



Clinical Aspects of Aging Skin: Considerations for the Wound Care Practitioner

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GENERAL PURPOSE: To provide information about changes associated with aging skin and the implications for wound care practitioners.

TARGET AUDIENCE: This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES: After participating in this educational activity, the participant should be better able to:

1. Describe proposed biologic theories of aging and the biology of aging skin.
2. Discuss the clinical consequences of aging skin and the implications for wound care practitioners.

ABSTRACT Aging is a complex phenomenon manifested by macromolecular damage, adverse changes to the genome, blunted immunologic function, alterations in body composition, and decreased adaptation to stress. Understanding the changes that skin undergoes with age is essential for wound care practitioners. Accordingly, this article will introduce the reader to theories of aging, the biologic changes associated with aging skin, and clinical considerations for the wound care practitioner, including the concepts of skin failure, Skin Changes At Life's End, and frailty.

KEYWORDS: aging, frailty, photoaging, skin, Skin Changes At Life's End, skin failure, wound care

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INTRODUCTION

Aging is a complex phenomenon manifested by macromolecular damage, adverse changes to the genome, blunted immunologic function, alterations in body composition, and decreased adaptation to stress.¹ The skin is the most visible organ of the body and undergoes numerous changes with age that have important physiologic consequences.² Aging skin is visually apparent in wrinkling, hair graying and loss, and pigmented age spots (Figure 1). A critical question is how aging skin intersects with disease states, leading to skin failure and impaired wound healing.³

The US is undergoing profound demographic change with a rapidly aging population. About 75 million people will join the ranks of the older population during the next 20 years.⁴ This has major implications for healthcare delivery, particularly because of the shift from acute to chronic illnesses that accompanies old age.⁵ Because many nonhealing wounds are the consequence of functional changes and diseases that accompany aging, it is important that practitioners are equipped to meet this healthcare challenge.⁶

This article introduces the reader to changes associated with aging skin, as well as clinical considerations for the wound care practitioner. It also explores the theoretical relationship among skin failure, Skin Changes At Life's End (SCALE), and frailty, which are components of the aging process.⁷ Finally, these concepts are

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Figure 1. AGING SKIN

The hand on the right belongs to a 28-year-old medical resident. The hand on the left belongs to a woman who is 92 years old and spent much of her life in a Mediterranean country with extensive sun exposure, who therefore has signs of both intrinsic and extrinsic aging (photoaging). Her skin exhibits thinning, loss of appendages, loss of hydration and elasticity, dryness, age spots, deep wrinkles, and loss of subcutaneous fat.



Photo courtesy of J. M. Levine, MD.

illustrated with a short case report. The goal is to unite known aspects of aging skin with common clinical observations from the bedside.

THEORIES OF AGING

There are several proposed biologic theories of aging. These are neither competing nor mutually exclusive and likely take place simultaneously in terms of their impact upon cellular and organ function.⁸ The following is a brief introduction to selected theories of aging.

Free Radical Theory and Mitochondrial DNA Damage

Mitochondria are organelles within cells that are responsible for respiration, which promotes energy production using oxygen and simple sugars to produce adenosine triphosphate. Mitochondrial DNA is in close proximity to the location where reactive oxygen species (ROS) are produced, and this type of DNA has limited protection and cannot repair itself.⁹ Reactive oxygen species are natural byproducts of cellular metabolism that cause damage to mitochondrial DNA, leading to mutations with a further increase of ROS and accumulation of free radicals such as superoxide and nitric oxide that result in apoptosis.

Free radicals are atoms or molecules containing unpaired electrons that initiate a damaging chain reaction resulting in DNA crosslinking that leads to aging and may contribute to cancer genesis. Antioxidants such as ascorbic acid are presumed to be helpful in mitigating this reaction because they donate electrons, neutralizing

the radical without forming another.¹⁰ Because of this biochemical reaction, antioxidants are credited with delaying the effects of aging.

Telomere Shortening

Telomeres are repetitive sequences of DNA located at the ends of each chromosome that do not encode any gene products. They protect the chromosomes from fraying and sticking to each other, which could scramble the genetic information. Telomeres therefore have a stabilizing function for the genome. However, telomeres shorten with each round of cell division and are also affected by UV exposure.¹¹ Telomere length is inversely proportional to cell age, which supports the theory that the shortening process contributes to aging and causes cells to enter a senescent, nonreplicating state.

Inflammaging

A major source of inflammatory stimuli includes misplaced or altered molecules and debris resulting from damaged or dying cells.¹² On a molecular level, this is manifested by secretion of proinflammatory cytokines that dysregulate the immune response (immunosenescence). The result is a state of low-grade inflammation, or "inflammaging." This is a process that fuels the onset or progression of chronic disease and accelerates or propagates the aging process. Many experts believe that inflammaging is a common link between aging and age-related diseases.¹³

The Stem Cell Hypothesis

The stem cell is an undifferentiated cell capable of self-renewal and differentiation into multiple lines of mature cell types.¹⁴ They maintain homeostasis by replenishing depleted reserves of differentiated cells in a variety of tissues and are a critical source of renewal for naturally dying cells. Stem cells are also involved in wound healing,¹⁵ including re-endothelialization and neovascularization.¹⁵ The stem cell hypothesis states that aging results from the depletion or failed differentiation of stem cells attributed to injury, illness, environmental challenge, or aberrant gene expression.¹⁶

INTRINSIC AND EXTRINSIC SKIN AGING

Intrinsic or endogenous aging refers to genetically dependent changes in the aging process, whereas extrinsic or exogenous aging refers to environmental influences.² It is sometimes difficult to separate intrinsic from extrinsic factors because of diet and lifestyle factors, but there are profound genetic and ethnic differences in the body's response to both.¹⁷

Intrinsic aging is dependent on cellular aging, telomere shortening, mitochondrial DNA mutations, oxidative stress, and changes in hormone levels. Intrinsic aging impacts multiple macromolecules that make up cells and tissues.

Collagen, a major component of the extracellular matrix of the dermis, becomes fragmented and coarsely distributed.¹⁸ Collagen deterioration and reduction lead to impaired fibroblast function and further decrease of dermal collagen.¹⁹ Other components of the extracellular matrix also are altered by aging, including elastic fibers, glycosaminoglycans, and proteoglycans.¹⁹

Extrinsic aging arises primarily from UV light exposure (photoaging) and biologic reactions to exogenous substances such as cigarette smoke and organic compounds in air pollution.²⁰ The biologic effect of UV radiation is based on light absorption; the conversion of energy into chemical reactions results in skin aging and carcinogenesis. There are two types of UV radiation: UVB is mainly absorbed in the epidermis, whereas UVA penetrates deeper, generating ROS that damage lipids, proteins, and DNA. Darker skin tones with increased melanocytes are protective against the deleterious effects of UV radiation.²¹ An example of sun-damaged skin in an exposed area is presented in Figure 2.

Extrinsic aging also is triggered by substances that induce xenobiotic metabolism such as cigarette smoke, traffic-related pollutants, and industrial effluents.²² Xenobiotic metabolism is the set of metabolic pathways that modify the chemical structure of compounds foreign to the organism's normal biochemistry. Cigarette smoke contains a variety of toxicologically significant chemicals and is a known cause of premature skin aging. Persons who smoke have deeper wrinkles than nonsmokers, and as with UV exposure, cigarette smoke induces the expression of harmful matrix metalloproteases.²³

Figure 2. SUN-DAMAGED SKIN (PHOTOAGING)

This back of this man's neck has been chronically sun exposed, resulting in a condition that dermatologists call cutis rhomboidalis nuchae. Note the deep crisscrossed wrinkles.



Photo courtesy of J. Levitt, MD, Department of Dermatology, Icahn School of Medicine at Mount Sinai.

Figure 3. MALIGNANCY ASSOCIATED WITH SUN EXPOSURE

This man has a malignancy known as lentigo maligna melanoma that typically occurs in sun-exposed areas.



Photo courtesy of J. Levitt, MD, Department of Dermatology, Icahn School of Medicine at Mount Sinai.

Air pollution is composed of organic and inorganic substances that include ozone, particulate matter, sulfur dioxide, carbon monoxide, nitrogen oxide and dioxide, heavy metals such as cadmium and lead, and others.²⁴ Exogenous toxins in air pollution cause premature skin aging through several mechanisms including free radical generation, inflammatory cascade induction, skin barrier disruption, hydrocarbon receptor activation, and microbiome alteration.²⁰ Skin on persons living in highly polluted cities is subject to higher oxidative stress and has higher lactic acid content and lower hydration level when compared with those living in less polluted areas.²⁵

THE BIOLOGY OF AGING SKIN

There are numerous biologic changes in aging skin that impair its adaptive and homeostatic capacity, as well as its response to mechanical and physiologic stress such as hypoxia and hypoperfusion.²⁶ These changes lead to an increased susceptibility to internal and external stresses that result in acute and chronic skin failure and impaired wound healing. Sun exposure leads to DNA damage that can lead to malignancy. An example of malignancy associated with sun exposure is presented in Figure 3. The cutaneous functions that decline with age are presented in Table 1.

A schematic diagram of age-related histologic changes is presented in Figure 4. In the epidermis, there is reduced keratinocyte proliferation and turnover time and atrophy of the stratum spinosum, and surface pH is less acidic.² Epidermal turnover is 50% lower in octogenarians than in persons younger than 60 years.² Desquamation

Table 1. CUTANEOUS FUNCTIONS THAT DECLINE WITH AGE

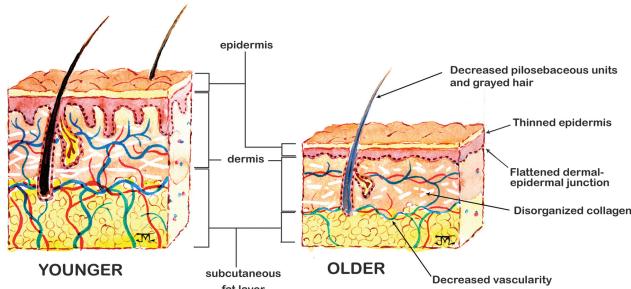
- Barrier function
- Cutaneous immune response
- Cellular replacement
- Injury response
- Dermal clearance
- Vascular response
- Sebum production
- Sweat production
- Thermoregulation
- Sensory perception
- Vitamin D production

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is less effective, and lipid biosynthesis in the stratum corneum is impaired. Fewer melanocytes exist to protect from UV radiation, and fewer Langerhans cells are available to process microbial antigens and present them to other immune system cells. This is accompanied by altered T- and B-cell function and a proinflammatory environment referred to as inflammaging (see the section on THEORIES OF AGING).¹³ Further, the dermal-epidermal junction is flattened; the effacement of the rete ridges leads to decreased contact between dermis and epidermis, predisposing the skin to separation along this interface.²⁶ The dermis becomes atrophic with reduced fibroblasts and mast cells, and collagen becomes disorganized, with an accompanying change in synthesis from type I to type III. For example, collagen synthesis declines by 30% in the first 4 years of menopause and then by 2% annually.²³ There is decreased elastin synthesis, and elastic tissue degrades. Decreased mechanoreceptors including Meissner and Pacini corpuscles result in a diminished sensation to touch, pressure, and vibration.

The number and function of skin appendages such as pilosebaceous units and sweat glands also decrease with age. Pilosebaceous units include hairs, sebaceous glands,

Figure 4. HISTOLOGIC CHANGES IN AGING SKIN



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and arrector pili muscles. Impaired thermoregulation results from loss of subcutaneous fat along with decreased autonomic nerves from the sympathetic nervous system and decreased dermal vascularity. The loss of sweat glands also contributes to impaired thermoregulation as well as a decreased ability to manage water balance in response to antidiuretic hormone. The number, growth rate, and diameter of hair follicles decline with aging.²⁷

With aging comes a reduction in microvascular reactivity and vascular dysregulation. Blood flow to the skin is reduced by 40% between the ages of 20 and 70 years.²⁸ Aging has a direct effect on microcirculation, including arterioles, capillaries, and venules, with effects that are both anatomic and physiologic. Arterioles are a major component of the microvasculature that contain endothelial smooth muscle that contracts (vasoconstriction) or relaxes (vasodilatation) to regulate blood flow and systemic BP. Atherosclerotic arteries become stiff, and there is decreased blood vessel density with increased vascular disorganization.²⁸

CLINICAL CONSEQUENCES OF AGING SKIN

Aging is associated with progressive loss of functional reserve of all organs, including skin. Under normal conditions, the physiologic compensation for age-related deficits is sufficient, but during times of stress, the lack of physiologic reserve becomes evident. This is further impacted by acute and chronic comorbidities. Many older individuals develop the clinical syndrome of frailty (discussed later). The result of age-related changes and superimposed comorbidities is increased vulnerability to mechanical stress with a predisposition to skin failure and impaired wound healing.^{29,30} Some authors have used the term "dermatoporosis" to encompass chronic cutaneous insufficiencies associated with aging.³¹ An example of skin fragility with age is presented in Figure 5.

Figure 5. FRAGILE, AGED SKIN

This 93-year-old woman has been bumping into objects at home and shows multiple abrasions and hematomas of both lower extremities. Her medical history includes venous stasis disease.



Photo courtesy of J. M. Levine, MD.

The process of wound healing occurs in overlapping phases that include inflammation, proliferation, angiogenesis, epidermal restoration, and wound contraction and remodeling.³² Wound healing is prolonged in older individuals, with increased rates of postoperative wound disruption and dehiscence.³³ There is decreased tensile strength of healing wounds in persons older than 70 years, and the rate of skin fibroblast migration slows with age.³⁴ The age-associated reduction in healing ability in conjunction with senescence of the immune system results in increased risk of secondary infection in older patients.³⁵

Surprisingly, little is known about the biologic mechanisms by which aging impacts wound healing.³⁰ The multifactorial pathogenesis and heterogeneity of chronic wounds have made it challenging to identify predictive and diagnostic biomarkers of wound healing.³⁰ Adding to the challenge is the diversity of the aging population; multiple comorbid conditions impair wound healing in addition to the aforementioned intrinsic and extrinsic factors. Mechanical factors and disease states that may impact skin integrity and promote skin failure are listed in Table 2.

Human skin, because of its complex multilayered structure, exhibits a range of effects resulting from mechanical deformation in both macrostructures and microstructures.³⁶ Experimental studies demonstrate that sustained deformations inflict cellular and tissue damage that results in skin ulceration.³⁷ It is postulated that tissue distortion leads to the loss of cellular cytoskeletal integrity, providing for the transport of abnormalities through the plasma membrane, resulting in a loss of homeostasis, apoptosis, inflammation, edema, and damage spread.³⁷ This theory may account for the deleterious effect of shear forces, which are considered a major risk factor for pressure injury.

In recent years, there has been extensive discussion on whether pressure injuries are always avoidable and whether some ulcers are associated with the dying process, also known as terminal ulceration.^{38,39} There is a need for a cohesive theory that unites aging and altered physiology with unavoidable pressure injuries and impaired wound healing, and this is accomplished with recognition of skin failure.^{29,38,40} Like any other organ, skin can fail, and failure can be acute or chronic.⁴¹ Skin failure is a topic that engenders controversy because it

Table 2. FACTORS BEYOND AGING THAT MAY IMPACT SKIN INTEGRITY

Tissue deformation	Causes cellular cytoskeletal distortion that leads to plasma membrane defects leading to cell death
Hypotension	Decreases perfusion in skin depriving it of oxygen and nutrients
Hypoxia	Cells are dependent upon oxygen and will die in states of inadequate oxygen delivery
Anemia	Low blood count will decrease the amount of oxygen available for cellular survival
Hypoalbuminemia	Causes fluid leakage into extravascular space (edema), which inhibits oxygen and nutrients delivery to cells
Congestive heart failure	Promotes states of decreased perfusion that decreases delivery of oxygen and nutrients to cells
Moisture-associated skin damage	Causes maceration, inflammation, and edema that result in increased vulnerability of skin
Fungal infection	Causes inflammation and local edema that results in increased vulnerability of skin
Nutritional disorders: malnutrition and obesity	Malnutrition alters skin structure with thinning and loss of adipose tissue and leads to hypoalbuminemia and edema. Obesity leads to an array of metabolic disorders and increased susceptibility to immobility
Frailty	A chronic, progressive condition, which is a final common physiologic pathway in older adults that accelerates vulnerability to adverse health outcomes including pressure injuries
Systemic inflammatory response syndrome (SIRS)	This is the complex pathophysiologic response to an insult such as infection, trauma, burns, and other injuries. Through multiple mechanisms including endothelial damage and hypoalbuminemia with edema, SIRS can cause decreased ability of the skin to respond to mechanical stress
Metastatic cancer	The combination of immobility, pain, debility, and nutritional depletion can lead to altered skin structure with increased susceptibility to mechanical stressors
Atherosclerotic disease	Atherosclerotic disease of major arteries leading to the lower extremities impairs circulation to the lower extremities, causing decreased delivery of oxygen and nutrients
Diabetic microvascular disease	Diabetes mellitus, particularly when longstanding and uncontrolled, causes changes in skin that result in impaired perfusion, barrier function, and response to infection
Edema	Fluid in the interstitial space interferes with delivery of oxygen and nutrients to cells and tissues and increases vulnerability of skin
Multiple organ dysfunction syndrome	This is the derangement of two or more organs arising in the wake of potentially life-threatening physiologic insult that results in SIRS, hypoalbuminemia, and other consequences such as lower stress tolerance

Table 3. SKIN FAILURE CLASSIFICATIONS AND DEFINITIONS^{29,40}

Acute skin failure	The state in which tissue tolerance is so compromised that cells can no longer survive in zones of physiologic impairment such as hypoxia, local mechanical stresses, impaired delivery of nutrients, and buildup of toxic metabolic byproducts
Chronic skin failure	Disruptions in skin integrity that fail to heal in a normal sequential manner to regain structure and function

overlaps with critical concepts of unavoidability and terminal ulceration and does not yet have a universally recognized definition.³⁸ This article uses the following definition, which builds upon the definition originally provided by Langemo et al:^{29,41} "Skin failure is the state in which tissue tolerance is so compromised that cells can no longer survive in zones of physiologic impairment such as hypoxia, local mechanical stresses, impaired delivery of nutrients, and buildup of toxic metabolic byproducts."⁴⁰

Most experts agree that skin failure is a true clinical syndrome that can be acute or chronic, although disagreements exist on precise definitions.^{38,41} A proposed conceptual schema of acute and chronic skin failure is presented in Table 3. According to this model, acute skin failure results from the compromise of physical structure of aging skin including deficits in microcirculation with impaired delivery of oxygen and nutrients and removal of waste products.²⁹ These deficits also give rise to delayed or absent wound healing, which can be characterized as chronic skin failure, because tissues cannot undergo the normal sequence of regeneration.^{38,41} A clinical example of acute skin failure is presented here.

CASE REPORT

A 66-year-old resident of a subacute facility was transferred to the hospital for shortness of breath. His history

Figure 6. PATIENT BUTTOCKS ON DAY 8 OF HOSPITALIZATION



Photo courtesy of J. M. Levine, MD.

Figure 7. PATIENT BUTTOCKS ON DAY 15 OF HOSPITALIZATION



Photo courtesy of J. M. Levine, MD.

included morbid obesity, obstructive sleep apnea, type 2 diabetes mellitus, chronic kidney disease, anemia, and inability to ambulate because of spinal stenosis. Laboratory values included hemoglobin 9.5 g/dL, white blood cell count 12.6 µL, glucose 305 mg/dL, blood urea nitrogen 42 mg/dL, creatinine 3.0 mg/dL, and albumin 2.8 g/dL. He was diagnosed with pneumonia, septic shock, and hypoxia and required intubation, ventilator support, and pressor agents.

He was maintained on a bariatric low air-loss mattress, but desaturation prohibited turning. Ventilation and feeding via nasogastric tube required head-of-bed elevation at 45 degrees. Figure 6 shows his buttocks on day 8, and Figure 7 shows the same view on day 15, illustrating progressive skin failure with tissue infarction.

His clinical condition and respiratory status improved, and he was extubated, but his wound required debridement and negative-pressure wound therapy. After a 28-day admission, he was returned to the subacute facility.

FRAILTY AND SCALE: A FINAL COMMON PATHWAY

In recent years, the concept of frailty in older adults has become widely accepted in the geriatric literature and may have relevance to the development of skin failure in its overlap with SCALE.⁴² Published in 2008, SCALE is a set of consensus statements regarding tissue breakdown at the end of life that emerged from a group of international opinion leaders.⁷ In contrast, frailty is a chronic and progressive clinical syndrome with no universally agreed-upon set of diagnostic criteria.⁴² However, experts concur that this clinical syndrome includes features such as sarcopenia or decreased muscle mass, slowed motor performance, decreased strength, physical activity and exercise tolerance, decreased metabolic rate, and inadequate nutrition intake.⁴³ An examination of both SCALE and frailty reveals similarities that provide a common conceptual link between these two concepts (Table 4).

Table 4. COMMONALITIES BETWEEN FRAILTY AND SCALE AS REFLECTED IN SCALE CONSENSUS STATEMENT 6⁷

Risk factors, symptoms, and signs associated with SCALE have not been fully elucidated, but may include

- Weakness and progressive limitation of mobility;
- Suboptimal nutrition, including loss of appetite, weight loss, cachexia and wasting, low serum albumin/prealbumin level, and low hemoglobin, as well as dehydration;
- Diminished tissue perfusion, impaired skin oxygenation, decreased local skin temperature, mottled discoloration, and skin necrosis;
- Loss of skin integrity from any of a number of factors, including equipment or devices, incontinence, chemical irritants, chronic exposure to body fluids, skin tears, pressure, shear, friction, and infections; and
- Impaired immune function.

Frailty is considered a common pathway of physiologic alterations that result in decreased ability to respond to stressors such as hospitalizations, illness, and environmental extremes, a phenomenon aptly named *homeostenosis*.⁴² Research has demonstrated that patients who are frail are at higher risk of mortality and multiple adverse outcomes including pressure injuries.⁴⁴ The similarities between SCALE and frailty lend support for the occurrence of skin failure as an unavoidable adverse outcome in this subset of the aging population.

ANTIAGING STRATEGIES

The search for a youthful appearance is as old as human civilization, and modern technology offers many interventions intended to achieve this goal. In 2018, the antiaging market was valued at more than \$50 billion, with a projected annual growth rate of 2.7%.⁴⁵ Antiaging cosmetics, sometimes referred to as cosmeceuticals, are a mainstay of the armamentarium.²⁵ There exists a strong demand for products that reduce wrinkles, restore texture and smoothness, lighten age spots, augment lipid layers, and so on. Strategies include covering up wrinkles and blemishes, preventing photoaging with sunscreen, applying topical antioxidants to reduce ROS, protecting and restoring skin from damage from environmental exposure, and boosting cell metabolism and cell renewal to restore mechanical properties diminished by the aging process.²⁵

There are numerous additional strategies to reverse or diminish the aging process including hair restoration, laser resurfacing, and antipigmentation therapies. Other procedures include implants, chemical peels, microdermabrasion, injectable dermal fillers, muscle relaxers such as botulinum toxin, liposuction, cryolipolysis, high-intensity focused ultrasound, radiofrequency microneedling, intense pulsed light rejuvenation, and apheresis techniques that filter substances that cause or promote aging from the

blood. Regenerative therapies on the horizon include stem cells that secrete paracrine factors or proteins that diffuse into neighboring cells to modify the aging effects of a variety of macromolecules such as collagen, elastin, and glycosaminoglycans.⁴⁶

Many patients opt for surgery to recover the appearance of youth, including procedures such as facelifts. There are numerous variations with a trend toward limited procedures with smaller incisions, supplemented by nonsurgical strategies, particularly in older patients.⁴⁷ Cosmetic surgery and most other aesthetic procedures are costly and generally not covered by insurance. Ultimately, despite the scope and cost of antiaging strategies, the basic pathophysiology of aging is not altered.

CONCLUSIONS

The skin is an organ that changes profoundly over a lifetime, becoming progressively compromised in numerous ways, even as medical technology and improvements in public health have endowed us with an extended life span and prolonged the trajectory of old age.^{48,49} The growth of the aging population has altered the epidemiology of chronic wounds, leading to the increased importance of wound care as an interdisciplinary specialty.⁵⁰ Understanding the changes that skin undergoes with age is essential for wound care practitioners. The knowledge of molecular, cellular, and physiologic components of skin aging will facilitate better understanding of the biology of wounds and assist in improved treatment decisions.

PRACTICE PEARLS

- Both intrinsic and extrinsic factors result in the multitude of anatomic and physiologic changes of aging skin.
- Skin failure is becoming accepted by the wound care community as an entity that accounts for unavoidable skin breakdown with multiple irremediable risk factors including the dying process.
- Frailty is a common pathway of physiologic alterations in advanced age that shares characteristics with the widely accepted concept of SCALE.
- Despite the scope and cost of antiaging strategies, the basic pathophysiology of aging is not altered. ●

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