Wound Healing

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Abstract

Wound healing is the biological response to tissue injury. It is a multifaceted and dynamic process. An overall understanding of this complex mechanism will optimize postoperative wounds as well as their appearance. This chapter will review the phases of wound healing and factors that can affect this process. Agents that can optimize this response will also be discussed.

4.1 Introduction

Wound healing is the biological response to tissue injury. The wound healing process involves a complex interplay of components, with disruptions leading to non-healing wounds or abnormal scarring. Local and systemic factors influence outcomes, as does maintenance of the healing environment. An overall understanding of the mechanism behind tissue healing remains integral to optimizing postoperative wounds and their appearance.

4.2 Basic Anatomic Concepts

The skin is comprised of two layers, the epidermis and dermis. The epidermis represents the outer barrier to the environment, providing physical protection, temperature regulation, and pigmentation. The epidermis can be subdivided into the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. Close to 90% of the epidermis is composed of keratinocytes, which serve as a barrier to microorganisms and a means to minimize moisture loss [1]. Other cell populations include melanocytes, Langerhans cells, and Merkel cells.

The dermis underlies the epidermis. Composed of thick fibroelastic tissue, the dermis is responsible for the strength and flexibility of the skin.

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A superficial layer is named the papillary dermis, containing fingerlike projections known as papillae, which carry capillary blood to the epidermis. Deep to the papillary dermis is the reticular dermis. Within this thick connective tissue layer are blood vessels and hair follicles, as well as oil and sweat glands.

4.3 Phases of Wound Healing

Wound healing can be divided into four main phases: hemostasis, inflammation, proliferation, and remodeling (Fig. 4.1). When the steps are perturbed, wound healing may delay or arrest, leading to improperly healed wounds or chronic non-healing wounds.

4.3.1 Hemostasis

Hemostasis is the body's initial response to minimize blood loss. Wounding leads to the rapid release of inflammatory cytokines, such as thromboxane and ADP, which promote vasoconstriction of the surrounding vessels [2]. Catecholamines are released into the systemic circulation by the adrenal medulla, further slowing blood loss [3].

The formation of a temporary platelet plug provides primary hemostasis. Upon encountering damaged endothelium, platelets increase the expression of surface receptors that enable binding to the site of injury. Degranulation by platelets releases ADP and thromboxane, which in turn recruits more platelets [4]. The overall aggregation of platelets forms a temporary plug at the damaged vessel wall.

The creation of a blood clot, known as coagulation, represents secondary hemostasis. The coagulation cascade is comprised of intrinsic and extrinsic pathways, which ultimately lead to the conversion of fibrinogen to fibrin. The intrinsic pathway becomes triggered by elements within the blood vessel, while the extrinsic pathway activates due to blood extravasation [5]. Both pathways lead to the activation of Factor X, which in turn activates the enzyme thrombin. Thrombin plays the key role in converting fibrinogen into fibrin. Fibrin strands strengthen the platelet plug and additionally trap erythrocytes in the meshwork, creating a mature clot [6].

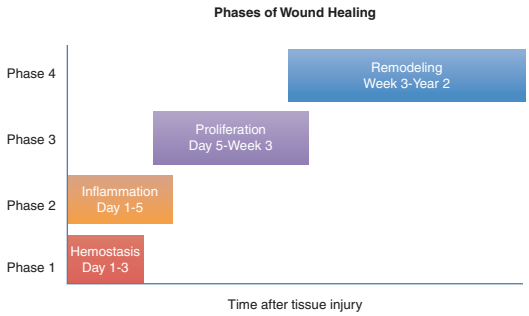

Fig. 4.1 The four phases of wound healing

4.3.2 Inflammatory Phase

In the inflammatory phase, cells and cellular elements migrate to the site of healing. In order to facilitate cellular transport, the initial period of vasoconstriction is followed by the release of histamine and subsequent vasodilation. Neutrophils predominate in the first 48 h following tissue injury and serve to clean the wound from microbes and cellular debris [7]. Macrophages play a primary role in wound healing over the following days. In addition to debriding the wound, macrophages secrete growth factors to promote new tissue creation as well as chemokines to recruit fibroblasts and endothelial cells [8].

4.3.3 Proliferative Phase

The proliferative phase is responsible for the generation of granulation tissue. Three to five days after injury, fibroblasts begin depositing collagen in the wound defect. Type III collagen predominates in the early period, with type I collagen eventually becoming the principal form [9]. Collagen adds strength to the healing wound and aids in restoring skin integrity.

Angiogenesis at the wound site gives granulation tissue its characteristic bright red color. New vessel formation is facilitated by the angiogenic factors secreted from macrophages in response to local hypoxia [10]. Increased blood flow provides granulation tissue with the necessary oxygen and nutrients to sustain the healing process.

Epithelialization of the wound surface occurs as epithelial cells migrate from the wound edges across granulation tissue. This process results in a protective barrier from the environment. Wound size is made smaller by contraction, in which myofibroblasts at the periphery of the wound function to bring wound edges closer together. Contraction commences soon after tissue injury and continues for 2–3 weeks [11].

4.3.4 Remodeling Phase

Remodeling is the final stage of wound healing, starting several weeks after injury and lasting up to 2 years. During this period, the rates of collagen synthesis and breakdown equalize, and type III collagen is replaced by type I collagen. Collagen fibers become organized and cross-linked, further reinforcing the wound.

The tensile strength of the wound gradually increases over time. At 3 weeks, the wound has achieved 20% of its full strength [12]. A wound's maximum tensile strength peaks at 3 months, where it reaches at 80% of its pre-injury level [13].

4.4 Factors Affecting Wound Healing

Patient characteristics play an important role in the rate and integrity of wound healing. Nutrition, age, diabetes, smoking status, and concomitant medications are among the significant factors impacting tissue repair on a systemic level. Microenvironmental factors, such as oxygenation, infection, necrotic tissue/foreign bodies, and wound tension, are also important considerations.

4.4.1 Systemic Factors

4.4.1.1 Nutrition

Adequate nutrition is central to optimal wound healing. Deficiencies in carbohydrates, proteins, fats, and vitamins have long been identified as inhibitors of tissue regeneration. Protein plays a primary role, as shortages can lead to reduced deposition of collagen in the wound matrix and an increased likelihood of wound dehiscence [14]. Animal studies have also demonstrated decreased tensile strength of wounds in the presence of low protein intake [15].

Vitamins A, C, and E are important cofactors. Vitamin C deficiency bears historical significance owing to its connection to the condition scurvy. Vitamin C is necessary for the hydroxylation of proline and lysine residues in pro-collagen, thereby providing mature collagen fibers with their structural integrity [16]. Vitamin A enhances the post-injury inflammatory response, increasing the number of monocytes and macrophages at the wound site [17]. It also likely has a stimulatory response on collagen accumulation and fibroplasia in healing wounds [18]. Vitamin E is a potent antioxidant and provides a stabilizing effect on cell membranes [19]. Topical application of vitamin E has been widely used to speed wound healing and improve the appearance of scars, based mostly on anecdotal evidence. However, scientific studies remain conflicting, with several clinical trials failing to show improvements in wound healing or scar appearance with topical vitamin E application [20–22].

4.4.1.2 Age

Increasing age is associated with declines in healing capability. Elderly patients (over 60 years old) exhibit temporal delays in wound healing, although the final scar quality may end up equivalent to that of younger patients [23]. Factors contributing to slower wound healing in the elderly include decreases in epithelialization, macrophage migration, angiogenesis, and collagen synthesis [24].

4.4.1.3 Diabetes

Patients with diabetes are particularly susceptible to wound healing complications. Diabetes is associated both with delays in healing of acute wounds and a heightened risk of developing chronic, non-healing wounds [25]. Nearly all phases of wound healing are impaired in the diabetic patient, an effect compounded by the reduced ability to fight infection and the common presence of neuropathy [26, 27].

4.4.1.4 Smoking

Smoking is associated with decreased capillary perfusion and tissue hypoxia [28, 29]. In maxillofacial surgery, smoking has been identified as a risk factor for delayed postoperative healing and heightened risk of infection [30]. Cosmetic outcomes are worse in patients who smoke, as seen with increased complication rates and tissue necrosis rates as well as a higher likelihood of required reoperation [31].

4.4.1.5 Concomitant Medications

Glucocorticoids are used to treat a wide range of inflammatory disorders. Acute corticosteroid use (<10 days) has not been shown to produce a clinically significant effect on wound healing [32]. Chronic use, however, impairs wound healing through several mechanisms. Glucocorticoids cause decreases in collagen synthesis and epithelialization, along with deficiencies in inflammatory cell migration [33]. As a result, patients on chronic steroids experience delayed healing as well as increased rates of surgical site infections and wound dehiscence [34, 35].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for pain management as well as several inflammatory conditions. Short-term, low-dose use of NSAIDs does not appear to play a significant role in recovery following soft tissue injury [36]. However, the effects of long-term treatment with NSAIDs have not been fully elucidated. Animal studies indicate that NSAIDSs may retard inflammation and reduce fibroblast proliferation, leading to decreased wound strength [37, 38]. Temporary discontinuation of NSAIDs, aspirin, and anticoagulants prior to cutaneous surgery may be advocated by clinicians as a means to reduce bleeding, but these measures should be weighed against the individual patient's increased risk of vascular complications [39].

4.4.2 Local Factors

4.4.2.1 Oxygenation

Tissue oxygenation is essential to cellular metabolism and directly impacts healing outcomes. After injury, wounds experience local hypoxia. This state results from reduced vascular supply, an increased oxygen demand of healing tissue, and the depletion of oxygen as inflammatory cells generate reactive oxygen species [40]. Although acute hypoxia stimulates the wound healing process, chronic hypoxia has a detrimental effect, eventually leading to anaerobic metabolism and inadequate ATP production [41]. Importantly, the administration of supplemental oxygen in the perioperative period has been shown to decrease the incidence of surgical wound infections [42].

4.4.2.2 Infection

Wounding causes a disruption of the skin barrier and facilitates the entry of bacteria into the tissues. Infection results from an imbalance between host defenses and bacteria, commonly defined when bacterial growth exceeds 100,000 organisms per gram of tissue [43]. Bacteria release pro-inflammatory endotoxins, such as interleukin 1 and tumor necrosis factor alpha, with continued contamination causing the inflammatory process to be abnormally prolonged [44]. Persistent infection leads to wound healing failure and the creation of a chronic wound.

4.4.2.3 Necrotic Tissue/Foreign Bodies

Necrotic tissue impairs wound healing by promoting bacterial growth and increasing the risk of infection. In addition, nonviable tissue releases toxic products and impedes granulation tissue formation and reepithelialization [45]. Foreign bodies in the wound elicit an acute inflammatory response. When these materials are retained, a chronic inflammatory response develops, which can be accompanied by the destruction of adjacent tissue, delayed wound

healing, and infection [46]. Debridement of nonviable tissue and foreign bodies is critical for the healing process to complete [47].

4.4.2.4 Tension

The tension present at closed wound edges affects the ability for the wound to heal. When wounds are closed under high tension, the strength and vascularization rate of regenerated tissue is impaired [48]. Obese patients are more susceptible to increased tissue pressure from wound closure, which can lead to decreased oxygenation and a heightened risk of dehiscence [49].

4.5 Acute vs. Chronic Wounds

4.5.1 Acute Wounds

Acute wounds occur due to trauma or surgical intervention. The integrity of the skin is breached and varying amounts of tissue loss may be incurred. Acute wounds progress through the phases of wound healing without noticeable disruption and typically heal within several weeks.

4.5.2 Chronic Wounds

Chronic wounds begin as acute wounds but experience perturbations in the wound healing process. Wounds are typically defined as chronic when signs of healing have not begun by 4 weeks and healing has not completed by 3 months [50]. Chronic wounds are sources of significant morbidity and mortality, affecting up to 6.5 million patients in the USA [51].

4.6 Healing by Primary vs. Secondary vs. Tertiary Intention

4.6.1 Primary Intention

Primary closure refers to the process of directly approximating edges of the wound. Sutures, staples, skin glue, or skin tape may all be appropriate methods of closure. Healing occurs with the aid of fibrous adhesion and minimal formation of granulation tissue.

4.6.2 Secondary Intention

With increased tissue loss or local tissue disruption, wounds may not be directly amenable to primary closure. In such cases, healing by secondary intention occurs, in which the wound bed is allowed to granulate and gradually fill the tissue defect. Healing by secondary intention occurs more slowly than by primary intention and may result in more noticeable scarring [52].

4.6.3 Tertiary Intention

Healing by tertiary intention may also be referred to as delayed primary closure. This method is most commonly employed in contaminated wounds, where immediate primary closure risks the development of infection. The wound is thoroughly cleaned and typically observed for several days until primary closure can be performed.

4.7 Excessive Scarring

4.7.1 Hypertrophic Scarring

Hypertrophic scarring occurs when collagen is overproduced at the wound site. This excess collagen deposition gives rise to a raised scar, which may be pruritic or painful [53]. Factors that impact the risk of hypertrophic scarring include age, infection, high wound tension, ethnicity, and degree of wound trauma [54].

4.7.2 Keloids

Similar to hypertrophic scars, keloids are pathological scars that result from the abnormal proliferation of dermal tissue at the wound. However, in contrast to hypertrophic scars, keloids extend beyond the geometric boundaries

of the wound. Keloids are unlikely to regress and often recur following surgical excision [55]. The etiology of keloid scar formation remains unclear; genetic predisposition appears to play an important role, with an incidence of keloid formation as high as 16% in African-American and Hispanic patients [56].

4.8 Agents that Optimize Wound Healing

4.8.1 Dressings

A wide range of wound dressings are utilized in clinical practice. Gauze-based applications historically served as a mainstay, but advances in synthetic materials have allowed for more tailored approaches to varying types of wounds. Different types of dressings may be appropriate for a single wound as it progresses through the various stages of healing.

4.8.1.1 Hydrocolloids

Hydrocolloid dressings contain carboxymethylcellulose, pectin, gelatin, and elastomers, which form into a gel-like substance over the wound. This material absorbs exudate and helps to create a warm and moist healing environment. Hydrocolloid dressings are occlusive and commonly used for wounds with mild to moderate exudate, including minor burns and pressure sores [57].

4.8.1.2 Alginates

Alginate dressings are derived from the alginic acid of seaweed and contain calcium and sodium salts. Alginates are highly absorptive and ideal for wounds with large amounts of exudate, such as advanced ulcers and full-thickness burns. Due to their dehydrating properties, alginates should not be used on dry wounds or those with hard overlying eschar [58].

4.8.1.3 Hydrogels

Hydrogel dressings are made from networks of hydrophilic polymer chains that hold significant water content. The polymer gel allows wounds to absorb water from the dressing, providing a hydrating effect. Hydrogels dressings are therefore used for necrotic or dry wound beds and should be avoided when heavy exudate is present [59].

4.8.2 Debriding Agents

Enzymatic debridement is used as a supplement or alternative to surgical debridement in treating wounds with necrotic tissue. These products contain exogenous enzymes that are designed to degrade nonviable tissue while preserving healthy areas of granulation. Enzymatic agents are commonly used for optimizing wound beds in pressure ulcers, leg ulcers, and partial-thickness wounds and may be preferred to sharp debridement in patients with bleeding disorders or those on anticoagulant therapy [60].

Collagenase and papain-urea-based products are the most commonly used enzymatic agents. Collagenase is derived from the bacterium *Clostridium histolyticum* and contains peptidases that digest collagen in the triple helix form. Papain-urea is activated by necrotic tissue, which stimulates it to degrade fibrinous material. Both collagenase and papain-urea formulations have been shown to provide debridement benefits in wounds with high bacterial loads [61].

4.8.3 Topical Antibiotics

Although the use of topical antibiotics in treating cutaneous infections is well established, its prophylactic role in the healing of non-infected wounds remains less clear. Some studies have demonstrated reduced infection rates with antibiotic versus placebo ointments after minor skin trauma and following suturing of lacerations [62–64]. However, evidence also exists that petroleum-based ointments may be equally efficacious to antibiotic preparations in promoting wound healing after minor cutaneous procedures, while also avoiding the potential for contact dermatitis caused by antibiotic ointments [65].

4.8.4 Growth Factors

Growth factors are important mediators in the wound healing process. These cytokines promote inflammatory cell migration, stimulate cell proliferation, and upregulate extracellular matrix deposition [66]. Platelet-derived growth factor BB (PDGF-BB) is a topical growth factor (produced as the drug becaplermin) that has received FDA approval in the treatment of diabetic ulcers. Additionally, PDGA-BB has shown utility in the healing of separated surgical wounds [67].

Conclusion

Wound healing is a multifaceted and dynamic process. Numerous components of the immune system integrate to achieve this objective, which may be affected on a systemic or local level by characteristics specific to each patient. Advances in wound dressings and adjuvant therapies have aided in speeding recovery and reducing chronic wounds. Addressing the wound healing process from the beginning of tissue injury allows the clinician to maximize proper wound healing and patient satisfaction.

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