# Aging Skin: Nourishing from Out-In. Lessons from Wound Healing

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## Abstract

Skin lesion therapy, peculiarly in the elderly, cannot be isolated from understanding that the skin is an important organ consisting of different tissues. Furthermore, dermis health is fundamental for epidermis integrity, and so adequate nourishment is mandatory in maintaining skin integrity. The dermis nourishes the epidermis, and a healthy epidermis protects the dermis from the environment, so nourishing the dermis through the epidermal barrier is a technical problem yet to be resolved. This is also a consequence of the laws and regulations restricting cosmetics, which cannot have properties that pass the epidermal layer. There is higher investment in cosmetics than in the pharmaceutical industry dealing with skin therapies, because the costs of drug registration are enormous and the field is unprofitable. Still, wound healing may be seen as an opportunity to "feed" the dermis directly. It could also verify whether providing substrates could promote efficient healing and test optimal skin integrity maintenance, if not skin rejuvenation, in an ever aging population.

## Introduction

The skin is the outermost defense organ protecting us from the environment. Wounds are probably the most ancient threat faced by living beings. Mammal skin is an evolution of the skin mucosal surface present in extremely ancient bony vertebrates, living in the sea. The epidermis (epi = over), the outermost layer of the skin, has an ectodermic origin. This is unlike the dermis, the inner skin layer, with a mesodermic origin, which provides oxygen and nutrition to the epidermis through blood and lymph vessels [1].

Therefore, the dermis nourishes the epidermis and not vice versa, which should be borne in mind when considering health maintenance of the skin from out-in. As a result epidermis health and healing require primarily dermis health and healing. Wounds allow the dermis to be in contact with the environment, and both are active in the healing process. As a result, the balance between the severity of environmental aggression and the efficiency of dermis cells mediates the degree and quality of the healing process.

As the skin is the outermost environmental defense, when it is broken, environmental threats (e.g., chemicals, viruses, or bacteria) have to be faced. However, the loss of liquids and proteins from wounds extending to the dermis has also to be faced. This insight should be taken into account as a possible threat to the integrity of the whole organism and not of the skin alone.

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The energy costs of wound healing are enormous, but as shown by studies on the dynamics of collagen in the dermis, it is also expensive to maintain skin integrity. This is because continuous remodeling of stressed structures that consume a large amount of body energy and substrates needed for protein metabolism [1] is required. For example, collagen, the most abundant protein in the human body, represents around 50 % of skin weight and 30 % of all body proteins. Synthesis of any individual collagen molecule requires around four high-energy bonds (~ATP equivalents) for each amino acid inserted into the molecule [2]. Similar energy costs have also been calculated for protein synthesis in bacteria [3].

An analysis of recent literature shows that there is consensus that for best healing, the wound microenvironment should be protected with moist or wet medication [4]. There is a continuous flow of literature which discusses different materials potentially useful for wounds treatment [5].

However, the wounds are considered almost exclusively as a loss of tissue integrity, so there is far less documentation concerning another pivotal question, i.e., is it useful to look at wounds as active sites for the refueling of cells involved in the management of tissue regeneration to improve the efficiency of healing?

Previously, it has been shown that shortening healing time can be promoted by feeding fibroblasts with a peculiar amino acid formulation. This formulation should be based on synthetic requirements suggested by the highly peculiar and repetitive composition of the collagen molecule [6].

Previous research has demonstrated that the major repair agents of wounds (TGF-β, eNOs and iNOs, VEGF) are highly modulated by medications providing the specific stoichiometric ratios between amino acids found in procollagen (glycine, proline, and lysine) when compared with untreated lesions in healthy animals [7]. Presently, further current research has explored how different nitrogen inputs could influence the wounds healing process in experimental models, testing a large variety of different substrates containing different ratios of amino acids.

## Characteristic Age-Related Changes of Normal Skin

The skin is the outermost defense organ of the body, which protects us from the environment. It is composed of three layers: the epidermis, the dermis, and subcutaneous tissue. The epidermis (epi = over) is the outermost layer of the skin. It consists predominantly of squamous epithelial cells (keratinocytes), and it produces cutaneous appendages, including the sebaceous glands, apocrine and eccrine sweat glands, hair follicles, and nails. The *stratum corneum*, the external surface layer, gives the skin its waterproofing barrier properties. This property depends on skin lipids (ceramides, cholesterol, and fatty acids) and on the mixture of natural moisturizing molecules, such as amino acids, organic acids, urea, and inorganic ions [8, 9], which can absorb large amounts of water.

The dermis lies between the epidermis and subcutaneous fat. The dermis, comprised of fibroblasts and the extracellular matrix (ECM) (formed by types I and III collagen, elastin, and glycosaminoglycans), is divided into the superficial papillary dermis and the deep reticular dermis. The papillary dermis forms ridges which maintain contact with the epidermis [1]. The dermis is the main contributor to skin thickness and provides oxygen and nutrition to the epidermis through blood and lymph vessels; as such it is very important for the skin's cosmetic appearance. Collagen gives the dermis its structural stability and resilience [9]. Therefore, the dermis nourishes the epidermis and not vice versa, as already mentioned. How nutrition affects the skin and dermis health is discussed in details in a later chapter of this textbook (please refer to chapter "▶ Aging Skin: Nourishing from In-Out").

Progressively, the aging skin undergoes a series of events that gradually reduce its structural integrity and its function. The thickness of the epidermis remains fairly constant with age [10], but there is a flattening of the dermal-epidermal junction, which allows the appearance of atrophy [11]. In addition, the

time taken by the keratinocytes to migrate from the basal layer to the skin surface, a key process in repair, increases by 50 % in the elderly [12]. Aging, the dermis loses its thickness, elasticity, and water content also as a consequence of the reduction of lipids and amino acids in the *stratum corneum*, moreover dermis loses the melanocyte and Langerhans cell density, the sebum production, and the number of dermal blood vessels. As a result blood flow decreases, reducing the supply of nutrients and altering thermoregulation [9]. In addition, there is a flattening of the papillary dermis, decreasing surface contact between the dermis and epidermis [13]. This predisposes separation of the dermal-epidermal junction with laterally applied tension [11]. Furthermore, the cellular content of the dermis (fibroblasts, mast cells, Langerhans cells, and macrophages) also decreases with age [14]. Finally, the functional characteristics of the skin are compromised.

Moreover, there is a decrease of the dermis proteins content, primarily collagen with age. This is the result of both decreased production and increased collagen degradation [15]. The quality of the remaining collagen is altered, with fewer organized fibers, ropelike bundles, and a greater degree of disorganization. The quantity of elastin, a determinant of skin elasticity, is fairly constant with age. However, like collagen, elastin in the aged dermis has a disorganized morphology, resulting in decreased skin elasticity [16, 17].

## Wound and Wound Healing

Wounds allow the environment to contact the dermis directly; thus, an efficient wound healing process must be activated quickly in order to protect the whole organism from environmental threats. Therefore, tissue repair and regeneration are important topics in aging. The main protein involved with the repair of the injured tissue is collagen. This is the most abundant protein in the animal kingdom, accounting for 30 % of total protein in the human body [18].

In normal tissues collagen provides strength, integrity, and structure. When tissues are disrupted, collagen is needed to repair the defect and restore the normal structure and function of the skin. Collagen mass in normal tissues is dependent on the balance between the rates of synthesis and degradation. A rapid increase of collagen production in wounds is indicative of higher rates of granulation tissue formation, resulting in faster reepithelialization.

The cells responsible for collagen deposition are the fibroblasts of the connective tissue. Within the wound bed, fibroblasts also produce two other important components of the ECM, glycosaminoglycans and proteoglycans, which play a fundamental role in the organization of collagen fibers and subsequently in wound closure. However, if too much collagen is deposited in the wound site, anatomical structure is lost, function is compromised, and fibrosis and scars occur. On the contrary, if an insufficient amount of collagen is deposited, the wound is weak and may dehisce [19].

A lot of interest has been generated by the observation that increased amounts of TGF-β are found in wounds that heal by scar formation as opposed to tissue regeneration. TGF-β is a negative regulator of wound reepithelialization. This finding has led to clinical efforts to block scar formation with antibodies and small molecules directed against TGF-β and other pro-inflammatory mediators. Recent evidence also suggests that changes in the wound physical environment might result in over-healing, by affecting the wound mechanical environment [20].

The healing of acute wounds is a very complex regenerative process. It is controlled by temporal interactions between cells, extracellular matrix components, and signaling molecules, and it is of great importance in clinical medicine. Acute wounds normally heal in an orderly and efficient manner characterized by distinct phases called hemostasis/inflammation, proliferation, and remodeling, which all overlap. Each healing phase depends on various factors such as tissue type, age, infections, health status, and, very importantly, nutritional status [20–28].

The first phase begins immediately after injury and is characterized by hemostasis and inflammation as a response to the injury. This phase usually lasts about 4–6 days after injury. During coagulation, the platelet releases several growth factors (PDGF, PF4, TGF-α, and TGF-β) and pro-inflammatory cytokines (TNF-α, iNOs, IL1) which initiate the inflammatory response [29]. These substances also act as chemoattractants for neutrophils and monocytes that clean the wound from foreign substances, increase vascular permeability, and promote fibroblast activity. In this phase the neutrophils elaborate ROS, protease, and metalloprotease (MMP) to kill bacteria and clear the extracellular matrix.

About 2–4 days after injury, monocytes transform into macrophages, which replace the predominant neutrophils and phagocytize debris product, bacteria, and apoptotic cells. Macrophages also release many chemoattractant molecules to recruit more macrophages and fibroblasts. Furthermore, macrophages initiate provisional matrix formation through the activation of TGF-β, which stimulates fibroblast proliferation and collagen synthesis [29]. The activation of macrophages and the balanced modulation of growth factors and cytokines during the inflammation phase direct the quality of tissue repair and are fundamental for the transition to the second step of wound repair, i.e., the proliferative phase.

The second stage of wound repair occurs 2–10 days after injury and is characterized by cellular proliferation (new tissue formation) and the migration of different cell types that overlap with the inflammatory phase. The new provisional matrix (the granulation tissue) invades the wound space. Fibroblasts and macrophages move into this space and provide a source of growth factors necessary to stimulate fibroplasia and angiogenesis. Macrophages and fibroblasts release protease that activates the TGF-β, which in turn stimulates fibroblast proliferation and collagen synthesis. The fibroblasts are responsible for the synthesis, deposition, and remodeling of the extracellular matrix [30].

The third stage of wound repair, remodeling, begins 2–3 weeks after injury and lasts for a year or more. During this stage, all processes activated after injury wind down and cease. Most of the endothelial cells, macrophages, and myofibroblasts undergo apoptosis (programmed cell death) or exit the wound, leaving a mass that contains few cells and consists mostly of collagen and other extracellular matrix proteins. This phase consists of the maturation and remodeling of new tissues inside the wounded area. The main feature of this phase is the deposition of collagen in an organized and well-mannered network, and so the fibroblasts play a pivotal role [29]. Epithelial-mesenchymal interactions probably continuously regulate skin integrity and homeostasis [20]. However, the tissue never regains the properties of uninjured skin [31].

The rate of wound healing is dependent on effective synchronization of these phases [32]. The biological and/or chemical agent with the ability to influence the repair process could improve their synchronization, thus lowering healing time.

Fibroblasts are cells that play a major role in the synthesis and reorganization of the extracellular matrix during all phases of wound repair. It is logical to think that maintaining the ideal nutritional environment for the fibroblasts is fundamental to facilitate the proper wound repair.

Alterations of the ECM that occur with advancing age, although less than in disease, may be linked to the altered functionality of fibroblasts, which decrease in number and size, slow their function, and fail to produce adequate amounts of molecules necessary to adjust wound repair. These age-related changes slow down the regeneration of tissue and wound closure in animal models as well as in human wounds [17]. However, the response of dermal fibroblast cultures derived from young and elderly subjects and stimulated with cytokines such as TGF-β1, EGF, TNF-α, and PDGF does not vary with the age of the donor [33]. They have also both demonstrated a significant increase in production of collagen-I and of other extracellular matrix proteins [34]. This suggests that proper nutrition and stimulation of cells may play a key role in the repair of skin lesions.

# Dressing and Wound Nutrition

The main goal in the management of surgical and nonsurgical skin wounds is to obtain the physiological wound closure in the shortest period of time, in particular in the case of aged skin. Furthermore, the modulation of the synthesis and degradation of collagen during the phases of the repair process is of particular importance.

Presently, there are a wide variety of dressings available for wound care. The aim of wound dressing is to apply compression for hemorrhage or venous stasis, to immobilize an injured body part, to reduce pain, and to protect the wound and surrounding tissue. But dressings are also important because they are capable of promoting healing. Indeed, the aim of all care products is to create an aseptic environment preventing infection and moisturizing the wound tissue, enhancing epithelization and granulation tissue formation [35]. So, the ideal dressing material has to maintain a moist environment, act as a bacterial barrier, and act as a medium for free exchange of gases while providing a barrier against toxic contaminants. Furthermore, logically, it should also contain all the nutrients needed for proteins synthesis and tissue regeneration. But since it is assumed that nutrients are transported to the site of injury through the bloodstream, products for wound dressing rarely take into account this nutritional component.

At present we are still far from an ideal dressing. This is demonstrated by the large amount of medications available on the market. Unfortunately, a very small number of the products most widely used to treat wounds take into account the strong demand of nutrients by the cells to regenerate tissue and close the wound. However, many other natural substances such as honey, plant extracts, vitamins, amino acids, etc., have been used as adjuvants of wound closure [36]. For example, honey, one of the oldest known wound dressings, is a bee-derived supersaturated solution composed mainly of fructose and glucose, also containing proteins and amino acids, vitamins, enzymes, minerals, antibiotics, and other minor components. The renewed interest in the use of honey for topical wound care is probably because it combines low-cost antimicrobial properties with the maintenance of hydration and the presence of nutrients useful in tissue protection and regeneration [37]. More recently it has been suggested that beneficial action of honey in wound care could be explained, at least tentatively, by the production of lactic acid by microbiota and by the presence of active compounds such as proteins, fatty acids, anesthetics, organic acids, volatiles, and hydrogen peroxide [38, 39]. All these substances could modulate the microenvironment of the wound.

Topical wound dressings based on plant extracts may also act by modulating the inflammatory and oxidative stress responses. For example, the flavonoid fraction and luteolin from *Martynia annua* leaves when used for diabetic rats may have potential benefit in enhancing wound healing [40]. In another clinical trial in patients with neuropathic diabetic foot ulcers, the natural compounds contained in the kiwi fruit improved various aspects of the wound healing process [41]. More recently, treatment of excision wounds with papaya extract reduced inflammation-associated oxidative damage apparently via cyclooxygenase-specific inhibition, improved arginine metabolism, and induced the upregulation of antioxidant enzymes, thus improving wound healing [42].

Topical vitamin application is another approach to wound care. Vitamins should normally be present in the human skin as cofactors of enzymatic activities and because they are part of a system of antioxidants that protect the skin from oxidative stress. Vitamins, mainly A, C, E, K, and $B_3$, have been shown to have potent antioxidant and anti-inflammatory properties demonstrating wound healing potential in full-thickness wound models and under diabetic conditions [43–45].

All these topical therapeutic "natural" approaches show obvious benefits aiding wound repair. They act mainly in the initial step of healing, by reducing inflammation and oxidative stress response. Indeed inflammation has been shown to delay healing and so increasing scarring and predisposition to cancer development [46]. Conversely, scar-free wounds are characterized by reduced inflammation

[47]. Numerous publications have highlighted the link between aging and inflammation [48]; therefore, the containment of chronic systemic and/or local inflammatory phenomena could help to slow the aging of tissues and promote wound healing.

A more fashionable molecular approach of wound repair in the last decade is the topical administration of growth factors and hormones. However, these approaches have not led to substantial advances in patient care. Indeed, they have only a moderate impact on wound repair in a clinical setting, probably due to the high plasticity and redundancy of the components of the wound repair process or because of their rapid degradation at the wound site [20].

Recently, a number of bioactive therapeutic peptides with significant in vitro activity have been identified from a wide variety of proteins, including collagen. Unfortunately, their action in vivo was often scarce or absent, probably because of rapid degradation. More recently, the multifunctional cryptic peptide E1 has been isolated from bovine tendon collagen type I and administered topically. However, being derived from a heterologous protein, it has been proposed as effective in accelerating the closure of wounds by lowering oxidative stress and promoting the rapid production of the ECM in excision and incision wound experimental models. This confirms the key role played by collagen peptides in accelerating the healing process and justifies their use as a pharmaceutical agent [49]. Although collagen-based dressing materials like hydrocolloids and hydrogels have been proven to be beneficial [50], topical applications of bioactive molecules such as the one derived from bovine tendon could be an effective way to sustain wound repair.

Over 30 years ago, a simple, safe, and effective method to improve repair and control of infection of human wounds from several causes has been proposed. This consists of debridement daily and application topically of a balanced solution of salts, amino acids, a high molecular weight D-glucose polysaccharide, and ascorbic acid [51]. In practice, the author tried to recreate the nutritional conditions and molecular setting suitable for tissue regeneration and for the containment of infection and oxidative stress.

The availability of adequate amounts of nutrients, in particular proteins, is essential for proper wound healing. This is probably due to the increased protein request needed for tissue regeneration and repair. Indeed, protein depletion appears to delay wound healing by prolonging the inflammatory phase; inhibiting fibroplasia, collagen and proteoglycan synthesis, and neo-angiogenesis (proliferation phase); and inhibiting wound remodeling [47]. However, proteins are formed from amino acids, and as such it seems logical to think that the availability of amino acids in the wound can accelerate and improve healing.

Researchers have investigated the effects of specific amino acids on the healing process and determined that arginine and glutamine appear to be necessary for proper wound healing [36, 52–55]. Recent data reveal that age-associated delay in acute healing is accompanied by a local reduction of arginase in wound granulation tissue associated with increased inflammation (increased iNOs expression) and defects in matrix deposition [56]. Glutamine accounts for about 60 % of the intracellular amino acid pool. It is considered to be conditionally essential, as a deficiency can occur rapidly after injury [54]. However, arginine and glutamine, although they may play a possible role in wound healing, are not the only amino acids needed by cells to activate the complex biosynthetic processes required for regeneration of the tissues.

In the past, the importance of the influence of nitrogen balance in the production of collagen for repair of skin wounds has been shown in weanling and young adult rats. This therefore demonstrates that age in itself is not necessarily a limiting factor for the speed of wound closure, which is, however, strongly influenced by the mix of nutrients available to the cells [57]. The importance of an optimal nutritional status of the patients with wounds is of fundamental importance for the right and rapid wound healing and is discussed in a separate chapter of this volume. Nevertheless, in addition to nutrition, the availability of medications that can adequately feed the tissues in injured area by maintaining the right nitrogen balance

could be a readily available source of nutrients essential for the sustenance of cells during tissue regeneration.

## Nourishing Fibroblasts Based on Analysis of Collagen Composition

Following the immediate vessel constriction needed to promote hemostasis, all steps of the wound healing process are primarily oriented toward providing the energy and materials necessary for the proliferative state. Oxygen is the most necessary substrate, but metabolism of the cells involved in the repairing process should also be replenished adequately. Thus, angiogenesis triggered by TGF-β1, platelet-derived growth factor (PDGF), and FGFs cooperates with hypoxia for VEGF-mediated neovascularization and repair of damaged blood vessels. The outer area of the wound is relatively avascular at the beginning, and diffusion from capillaries at the wound edge is the sole way of substrates to be provided. Thus, is medical intervention from out-in helpful to provide substrates and so help reduce the wound healing span and possible other related damage?

It was shown that lesion dressing of chronic human wounds of various etiologies, with a patented mixture of four specific amino acids (AAs) needed for collagen synthesis [glycine (29,28 %), L-proline (46,22 %), L-lysine (5,55 %), L-leucine (3,54 %)] plus Na hyaluronate (15,41 %), identified as GPLL-NaHy [according to US Patent n° 5,198,465, released on March 1993], induces rapid tissue regeneration and wound closure, thus opening new perspectives in chronic ulcer treatment [58]. The rationale for treating wounds by hydrocolloidal medications enriched with the formulation of AA by providing the peculiar stoichiometric composition of the AA most contained in collagen was carefully discussed by the author [6].

Subsequently, it was experimentally demonstrated that the topical therapy of wounds in aged rats by using a gel containing a specific formulation of four AAs required for collagen production shortens wound healing time and effectively reduces inflammation modulating the expression of the major controlling players of wound repair (TGF-β, eNOs and iNOs, VEGF). Furthermore, eNOs expression was found both to parallel TGF-β1 immuno-localization and to be associated with the increase density of fibroblasts and thus the promoted synthesis of collagen fibers. This was associated with a shorter healing time, when compared with the gel containing NaHy but AA free, used in control wounds. Also, TGF-β1 expression and suppression patterns were more precocious than in controls [7], providing support to the rationale that feeding wounds from out-in is an efficient approach promoting a more efficient dynamic homeostasis of wound healing. How changes in nitrogen content provided by nutrition affect skin and dermis health has been discussed in detail in a specific chapter of this textbook (please refer to chapter "► Aging Skin: Nourishing from In-Out").

There is a question concerning the use of NaHy to improve wound closure physiology. That is, are the formulations of proline, glycine, and lysine in the stoichiometric ratios used (25:50:25) the sole agents responsible for success, or is there also a role for L-leucine (a neutral branched chain AA), even if present in smaller amounts compared to other AAs?

To try to answer this question, an experimental study on an excisional wound model in healthy aged rats to test and compare a full set of different AA formulations (Table 1) as topical dressing has recently been launched. The control wounds did not receive any medication. Preliminary data had shown that dressing wounds with balanced mixture of essential AA (EAAs), branched chain AA (BCAA) alone, and a formulation containing all EAAs plus proline and glycine, identified by the letter T, significantly shortens the closure of wounds compared to other formulations. Wounds medicated with placebocream (vehicle of all cream dressing), NaHy, GPLL, and GPLL-NaHy and obviously undressed wound closed slower (Fig. 1). Interestingly, the topical dressing with the only essential non-BCAA (NBCAA) had longer

**Table 1** AA mixture composition of dress cream. *EAA* essential amino acid mixture, *BCAAs* branched chain amino acids, *T* EAA + proline + glycine, *GPLL* glycine + L-proline + L-lysine + L-leucine, *Plac* placebo, *NaHy* sodium hyaluronate

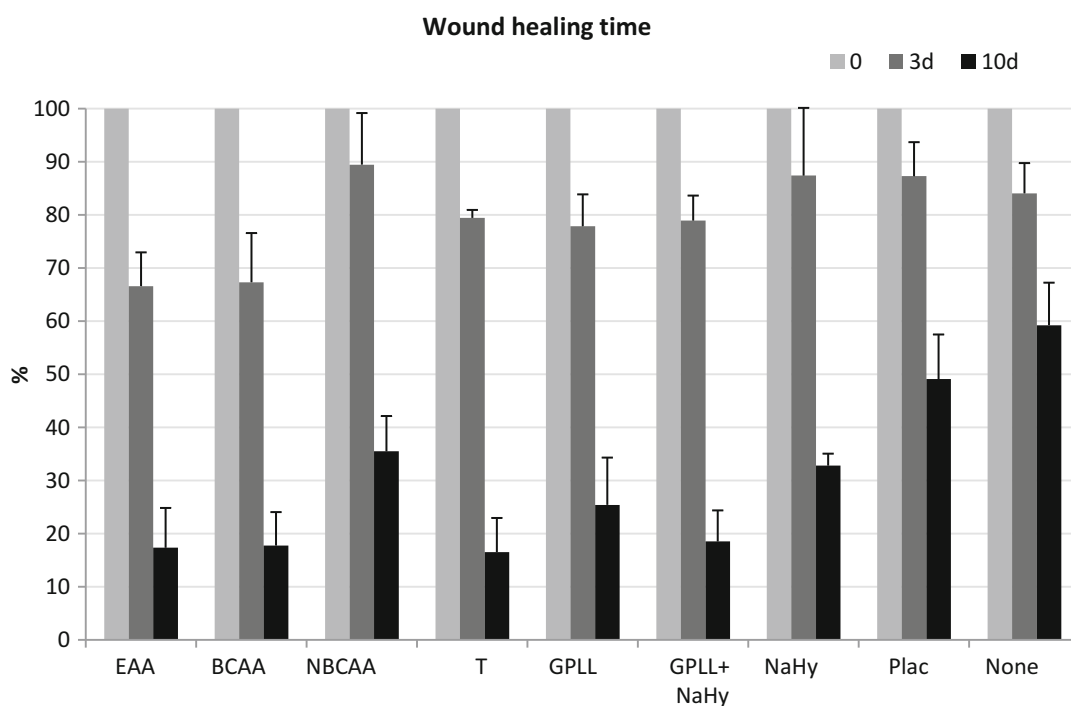| | EAA | BCAA | NBCAA | T | GPLL | GPLL + NaHy | NaHy | Plac |
|---|---|---|---|---|---|---|---|---|
| L-Leucine | x | x | | x | x | x | | |
| L-Lysine | x | | x | x | x | x | | |
| L-Isoleucine | x | x | | x | | | | |
| L-Valine | x | x | | x | | | | |
| L-Threonine | x | | x | x | | | | |
| L-Cysteine | x | | x | x | | | | |
| L-Histidine | x | | x | x | | | | |
| L-Phenylalanine | x | | x | x | | | | |
| L-Methionine | x | | x | x | | | | |
| L-Tyrosine | x | | x | x | | | | |
| L-Tryptophan | x | | x | x | | | | |
| L-Proline | | | | x | x | x | | |
| Glycine | | | | x | x | x | | |
| Na hyaluronate | | | | | | x | x | |
| Vehicle *(water, glucomannane, vegetal glycerin)* | x | x | x | x | x | x | x | x |



**Fig. 1** Percentage of wound area from the original wound (day 0, pale grey column) and after 3 and 10 post-wounding days according to dressing composition. See also Table 1 for cream composition (Source Corsetti et al. [7])

wound closure times. Conversely, the only BCAA dressing had the same effect on the closure timing of the wound shown by the complete EAA mixture. However, it should be considered that the aged animals used in these experiments were healthy and they had food and water ad libitum. So, the proper amount of NBCAA needed for optimal wound closure could presumably derive from the diet. The NaHy dressing

seemed to favor wound closure when compared to placebo, but when compared to any of the blends of AA, its effectiveness was poor.

Therefore, although the addition of amino acids specific to collagen synthesis has been demonstrated to be a promising approach to wound dressing, the cells at wound margins, such as newly formed cells, need the right amount of all EAAs in each phase of the healing process in order to proliferate efficaciously, regenerate tissues, and then quickly promote wound closure.

# Conclusions

While laboratory studies are still in progress and will be reported elsewhere when accomplished, it can be concluded that wound healing in healthy living mammals is a naturally successful process, which may be favorably influenced by wet medications providing substrates from out-in. Wet medications are a simple and efficient medical aid and should be recommended in wound therapy. There are numerous approaches to skin wound treatment, both acute and chronic, which are helping to gradually understand mechanisms that drive wound repair. Although all potentially promising, an ideal dressing is still far from being identified.

However, an important aspect that should be taken into account and should accompany all other approaches to wound care is the proper nutrition of patients as a preliminary approach to the success of any topical wound medication. This is particularly important in the elderly, where protein malnutrition is too often present and underestimated as a comorbidity of skin aging, as discussed in chapter "► Aging Skin: Nourishing from In-Out" of this textbook. Thus, creating a microenvironment where cells can constantly find the right amount of all necessary substances, particularly AA in the proper ratios, may be a safe and efficient therapeutic approach. This is particularly important in the elderly, where the prevalence of chronic inflammation, as well as altered nutrient availability, can slow or prevent complete healing of wounds. In conclusion, the proper nutrition of all tissues and particularly in injured areas appears to be a key factor that physicians should consider for the success of wound repair therapy.

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