Wound Healing: A Comprehensive Review

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Abstract

Wound healing is an intricate, tightly regulated process that is critical to maintaining the barrier function of skin along with preserving all other skin functions. This process can be influenced by a variety of modifiable and nonmodifiable factors. As wound healing takes place in all parts of the human body, this review focuses on cutaneous wound healing and highlights the classical wound healing phases. Alterations in any of these phases can promote chronic wound development and may impede wound healing.

Keywords
- wound healing
- inflammation
- chronic wounds

Any violation of live tissue integrity may be regarded as a wound. Skin is the largest organ of the human body and one of its key functions is to protect water-rich internal organs from the dry external environment.[1] Maintaining skin integrity and possessing a robust wound healing capacity are key prerequisites for healthy survival. Furthermore, wound healing can also present a significant challenge and burden on health care systems. Medicare cost estimates for acute and chronic wound treatments ranged from $28.1 billion to $96.8 billion during 2014.[2] The highest wound-related expenses were attributed to surgical wounds followed by diabetic foot ulcers.[3] A solid command of this fundamental topic can be a great asset in optimizing the healing of surgical wounds and incisions.

The wound healing process is a cascade of synchronized events aimed at restoring skin integrity. This article aims to present an overall outline of the acute cutaneous wound healing process while other articles within this series will address chronic wounds, experimental skin substitutes, and abnormal wound healing (keloids and hypertrophic scars).

There are three broad approaches to wound management. These include primary closure with suture material,[4] healing by secondary intention which allows the wound to heal without surgical intervention, and finally healing by tertiary intention in which wounds are surgically closed after a period of secondary healing.[5]

Phases of Wound Healing

Overall wound healing is accomplished through three overlapping but distinct biological processes, namely hemostasis and inflammation, proliferation and remodeling.[6–8] These phases, taken as a whole, represent the wound-healing cascade, and any deficiency within these phases may hinder the body's capacity to heal wounds.

Hemostasis begins immediately after any injury affecting skin integrity.[9] As blood vessels constrict, platelets are activated by contact with exposed collagen and release their granules, resulting in further platelet activation and aggregation. In conjunction with activation of the coagulation cascade, this results in deposition of a provisional fibrin matrix within the wound.[10]

As a result of platelet activation during hemostasis, a large number of cytokines, including transforming growth factor-β (TGF-β) and platelet-derived growth factor are secreted to promote chemotaxis of neutrophils and macrophages leading to the commencement of the inflammatory phase.[11,12] Neutrophils are among the first cells to appear acutely. Experimental data suggests wound healing may progress in the absence of neutrophils, unlike macrophages, that have been found to be critical to this phase and overall wound healing.[13,14] Macrophages, derived from activated monocytes, aid in phagocytosis and produce more cytokines and growth factors that promote fibroblast proliferation, angiogenesis, and keratinocyte migration. Dysregulated wound

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macrophage function has been associated with impaired wound healing in diabetic wounds.[15]

Within 2 to 3 days of the initial injury, a sufficient number of fibroblasts migrate to the wound and herald the beginning of the proliferative phase that lasts up to 3 weeks in a healing cutaneous wound.[16] Fibroblasts play a key role in this phase by production of disorganized collagen, high in immature type III collagen, into this provisional matrix.[16] Fibroblasts recruited to the wound may transform to become myofibroblasts under the influence of several cytokines leading to increased collagen production and eventual wound contraction.[17,18] A wide number of signaling pathways were found to be implicated in modulating the wound healing process including but not limited to angiotensin II, TGF-β through the canonical and noncanonical signaling pathways among others.[19,20]

In the final remodeling phase of wound healing, granulation tissue is replaced by permanent scar. Net collagen production continues actively for 4 to 5 weeks followed by replacement of type III reticular collagen with type I fibrillar collagen over the next year.[21,22] Zinc-dependent endopeptidases, known as matrix metalloproteinases secreted by epidermal cells play a central role in tissue remodeling.[23,24] Wound tensile strength continues to increase with increasing collagen production from 3% on week 1 and 20% after 3 weeks. At 3 months post injury, tensile strength peaks at 80% of uninjured skin, never reaching 100%.[25,26]

Each one of these phases, hemostasis/inflammation, proliferation, and remodeling is vitally important to the success of wound healing process.[27]

Nutritional and Environmental Factors

Wound healing is an energy-intensive process requiring adequate nutritional status.[28,29] This process requires macronutrients as well as micronutrients to facilitate skin integrity restoration. Macronutrients such as carbohydrates, fats, proteins, fluids, and micronutrients that include amino acids, vitamins, and minerals are all vital for an unimpeded wound healing process.[30] Overall caloric requirements to synthesize proteins are estimated to be 0.9 kcal/g and a 1-mm thick section of granulation tissue would require 10 mg of collagen.[31] Therefore, small wounds may not always pose a nutritional challenge, however, the nutritional deficit begins to widen with increasing wound size especially with large thermal burns. This is also an important consideration for patients postoperatively who may have been fasting for a prolonged period and a timely discussion with patients on the resumption of diet can be beneficial.[32] Tight glycemic regulation is key for optimizing wound healing as uncontrolled hyperglycemia has been shown to impair fibroblast and endothelial cell function in poorly controlled diabetic patients.[33]

Historically, vitamin C has been widely associated with healing and linked to the development of scurvy.[34] It functions as a co-substrate for hydroxylase enzymes required for collagen synthesis, however, supplementation in patients with no clear nutritional deficits has not been conclusively found to be beneficial in wound healing.[35,36] Vitamin A has also been found to play a role in epithelial growth, angiogenesis, and collagen synthesis.[37,38] Additionally, zinc has been documented to facilitate increasing wound strength and epithelization, however, as with many other micronutrients, there is no conclusive evidence to support supplementation in the nondeficient patient.[39]

Numerous studies have demonstrated the detrimental effect of smoking on wound healing, with over 400 substances found in cigarettes that may negatively impact wound healing.[40] Nicotine specifically strongly promotes vasoconstriction disrupting microcirculation and negatively impacting wound healing.[41] Smoking also impedes cellular migration and reduces neutrophil activity during the inflammatory phase of wound healing.[42] Overall, smokers exhibit more wound healing complications compared with nonsmokers.[43]

Unlike the well-studied effects of smoking on wound healing, the impact of excessive alcohol intake is beginning to be recognized and examined. Patients with a history of alcohol abuse were noted to have an increased incidence of surgical wound infection.[44] Additionally, some studies indicate that acute alcohol intoxication may also have a detrimental effect on wound healing, not just chronic abuse.[45,46]

Impact of Radiation and Medications

Ionizing radiation can damage DNA, through excited subatomic particles leading to single- or double-strand breaks or crosslinking of the double helix.[47] Radiation also creates free radicals that damage proteins and cell membranes.[48] This affects cells involved in wound healing, including fibroblasts resulting in impaired proliferation, migration, and contraction.[49] These abnormalities lead to suboptimal wound repair and slower epithelialization, decreased tensile strength, as well as higher infection and dehiscence rates.[49,50] Limiting the radiation field and shielding areas that are not actively radiated may minimize the deleterious impact of radiation on wound healing.

Some of the most commonly used medications may impact wound healing. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have a depressant effect on wound healing.[51,52] Based on preclinical data, NSAIDs inhibit COX-1 and COX-2 and decrease PGE2 production, therefore, may impede tissue repair by virtue of retarding inflammation. Importantly, NSAIDs may have an antiproliferative effect on angiogenesis, thereby delaying the healing rate.[53] Importantly, it must be emphasized that conservative short-term use of NSAIDs may be beneficial for acute pain control with limited bearing on wound healing, however, patients with chronic wounds or diabetes may be more dramatically susceptible to NSAID's effect on fibroblast inhibition.[54] This concept can also be applied to steroids, where acute, high-dose systemic corticosteroid use likely has minimal clinical sequelae on wound healing.[55] Vitamin A and steroids have antagonistic actions on wound healing, and vitamin A may be used to reverse the impact of steroids on wound healing.[56]

Chemotherapy, like radiation therapy, is also felt to have a deleterious effect on wound healing. Chemotherapeutic medications adversely affect and delay the inflammatory phase of healing leading to decreased fibrin deposition and collagen synthesis, and delayed wound contraction.[57] However, a review of National Surgical Quality Improvement Program data suggests no increase in wound complications after breast surgery in patients receiving neoadjuvant chemotherapy.[58]

Genetic Factors Influencing Wound Healing

There are several genetic connective tissue disorders which place patients at a higher risk for wound healing complications. Cutis laxa (CL) is characterized by increased vascularization in the dermis, reduced collagen bundle size, underdeveloped elastic fibers, and may potentially lead to suboptimal wound healing in certain severe cases, however, CL does not pose a contraindication for elective surgery for most CL patients as many will be able to heal normally or near normally.[59–61] Ehlers–Danlos syndrome is a group of disorders characterized by abnormalities in collagen structure.[62] It is characterized by generalized joint hypermobility, skin hyperextensibility, and generalized tissue fragility. Additionally, hyperhomocysteinemia can be an independent risk factor for suboptimal wound healing and may deprive healing tissue from required nutrients through thrombosis especially in wounds involving the lower extremities.[63]

Conclusion

Wound healing is a multiphase process involving well-calibrated and synchronized responses to an injury to the skin. Alterations in any of these phases can promote chronic wound development and may impede wound healing. Identification and optimization of modifiable risk factors play a critical role in wound management.

Conflict of Interest
None declared.

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