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Review

Basics in nutrition and wound healing

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ABSTRACT

Wound healing is a process that can be divided into three different phases (inflammatory, proliferative, and maturation). Each is characterized by certain events that require specific components. However, wound healing is not always a linear process; it can progress forward and backward through the phases depending on various intrinsic and extrinsic factors. If the wound-healing process is affected negatively, this can result in chronic wounds. Chronic wounds demand many resources in the clinical daily routine. Therefore, local wound management and good documentation of the wound is essential for non-delayed wound healing and prevention of the development of chronic wounds. During the wound-healing process much energy is needed. The energy for the building of new cells is usually released from body energy stores and protein reserves. This can be very challenging for undernourished and malnourished patients. Malnutrition is very common in geriatric patients and patients in catabolic phases of stress such as after injury or surgery. For that reason a close survey of the nutritional status of patients is necessary to start supplementation quickly, if applicable. Wound healing is indeed a very complex process that deserves special notice. There are some approaches to develop guidelines but thus far no golden standard has evolved. Because wounds, especially chronic wounds, cause also an increasing economic burden, the development of guidelines should be advanced.

Wound-healing process

The wound-healing process is a complex series of events that starts with an injury and can continue for months to years (Fig. 1). The entire process is a dynamic one, which can be divided into three phases (Table 1). The wound-healing process is not linear and can progress forward and backward through the phases depending on various intrinsic and extrinsic factors.

Inflammatory phase

The inflammatory phase is characterized by its cardinal signs: *rubor* (redness), *calor* (warmth), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function). Immediately after acute skin injury, hemostatic mechanisms and pathways commence.

The initiation of the extrinsic coagulation cascade starts due to injury to vascular tissue with reflex vasoconstriction. Tissue factors and calcium activate factor VII and subsequently the whole coagulation cascade, with final blood clotting and vasoconstriction. This prevents further blood losses. However, many mediators connected with the coagulation process (proteins of coagulation cascade, platelet-derived factors, and local hormones) also initiate processes of local inflammation. After initial vasoconstriction, the classic signs of inflammation are manifested from increased vascular permeability. Rubor results from vasodilation, mediated by prostacyclin, prostaglandin A, prostaglandin D, and prostaglandin E (PGE). Tumor (swelling) is due to increased vascular permeability as vascular endothelial gaps enlarge, allowing an escape of plasma proteins and fluid into the interstitial space. These changes are potentiated by PGE2 and prostaglandin F2α and support the ingress of inflammatory cells into the area of injury. This also leads to an increase in local temperature (calor), which supports an environment that is hostile to micro-organisms. Dolor (pain) is sensed as prostacyclin, PGE, and PGE2 act on peripheral nociceptors [1].

At this stage the process creates a barrier against microbial invasion that is potentiated by all types of white blood cells and macrophages. Even pain plays an important role because it decreases the activity of the injured part of the body.

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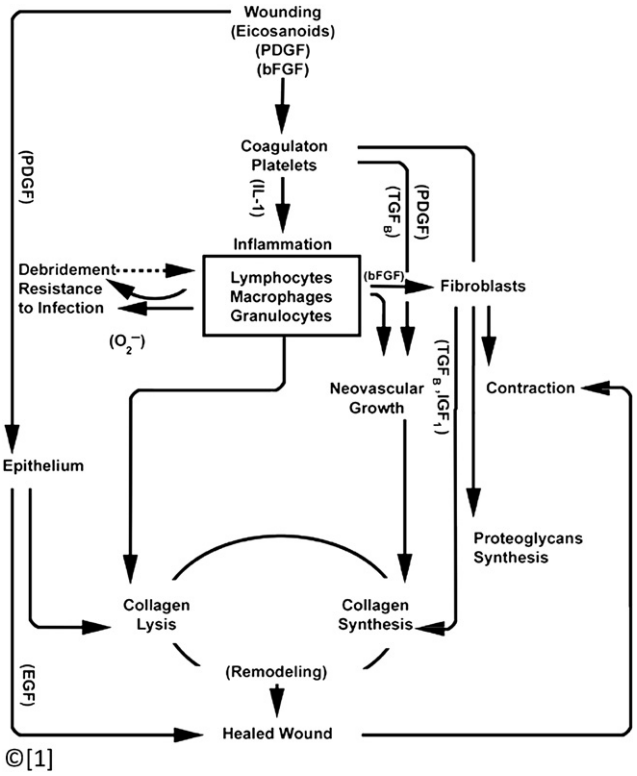

Fig. 1. Scheme of wound healing [1]. bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; IGF_1, insulin-like growth factor; IL-1, interleukin-1; PDGF, platelet derived growth factor; TGF_B, transforming growth factor.

Inflammation also starts the healing process. Toward the end of the inflammatory cycle, the evolving milieu of eicosanoids in the wound interacts with the present cell types, resulting in fibroblast synthesis of collagen and ground substance (from the increased ratio of prostaglandin F2α to PGE2). In addition, the macrophage-derived growth factors are at optimal levels, strongly influencing the influx of first fibroblasts, keratinocytes, and then endothelial cells into the wound. As mononuclear cells continue to replace white blood cells and macrophages, the proliferative phase begins.

Role of inflammation in scar formation

The proliferative phase is different in the early fetal and adult periods of life. The fetus has the ability to heal wounds by regenerating not only normal epidermis but also deeper structures such as the dermis with complete restoration of the extracellular matrix architecture, strength, and function without inflammation. In contrast, wound healing in adults is always connected with fibrosis and subsequent scar formation. Scar tissue remains weaker than normal skin with an altered extracellular matrix composition. Despite extensive investigation, the mechanism of fetal wound healing remains largely unknown. However, the lack of an inflammatory process as described earlier can explain some aspects of fetal wound healing. Fetal wounds heal rapidly with a paucity of inflammatory cells. Scarless wounds are characterized by a relative lack of inflammation. Furthermore, the introduction of inflammation into scarless wounds produces dose-dependent increases in wound macrophages, neutrophils, collagen deposition, and scarring. This suggests an important role of inflammation in scar formation.

Proliferative phase

Fibroblasts start migrating inward from wound margins over the fibrinous matrix. They are stimulated by basic fibroblast growth factor (bFGF) and tumor growth factor-β from macrophages and platelet derived growth factor (PDGF) from platelets. In the first week, fibroblasts produce glycosaminoglycans (hyaluronic acid), proteoglycans, and collagen; these products are the main extracellular substances of granulation tissue.

Subsequently, the fibroblasts become the dominant cell type in the wounded tissue. In addition to glycosaminoglycans, proteoglycans and collagen generate cytokines such as PDGF, tumor growth factor-β, bFGF, keratinocyte growth factor, and insulin-like growth factor-1. Fibroblasts also assemble collagen molecules into fibers, which are cross-linked and organized into bundles. Hence, collagen is the major component of acute wound connective tissue, with net production continuing for the next 6 wk. The growing content of wound collagen correlates with an increasing tensile strength [2,3].

Proliferation of keratinocytes and endothelial cells is also evident in this phase; these cells produce autocrine growth factors that maintain their growth. Synchronous endothelial expansion contributes to angiogenesis as intact vessels generate buds in granulation tissue. Neovascularization facilitates growth of the advancing line of fibroblasts into the wound, providing them with necessary nutrients and cytokines.

The degradation of the fibrin clot and provisional matrix is accompanied by the deposition of granulation tissue (ground substance, randomly deposited collagen, capillaries, fibroblasts), which continues until the wound is covered. Simultaneously, epithelial cells continue to migrate inward from the wound edge until the defect is covered. At this point, contact inhibition induces the transformation of fibroblasts into myofibroblasts, which contain contractile actin fibers. Wound contraction follows, replacing injured tissue volume with new tissue, although the exact role of the myofibroblast has not been fully elucidated [4]. Then a decrease of hyaluronic acid and an increase of chondroitin sulfate levels in ground substance—or intercellular matrix—slow fibroblast migration and proliferation and induce fibroblast differentiation. This initiates the maturation phase of wound healing.

Maturation phase

The newly synthesized collagen, which is deposited randomly in the granulation tissue, is typical for the newly formed granulation tissue (described earlier). Subsequently, the collagen is remodeled into a more organized structure with increased tensile strength. Gradually, type I collagen replaces type III collagen until the normal skin ratio of 4:1 is achieved. As remodeling continues, matrix metalloproteinase collagenolysis achieves a steady state with collagen synthesis. Tensile strength plateaus at 80% of the original strength approximately 1 y after injury [5–7].

Chronic wounds

The wound-healing process can be inhibited or negatively influenced by many factors that can be divided into systemic and local factors (Table 2). These influences frequently result in the development of chronic wounds.

The chronic wound is defined as a skin defect persisting longer than 6 wk or frequent reoccurrence of the defect. Compared with acute wounds, chronic wounds represent a medical challenge due to various complicating factors

Table 1
Phases of wound healing [1]

Phase	Time	Events
I. Inflammatory phase	immediate	hemostasis vasoconstriction platelet aggregation blood clotting inflammation vasodilatation inflammatory cell migration phagocytosis
II. Proliferative phase	days to weeks	granulation fibroblasts → collagen, which fills defects and promotes formation of new capillaries (angioneogenesis) contraction wound edges pull together to decrease defect surface epithelialization crosses moist surface cell travels about 3 cm from point of origin in all directions
III. Remodeling phase	weeks to years	new collagen forms, which increases tensile strength to wounds scar tissue is only 80% as strong as original tissue

connected with wound presence (chronic systemic inflammation, infection complication including sepsis, destruction of neighboring tissues). The chronic skin defect is usually in a permanent inflammatory state; however, there is no simple hypothesis that clearly describes the mechanism of this inflammation.

Moreover, a high and permanent proteolytic activity is typical for chronic wounds. Although bacteria have the ability to produce numerous proteases, the major part of proteases is produced by chronic wounds themselves in excessive amounts. Especially effete neutrophils release proteolytic enzymes (mainly elastase), which diminish the recognition and subsequent removal of the cells by macrophages. This promotes necrotic disintegration. The soluble fragments from the host elastase-degraded chemokine receptor (CXCR1) chemokine receptors can stimulate toll-like receptor 2 (TLR2 receptors), producing additional proinflammatory cytokines (PCs) that feed the inflammatory cycle and recruit additional neutrophils. This perpetual cycle produces and sustains elevated levels of inflammation, which decrease wound healing. Therefore, a detailed and systematic evaluation of a patient with a non-healing wound is generally required to determine the etiology and likelihood of responding to therapeutic interventions. These mechanisms for the development of chronic wounds are evident especially in venous ulcers, arterial ulcers, diabetic foot ulcers, pressure ulcers, and wounds due to autoimmune diseases (e.g., vasculitis or pyoderma gangrenosum).

Table 2
Factors that negatively influence wound healing

Local factors
Scalds and burns, physical and chemical
Local pressure
Compromised vascular perfusion—arterial, venous, or mixed
Neurologic defects
Systemic factors
Trauma (initial or repetitive)
Immunodeficiency
Malignancy
Autoimmune diseases of connective tissue
Metabolic diseases, especially diabetes mellitus, uremia
Malnutrition and nutritional deficiencies
Psychosocial stress
Inborn errors of metabolism
Treatment with corticosteroids or immunosuppressive drugs
Chronic diseases, especially wasting diseases
Advanced age

Chronic wounds (or skin ulcers) account for approximately 6 million skin wounds in the United States and 37 million skin wounds globally ("World Wound Care Markets 2008" Kalorama Information, May 2008, New York).

Pressure ulcers account for the largest portion of these figures, with an estimated 2.5 million cases each year in the United States and 9 million around the world. Treating these wounds only in the United States costs an estimated $5 billion to $10 billion each year, according to Adrian Barbul, M.D. (president of the Wound Healing Society, a professional organization for basic and clinical scientists; available at: http://www.woundheal.org/). Despite the clinical and economic effects of chronic wounds, there has been little consensus on the best ways to diagnose and treat them [8].

Local wound management

The methods of managing wounds have changed dramatically in recent decades. The concept of moist wound healing has led to hundreds of different dressings. Selecting the optimal dressing for a particular wound requires careful consideration and experience.

The wound-care products include various wound dressings (gauzes, films, hydrogels, hydrocolloids, alginates and hydrofibers, and foams; Table 3), ointments (e.g., Calmoseptine ointment [Calmoseptine Inc., Huntington Beach, CA, USA]), paste (zinc oxide paste), and petroleum jelly. Compression dressings or bandages are used to relieve edema and stasis. Topical negative pressure devices (or vacuum-assisted closure devices) recently have been developed to hasten wound healing. Moreover, a few types of biological wound-care products have been developed to support wound healing, including recombinant human platelet-derived growth factor isoform BB (becaplermin; Regranex, Janssen-Cilag, Pharma GmbH, Vienna, Austria) and allogenic and synthetic skin substitutes [9].

Documentation

Correct identification of a chronic wound etiology, the type of wound, and factors that may contribute to poor wound healing are key factors to successful wound treatment. In addition, high-quality wound documentation is extremely important for objective and effective wound-healing management and wound care. It is also a necessary condition for an existing binding quality certification [9].

The macroscopic characteristics during a wound assessment should be part of patient medical documentation. The methods of wound analysis should be objective, not invasive, applicable to everyone, easy, and efficient. Wound healing is a very individual lasting process. Each parameter and objective documentation enable an objective assessment of wound status [10].

Modern wound-management documentation should include:

- Complete medical history, etiologic factors, and wound history, with a detailed history of previous wound treatment(s)
- Individual treatment plans, taking into account close cooperation between medical and nursing care
- Objective information about wound care, taking into account the basic principles of moist wound care and causative factors

Table 3
Summary of basic wound dressings [9]

Product	Advantages	Disadvantages	Indications	Comment
Gauzes	inexpensive, accessible	drying, poor barrier	packing deep wounds	change every 12–24 h
Films	moisture retentive, transparent, semiocclusive, protects wound from contamination	no absorption, fluid trapping, skin stripping	wounds with minimal exudate, secondary dressing	can leave in place up to 7 d or until fluid leaks
Hydrogels	moisture retentive, non-traumatic removal, pain relief	may overhydrate	dry wounds, painful wounds	change every 1–3 d
Hydrocolloids	long wear time, absorbent, occlusive, protects wound from contamination	opaque, fluid trapping, skin stripping, malodorous discharge	wounds with light moderate exudate	can leave in place up to 7 d or until fluid leaks
Alginates and hydrofibers	highly absorbent, hemostatic	fibrous debris, lateral wicking (alginates only)	wounds with moderate to heavy exudate, mild hemostasis	can leave in place until soaked with exudate
Foams	absorbent, thermal insulation, occlusive	opaque, malodorous discharge	wounds with light to moderate exudate	change every 3 d

- Objective, comprehensive, complete wound documentation, and wound analysis with a digital camera and follow-up
- Evaluation of treatment effect, taking into account the costs versus benefits

Documentation is necessary for cooperation of all persons who are involved in treatment brought by the patient or by computer networks.

Nutrition and wound healing

Wound healing is a complex process of cellular and biochemical events that are obviously dependent on the nutritional substrates available. The wound-healing phase is extremely energy demanding: The strong increase in cell proliferation, protein synthesis, and enzyme activity during the healing process requires energy and building substrates. Normally these substrates are released from body energy stores and protein reserves. However, undernourished subjects need increased food intake or supplements with high energy and protein density [11]. In addition to basic macronutrients as protein or amino acids, carbohydrate, fat, and all electrolytes and micronutrients are necessary.

The daily energy requirement of a healthy person is 30 to 35 kcal/kg of body weight, depending on physical activity. In diseases such as the usual multiple morbidities of a geriatric patient with coexisting wounds (decubitus ulcer, other ulcer, postoperative phase, traumatic lesions), energy intake should be increased 35 to 40 kcal per kilogram and day [11].

Influence of undernutrition on wound healing

Even in uncomplicated starvation, as during a prolonged fasting, the body of an average adult subject loses 60 to 70 g of protein (240–280 g of muscle tissue) per day. However, severe trauma or sepsis can increase the loss of body protein up to 150 to 250 g (600–1000 g of muscle tissue) per day. Wound healing is delayed in subjects who had periods of starvation (simple or stress starvation) before injury or a surgical procedure due to the lack of endogenous substrates. Further undernutrition impedes wound healing in addition to:

- Delayed neovascularization and decreased collagen synthesis
- Prolonged phase of inflammation
- Decreased phagocytosis by leukocytes
- Dysfunction of B and T cells
- Decreased mechanical strength of the skin

Nutritional support

A systemic review by Stratton et al. [12] showed that high-protein oral nutritional supplements can significantly decrease the risk of developing pressure ulcers. Nutritional supplementation before planned elective operations in malnourished patients significantly decreases postoperative operations [13]. The nutritional supplement should be as specific as possible to a patient's perceived nutritional deficiency, and substrates that are turned over rapidly (e.g., arginine) should be included. Recent reports in the literature have suggested that perioperative restoration of the immune system by L-arginine improves immune function [14–16].

Because even brief periods of malnutrition can have significant negative effects on wound healing, nutritional deficiencies must be recognized early and repletion initiated as soon as possible. The clinical significance of nutrition and wound healing involves individual patients with unique needs. The goal of the physician is to determine whether, when, and how nutritional supplementation is needed [17].

Although an optimal nutritional supply is essential for good wound healing, the question of the type of supplementation remains open. Although glutamine and arginine have positive effects on wound healing, their clinical significance has yet to be proved. Zinc and iron are indicated for subjects with pre-existing deficiency states.

The main macro- and micronutrients that contribute significantly in the wound-healing process are described in the following sections.

Proteins

Proteins play the most important role throughout the entire wound-healing process. Lymphocytes, leukocytes, phagocytes, monocytes, and macrophages—immune system cells—are mainly comprised of proteins and are necessary to initiate a healthy inflammatory response in the healing process [18,19]. An adequate supply with proteins is necessary for consistent wound healing. Because collagen is the protein that is produced mainly in the healing wound, a lack of protein decreases the synthesis of collagen and the production of fibroblasts.

Of course, all proteinogenic amino acids are important during wound healing. There is evidence that some amino acids are especially important for the process. Methionine and cysteine are involved in the synthesis of connective tissue and collagen. Arginine is thought to have a major influence on the proliferation of collagen accretion and on an improved immune reaction.

Fatty acids

Fatty acids are important components of cell membranes and are the substrate for eicosanoid synthesis, which promotes the inflammatory process. Local application of ω-3 fatty acids was found to improve wound healing [20]. Surprisingly, supplementation with these fatty acids was found to increase local inflammation in experimental wounds [21]. However, the clinical relevance of ω-3 fatty acids on wound healing should be determined.

Vitamin C

Ascorbic acid is necessary for hydroxylation of proline and lysine in the synthesis of collagen, where it cross-links and stabilizes the triple helix structure of collagen. It is also necessary for an optimal immune response, cell mitosis, and monocyte migration into the wound tissue that transforms into macrophages during the inflammatory phase of wound healing. The main sources of vitamin C include citrus fruits and juices, strawberries, tomatoes, sweet peppers (especially red), potatoes, broccoli, cauliflower, brussels sprouts, and cantaloupe [18,22,23].

Zinc

Zinc is a cofactor for many enzymatic reactions that are involved in the biosynthesis of RNA, DNA, and proteins. Hence, zinc is essential for all proliferating cells and a low zinc status decreases closure and draft pressure of the wound and suppresses the inflammatory process [20]. The efficacy and risk of zinc supplementation for pressure ulcer management is a subject of much discussion in the literature. The general belief is that zinc supplementation is beneficial when a patient/resident is deficient in zinc but not in the absence of deficiency [18,24,25].

Iron

Iron is a cofactor of prolyl and lysyl hydrolysis enzymes, which are essential for the synthesis of collagen. In consequence, a severe iron deficiency interferes strongly with the wound-healing process. Possible symptoms of iron deficiency include loss of energy (mild fatigue to exhaustion), pallor, sore tongue, digestive tract disturbances, appetite disorders, and brittle spoon-shaped nails [18,26]. In addition, iron as part of hemoglobin plays an important role in the oxygen transport to regenerating wounding tissue [27].

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