supported by clinical observation that there does not seem to be a significant difference in surgical wound healing in healthy older persons undergoing elective surgery. The rate of epithelialization does seem to be slower in older persons, but the magnitude of the delay may not be clinically important. The response to TGF-β and wound contractility does not seem to be different with aging.[69] Most age-related effects on the inflammatory process are modest.

Chronic wounds are defined as wounds that fail to proceed as expected in structural and functional integrity. Loss of subcutaneous tissue, failure of re-epithelization, necrosis, or infection can complicate wound healing. The use of growth factors found in acute wounds to accelerate healing in chronic wounds has received considerable attention in the field of wound healing.[70] Unfortunately, despite initial success in animal models, the only growth factor proven to improve wound healing in a double-blind randomized trial is PDGF, and those results were only modest.[71] Ultimately, it should not be too surprising that treatment with one growth factor is not likely to cure chronic wounds, considering that wound repair is the result of a complex set of interactions among cytokines, growth factors, extracellular matrix, and cells.

SUMMARY

Evidence for age-related effects on wound healing has been derived mostly from empirical observations without adjustment for confounders. Changes in the structure of the skin have been observed with aging, but the effects in skin unexposed to solar radiation appear modest. The clinical impact of these changes in acute wound healing seems to be small in comparison to other factors. Poor healing of chronic wounds, predominantly seen in older populations, is more often attributable to comorbid conditions rather than age alone.

CLINICS CARE POINTS

- When caring for older patients, it is important to keep in mind the physiologic changes of the skin associated with aging and how this can affect wound healing.

DISCLOSURE

The authors have nothing to disclose.

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