Impairments to wound healing

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Wounds come in various forms and result from a multitude of factors, such as hypoxia, trauma, or pressure. When unabated, wound healing progresses in an orderly and predictable fashion: inflammation (reactive), proliferation (regenerative), and maturation (remodeling). Numerous factors, however, play a detrimental role in the wound-healing process (Table 1). Poor nutritional status, various drugs, radiation, smoking, and hypoxia impair wound healing. A precise understanding of these mechanisms of impairment is necessary when treating acute or chronic wounds.

Nutrition

Without proper caloric intake and nutritional balance, delayed wound healing is inevitable (see Table 2) \cite{1}. Malnutrition may result from decreased intake or a pre-existing disease state. As part of the initial assessment in wound care, a patient’s nutritional status must be carefully examined \cite{2}.

Energy is derived from carbohydrate, fat, and protein. Normal stores of available energy in the average-sized adult are carbohydrate, 600 kcal; protein, 9600 kcal; and fat, 58,000 kcal. Without replenishment, carbohydrate stores are exhausted in less than 24 hours, whereas protein and fat stores last approximately 40 days. The average caloric requirement for an adult is 25 to 35 kcal/kg/d. The energy requirement is inversely proportional to age (infant, 90–120 kcal/kg/d; elderly [age > 70], 15–20 kcal/kg/d). Energy needs can be estimated using the Harris-Benedict equation, which calculates the resting energy expenditure (REE) for males and females based on body surface area.

Male : $\text{REE (kcal) = } (789 \times \text{BSA}) + 137$
Female : $\text{REE (kcal) = } (544 \times \text{BSA}) + 414$

Protein requirements :
1.0 to 1.5 gm/kg/d (average adult)
1 gm of protein = 1 gm of nitrogen
Calorie-to-nitrogen ratio :

100 to 150 : 1 (average adult)

It is important to remember that the REE will be increased in patients with traumatic wounds or other stress sources such as organ failure or severe infection. On average, the REE is increased 20\% for hospitalized patients.

Regardless of the nature of the wound, several initial steps should be included in the initial assessment. A careful history should include questions about weight loss, appetite, vomiting, diarrhea, and eating habits (including nutritional supplements) \cite{3,4}. The physical exam should include observations about muscle wasting, subcutaneous fat loss, or edema associated with hypoproteinemia. A daily calorie count with fat, carbohydrate, and protein percentages can be utilized to identify any nutritional deficiencies. Laboratory data such as serum protein and albumin can also be used to assess nutritional status. When available, a consultation with a nutritionist may be beneficial.
In terms of nutrition, protein plays a central role in wound healing through the production of collagen (Fig. 1). Therefore, the goal of nutritional support should be to minimize protein catabolism. Protein depletion can be caused by trauma, sepsis, nephrotic syndrome, liver disease, chronic open wounds, and burns. Protein depletion can be accurately measured using various markers of protein stores such as albumin, prealbumin, transferrin, and insulin-like growth factor I. These laboratory tests are somewhat limited in terms of reflecting the current nutritional status of the patient. For example, albumin has a half-life of 3 weeks and protein malnutrition may exist before a decrease in this serum marker is evident.

The consequences of protein depletion for wound healing include decreases in angiogenesis and fibroblast proliferation. This results in decreased synthesis, accumulation, and remodeling of collagen [5,6]. The degree of protein depletion necessary to impair wound healing, however, is not clearly understood. Deficiencies in wound healing have been noted at levels ranging from as high as 3.0 g/dL to less than 2.0 g/dL. Hypoalbuminemic tissue edema occurs with an albumin level below 3.0 g/dL. In addition to the above-described impairment in collagen formation, hypoalbuminemic tissue edema can also result in decreased oxygen delivery as diffusion distances are increased. Others have demonstrated that wound healing is significantly altered at levels of 2.5 g/dL [7,8]. Most authorities would agree, however, that normal wound healing cannot occur at levels less than 2.0 g/dL [9].

In contrast, wound healing can be improved with adequate protein replacement. Studies [4,10,11] have demonstrated decreased rates of muscle catabolism, increased fibroblast activity with increased collagen synthesis, and improved immune response. Improved healing of pressure sores in patients receiving high levels of protein supplement has also been demonstrated [12].

Specific amino acids such as arginine and glutamine have been shown to enhance wound healing. In elderly patients, collagen deposition was significantly enhanced when diets rich in arginine and glutamine were administered [13]. Acting alone, glutamine supplementation counteracts the catabolic effects of trauma and has been shown to decrease infection in surgical patients [14]. The exact mechanism to explain these positive effects remains unknown, however. The role of arginine in wound healing is slightly better understood. In animals models, supplemental dietary arginine enhances wound healing [15,16]. It is thought that the metabolism of arginine via the nitric oxide pathway (which increases NO) is one mechanism by which arginine enhances wound healing.

**Protein**

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**Vitamins**

Vitamins C, A, E, and K play important roles in the wound healing process. These specific vitamin defi-
ciencies are more common in underdeveloped countries where diets are lacking in fruits and vegetables. In the United States, specific vitamin deficiencies are usually seen in conjunction with generalized malnutrition as opposed to an isolated phenomena.

**Vitamin C**

Some authorities consider vitamin C (ascorbic acid) deficiency to be the only true vitamin deficiency to impair wound healing. Vitamin C’s critical role in wound healing was first linked to scurvy in the early days of the British Navy. Vitamin C is a cofactor in the hydroxylation of proline and lysine for procollagen formation. Procollagen residues are then altered intracellularly to form collagen. Any deficiency of ascorbic acid will impact both the rate and the quality of collagen production, with the net result being marked delays in healing, weaker scars, and abnormal capillary formation. Severe vitamin C deficiency can even result in the dehiscence of previously healed wounds.

In addition to impairing collagen formation, vitamin C deficiency results in immune system compromise. Vitamin C allows wounds to resist infection by facilitating leukocyte migration into a wound. It also plays a bactericidal role by contributing to the formation of neutrophil superoxides.

Recent research targets vitamin C’s antioxidant potential in wound healing. In ischemic wound models, oxygen free radicals contribute to the failure of wound healing. The concentration of free radical scavengers has been shown to decrease with wounding and to increase as the healing process progresses [17]. Antioxidants, such as vitamin C, have been shown to improve healing in an ischemic skin wound model [18]. By preventing molecular damage, vitamin C appears to facilitate wound healing.

To treat vitamin C deficiencies, supplementation with 100 to 1000 g/d may be given. Supraphysiologic doses of vitamin C have been shown to improve wound healing in animal and clinical studies. Although the safety profile for vitamin C is good, some caution must be exercised when giving large doses, because megadoses may lead to the formation of oxalate stones in the kidneys, which can potentially lead to renal dysfunction.

**Vitamin A**

Vitamin A has been shown to influence most of the stages of wound healing, adversely affecting monocyte and macrophage stimulation, fibronectin deposition, cellular adhesion, and tissue repair [19]. Decreased vitamin A levels resulted in decreased breaking strength in rat wounds as a result of decreased collagen production with less cross-linking [20]. Vitamin A deficiency has also been shown to decrease transforming growth factor β receptors in rats [21].

Since 1968, it has been known that vitamin A can improve wound healing compromised by steroids [22]. Glucocorticoids (corticosteroids) slow the release of lysosomal enzymes, cause delays in the healing of surgical wounds, and increase the risk of wound infection. They interfere with inflammation, fibroblast proliferation, collagen synthesis and degradation, deposition of connective tissue ground substances, angiogenesis, wound contraction, and re-epithelialization.
Vitamin A counteracts some of these effects by restoring the inflammatory response and promoting re-epithelialization and the synthesis of collagen and ground substances, but does not reverse the detrimental effects of glucocorticoids on wound contraction and infection [23]. Nevertheless, vitamin A does play a fundamental role in the immune response. Vitamin A contributes to lysosomal membrane stabilization and phagocytosis in a wound, and functions in cell-mediated cytotoxicity, cytokine production, and antibody response [24].

Vitamin A deficiency is probably more common among hospitalized patients than might be expected. Laboratory tests to detect serum levels are costly and difficult to perform, thus making diagnosis difficult. Isolated vitamin A deficiencies are rare, and most patients are asymptomatic. Care must be taken when supplementing vitamin A to avoid hypervitaminosis and the effects on the liver and cornea. The tetratogenic effects of hypervitaminosis are well established.

Vitamin E

The role of vitamin E (α-tocopherol) in wound healing is controversial, because possesses positive and negative effects. Vitamin E is a known antioxidant that has anti-inflammatory properties. It alters prostaglandin production by inhibiting phospholipase A₂ activity, resulting in decreased collagen production and decreased inflammation. Most authors agree that high doses of vitamin E lead to delayed wound healing [25]. For cutaneous wounds, topical vitamin E appears to offer no cosmetic benefit and its application may actually be detrimental [26].

For diabetics, vitamin E may offer some benefit in wound healing. Two studies [27,28] using diabetic mice models have shown improvement in wound healing using vitamin E, by a proposed mechanism of inhibition of lipid peroxidation. Although the exact role of vitamin E in wound healing is not understood, it appears to involve cell differentiation, epithelialization, cell-mediated immunity, the early inflammatory response, and angiogenesis [29,30].

Vitamin K

Vitamin K is vital in the normal clotting cascade. Because the initial events of the inflammatory stage of wound healing depend on blood clotting, deficiencies in vitamin K will affect the synthesis of prothrombin and factors II, VII, IX, and X.

Trace elements

Trace elements are critical for wounds to heal properly. Deficiencies are often overlooked. The elements most often implicated in delayed wound healing are zinc and iron.

Zinc

Zinc deficiency is uncommon but is seen in patients with large burns, profuse sweating, severe surgical trauma, chronic alcoholism, cirrhosis, and gastrointestinal fistulas. Zinc is an essential cofactor in normal cellular growth and replication, and is involved in more than 100 different enzymatic reactions. Those reactions that are specifically related to wound healing include the production of DNA polymerase (essential for cellular proliferation) and superoxide dismutase. Zinc directly impacts epithelialization and fibroblast proliferation through its effects on metalloenzymes, such as RNA polymerase, DNA polymerase, and DNA transcriptase. Zinc is also involved in many aspects of the immune response, including phagocytosis, cellular and humoral immunity, and bactericidal activity.

Animal studies have demonstrated that zinc deficiency contributes to wound-healing delays. For up to 12 days postwounding, there is a decrease in the bursting strength of wounds. Normal wound healing is seen at 3 weeks postwounding in zinc-deficient animals, thus demonstrating that zinc deficiency is responsible only for early wound delays [31–33]. Unfortunately, the same correlation has not been proved as convincingly in human trials [34,35].

Iron

Iron is an essential cofactor in the replication of DNA. In conjunction with ribonucleotide reductase, iron is involved in producing the deoxyribonucleotides needed for DNA synthesis. Ferrous iron is a cofactor in the hydroxylation of proline and lysine in collagen synthesis. Without this, the normal collagen triple helix is not possible.

Multiple studies have examined the effects of iron deficiency anemia on wound healing. Most have failed to identify a link between acute or chronic iron deficiency anemia on wound healing [36]. One study [37], however, found tensile strength differences in the first 6 days, with normalization after day 9. Importantly, none of these studies measured tissue oxygenation in the wound bed, and the question remains whether iron deficiency can lead to decreased oxygen delivery, which in turn may increase the susceptibility to infection and delayed healing.

Recent studies suggest that iron may retard wound healing through its action as a free radical. Increased free iron and an increase in reactive oxygen species released from neutrophils represent pathologic key steps (via the Fenton reaction) that are thought to be
responsible for the persistent inflammation, increased connective tissue destruction, and lipid peroxidation that contributes to the pro-oxidant hostile environment of chronic wounds [38]. Thus, by contributing to toxic free radicals, iron may also impair wound healing [39].

**Copper and magnesium**

Two other trace elements that merit reference are copper and magnesium. Through its promotion of vascular endothelial growth factor, copper may be harnessed to accelerate wound healing by stimulating angiogenesis [40]. In an in vitro model, copper and zinc stimulated integrins expressed by basal layer keratinocytes that are known to play an essential part in wound healing [41]. In a rat wound model, concentrations of magnesium and zinc were increased in the early (before day 5) stages of wound healing [33]. In humans, magnesium has been observed to enhance the mechanical properties of scar, although the precise mechanism is poorly understood [39].

**Drugs**

Many drugs are known to impair wound healing (Table 3). Many more possess the ability to delay healing but are overlooked because the patient has more significant comorbid factors.

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<thead>
<tr>
<th>Table 3</th>
<th>Medications associated with wound-healing delays</th>
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<td>Anticoagulants</td>
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<td>Antihistamines</td>
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<td>Antimicrobials (some)</td>
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<td>Aspirin</td>
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<td>Azathioprine</td>
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<td>B-aminoproprionitrile (BAPN)</td>
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<td>Povidone-iodine</td>
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<td>Chemotherapeutic agents</td>
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<td>Chlorhexidine</td>
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<td>Colchicine</td>
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<td>Cyclosporine</td>
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<td>Dakin’s solution (sodium hypochlorite 0.25%)</td>
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<td>Phenytoin</td>
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<td>Glucocorticoids</td>
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<td>Immunosuppressive agents</td>
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<td>Lathyrogens</td>
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<td>Nonsteroidal anti-inflammatory agents</td>
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<td>Papaverine</td>
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<td>Penicillamine</td>
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<td>Phenylbutazone</td>
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<td>Quinoline sulfate</td>
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<td>Retinoids</td>
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<td>Thiphenamil hydrochloride</td>
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**Chemotherapeutic agents**

Drugs used to treat cancer are by far the largest group known to delay wound healing. Wound healing and tumor growth share many physiologic and metabolic pathways. Drugs that impair tumor growth will also impair wound healing because they target rapidly dividing cells. Nine different classes of chemotherapeutic agents are commonly used to treat cancer (Table 4). Many of these are thought to work in a similar manner to impair wound healing. These drugs tend to attenuate the inflammatory phase of healing by interfering with the vascular response. Delays in the cellular infiltration in the healing wound and decreased fibrin deposition lead to poor or incomplete scaffolding for healing. These delays interfere with DNA and RNA production, protein synthesis, and cell osmosis. The primary cells affected are the fibroblasts, with decreased collagen synthesis. The myofibroblasts are also impaired, causing delayed wound contraction in treated animals [42–44].

Many of the commonly used drugs have been linked directly to delayed healing in animal studies, but the same impairment in the clinical setting is less common. Clinical studies have shown 5-fluorouracil, methotrexate, and 6-mercaptopurine to be safe, especially if treatment is not initiated until 2 weeks after surgery [45,46]. The more significant effects on healing are believed to occur when the agents are used preoperatively. This is particularly true of agents that are classified as alkylating drugs, antimetabolites, antitumor antibodies, or corticosteroids.

**Steroids**

Systemic glucocorticosteroids have been shown to impair wound healing by directly blunting the cellular response. This impairs fibroblast proliferation and ultimately collagen synthesis. The formation of granulation tissue and extracellular matrix is also decreased in steroid-treated animals. As expected, both epithelialization and wound contraction are
decreased in a dose-dependent manner. Gene transcription, particularly that associated with production of platelet-derived growth factor, is also impaired.

As stated earlier, the anti-inflammatory effects of steroids can be reversed by the administration of vitamin A [22,25]. Steroids stabilize lysosomal membranes, which are necessary to initiate part of the inflammatory response during wound healing. Vitamin A is thought to antagonize this effect and allow the release of the lysosomal products.

The effect of steroids on wound strength is dose and time dependent. Low doses given for short periods will not interfere with wound healing. With chronic administration, however, wound healing is impaired for up to 1 year after cessation of the drug.

Nonsteroidal anti-inflammatory agents

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a relatively newer class of analgesics. It is still unclear as to whether low or moderate doses of these drugs impair wound healing. Several recent studies have suggested that lower doses of these drugs may in fact cause delays in wound healing [47,48]. Some what less controversial is that high doses of NSAIDs have been implicated in delayed healing [49,50]. In ischemic wounds, NSAIDs may limit necrosis and actually improve healing [51].

Radiation

As early as 1895, the investigators who discovered radiation therapy described delayed wound healing. Becquerel noted erythema and ulceration in a chest wound he sustained after carrying radium in his pocket for several hours. The wound was red and painful and required significant time to heal.

Plastic surgeons should be familiar with the different types and effects of radiation therapy. At present, high-energy megavolt therapy has replaced low-energy orthovoltage therapy. This treatment produces a high-energy electron beam that is capable of sparing the skin while delivering a full dose of radiation to the deeper tissues that are its target. Radiation has both acute and chronic effects on the skin. Acute effects include erythema, dry desquamation at moderate dose levels, and moist desquamation at higher dose levels. Delayed effects include increased or decreased pigmentation, thickening and fibrosis of the skin and subcutaneous tissues, telangiectasias, and alterations in sebaceous and sweat gland function. Further chronic effects can include necrosis and ultimately tumorigenesis. These effects lead to delays in wound healing because radiation therapy impacts the various components of skin and their roles in wound healing, including keratinocytes, fibroblasts, cutaneous vasculature, and adnexal structures.

Radiation damage affects the blood vessels of the skin, creating a hypoxic skin bed. Unlike most hypoxic wound beds, however, angiogenesis is not initiated. In a radiated wound, the oxygen gradient decreases from the wound edge to the center of the wound at such a gradual rate that the hypoxic stimulus for angiogenesis is not initiated. This results in wounds with poor granulation tissue. Histologic examinations of skin from radiation fields have demonstrated endarteritis obliterans of the microvasculature [52,53]. These vascular changes contribute to the ischemia inherent in radiation wounds. Although this is an important component in radiation injury, cellular injury is considered to be the most significant contributor to the problem.

The keratinocytes are the critical cells in epithelialization and account for most cells in the epidermis. The keratinocytes in the basal layer divide readily and continue to cause shedding of the upper layers of the epidermis. Radiation therapy is most effective on cells in the active part of the cell cycle. Rapidly dividing cell populations are therefore most sensitive to radiation. Because of their superficial location on the skin and high replication rate, keratinocytes are highly susceptible to the effects of ionizing radiation.

Activation of proteolytic enzymes is responsible for the erythema seen just after delivery of ionizing radiation. Capillary permeability is increased, which in turn causes a local inflammatory response. Cells in the basal skin layer are affected most. These cells are a major part of the immunologic system within the dermis. Injury to the basal membrane generally evokes a significant cellular response, with release of serotonin and histamines. The erythema usually develops 2 to 8 days after treatment and may persist for 2 to 3 weeks. Dry desquamation is caused by an intermediate dose of radiation that kills epidermal cells, although enough survive to repopulate the radiated area. At higher doses, insufficient epidermal cells survive to repopulate the radiated field, and moist desquamation occurs with serous oozing from the surface of the exposed dermis [53]. In most cases, the dose delivered to the skin is not lethal to epidermal cells but does impair their mitotic ability, causing a slow progressive desquamation.

Depending on the extent of radiation delivered to the bed, re-epithelialization can continue from the adnexal structures. The rate of re-epithelialization depends on the effect of radiation on the adnexal structures and the quantity of adnexal structures
present. If all of the adnexal structures in the dermis are injured, re-epithelialization occurs from the periphery, and the long-term effect is a fragile and injury-prone epidermis. These areas are atrophic and can alternate with areas that appear thickened or hyperkeratotic. This skin is also more susceptible to the development of squamous cell tumors as a result of the atypia within the cells.

The cells most frequently injured by irradiation are the fibroblasts. As in the epidermis, irradiation causes an intense inflammatory response within the dermis. This subsequently leads to edema of the collagen bundles. Coupled with a diminished ability of the dermal fibroblasts to proliferate, this causes decreased breaking strength. If the radiation injury is severe enough, full-thickness loss may ensue with necrosis and ulceration.

Smoking

Cigarette smoking has long been known to have a detrimental effect on wound healing. Although the association between cigarette smoking and delayed wound healing is accepted in clinical practice, no controlled clinical studies have proved this relationship. Most studies are derived from animal models that examined the individual components of cigarette smoke and tobacco, including nicotine, carbon monoxide, and hydrogen cyanide. The cutaneous manifestations of cigarette smoking have been described [54]. It has been demonstrated that collagen production is reduced in smokers [55]. Cigarette smoking dramatically increases the risk of microvascular surgery [56].

Nicotine has significant vasoconstrictive effects that can last for up to 50 minutes after completion of smoking [57]. Nicotine also increases platelet adhesion, increasing the risk of thrombus formation in the microvasculature. Nicotine is known to have an inhibitory effect on the proliferation of red blood cells, macrophages, and fibroblasts. These effects combine to impair wound healing [58].

Carbon monoxide serum levels are elevated in patients who smoke. This results in decreased tissue oxygenation because carbon monoxide competitively competes with oxygen for transport on the hemoglobin molecule, resulting in decreased delivery of oxygen to the tissues. Hydrogen cyanide is a common by-product in tobacco smoke. Its enzyme system selectively inhibits oxidative metabolism in oxygen transport on the cellular level, thus interfering with cellular respiration.

A variety of different techniques have been developed to ameliorate the effects of cigarette smoking on wound healing. Unfortunately, most plastic surgeons are faced with the realization that many of their patients who desire elective procedures also smoke [59]. If patients can stop smoking 2 weeks before a procedure, however, the rate of healing is no different than that of nonsmokers [60].

Wound hypoxia

Decreased oxygen in a wound is detrimental to wound healing [61–63], and results in the formation of a nonhealing ulcer or impaired healing of an incision [64]. Although hypoxia is a stimulus for angiogenesis, the wound will not proceed through the later stages of healing without higher tissue oxygen levels [65]. Many clinical conditions affect blood vessels and can be associated with impaired healing (Table 5).

In the microenvironment of the skin, tissue oxygen tension levels below 35 mm Hg are associated with poor healing. At this level, wound fibroblasts are unable to replicate, and collagen production is severely impaired. Lower extremity wounds with skin oxygen tension readings below 35 to 40 mm Hg will not heal. When possible, vascular bypass is the standard means to improve tissue oxygenation in patients with poor arterial inflow.

Delayed healing and chronic wounds are significant problems for patients with venous insufficiency. Although the exact mechanism is not known, evidence suggests that impaired diffusion of oxygen from the capillaries to the surrounding tissue is the cause.

| Table 5
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<th>Disorders associated with impaired blood flow</th>
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<td><strong>Occlusive arterial disease</strong></td>
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<td>Arteriosclerosis obliterans</td>
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<td>Microembolism</td>
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<td>Thromboangiitis obliterans (Buerger disease)</td>
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<td><strong>Vasospastic disease</strong></td>
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<td>Cold sensitivity (Raynaud type)</td>
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<td>Erythromelalgia</td>
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<td>Livedo reticularis (severe forms)</td>
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<td><strong>Vasculitis</strong></td>
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<td>Scleroderma</td>
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<td>Systemic lupus erythematosus</td>
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<td>Periarteritis nodosa</td>
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<tr>
<td><strong>Hematologic disorders</strong></td>
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<tr>
<td>Cryoglobulinemia</td>
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<tr>
<td>Polycythemia vera</td>
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<td>Hypertensive ulcers</td>
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Proteinaceous exudate accumulates in the interstitium surrounding capillaries. This fibrin-rich fluid forms a clot, and subsequent fibrosis ensues. Over time this scar creates a barrier across which oxygen and cells must diffuse to reach the wound. Ultimately, diffusion is no longer sufficient to allow normal healing. As fibrosis occurs, leukocytes trapped in the interstitium release lysosomal enzymes and proinflammatory mediators that can exacerbate the problem and ultimately lead to tissue destruction [62].

In the past, anemia has been considered a risk factor for impaired healing [37]. When rats are bled to an acute anemic state, wound strength is decreased [66]. When resuscitated, similar rats did not show reduced wound strength. Any delays in resuscitation impair wound strength, but not to the extent of unresuscitated subjects. The conclusion is that hypoperfusion, more than anemia, is responsible for impaired healing [37].

In a study of wound healing in rats made iron deficient from blood loss and diet restriction, breaking strength of wounds was impaired [67]. This finding, however, has been both confirmed and refuted. The clinical data regarding this question are also mixed. Pure anemia without associated malnutrition or other underlying significant medical problems is uncommon.

Summary

Impaired wound healing is a complication faced by all physicians, regardless of their field of practice. Plastic surgeons are frequently called on to help treat patients who fail to heal properly. Therefore, plastic surgeons must be well versed in the intrinsic and extrinsic factors that can impair wound healing, such as nutrition, drugs, radiation, smoking, and hypoxia. Only by limiting detrimental factors can wound healing progress in a beneficial fashion.

References


