

Cofactors in Impaired Wound Healing

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Objectives

The reader will be challenged to:

- Examine the major cofactors associated with impaired healing in chronic wounds
- Analyze the wound healing impairment caused by various cofactors
- Assess the mechanisms by which the major factors impair healing.

Additional Resources:

Efficacy of a disease-specific nutritional support for pressure ulcer healing: A systematic review and meta-analysis
<https://link.springer.com/article/10.1007%2Fs12603-016-0822-y>

Systematic review of the impact and treatment of malnutrition in patients with chronic vascular wounds
www.woundsaustralia.com.au/journal/2502_03.pdf

Introduction

Healing of chronic wounds is a complex process that requires the interaction of many factors for normal repair. Healing is the restoration of structure and function after tissue injury. In acute wounds, healing progresses in an established sequence and in a broad but accepted timeframe.¹ When this sequence or timeframe is interrupted or altered for any reason, the result is a chronic wound. The rate of healing in such wounds is slower and not as predictable. Impairment in healing is manifest as a delay in the rate of healing and/or the development of wound-related complications.

Many factors are associated with impaired healing of chronic wounds. These factors vary to some extent by the nature of the wound. A complete list of the factors related to impaired healing across all populations would be long and not very meaningful. There are, however, factors related to healing that cross the various wound populations. Assessing these factors will allow the practitioner to screen patients and address the major and most common factors known to impair healing in chronic wounds. Thus, this chapter describes the major factors in impaired healing of chronic wounds, the effect of each factor on wound healing, and the mechanism by which each is thought to lead to impairment. Common factors that impair wound healing include *old age, insufficient oxygenation/perfusion, malnutrition, increased bioburden, old wound tissue, excess pressure, psychophysiological stress, concomitant conditions, and adverse effects of therapy* (Table 1). Identification of these factors is critical

Stotts NA, Wipke-Tevis DD, Hopf HW. Cofactors in impaired wound healing. In: Krasner DL, van Rijswijk L, eds. *Chronic Wound Care: The Essentials e-Book*. Malvern, PA: HMP; 2018:79–86.

Table 1. Cofactors in impaired healing

Old age
Insufficient oxygenation/perfusion
Malnutrition
Increased bioburden
Old wound tissue
Excess pressure
Psychophysiological stress
Concomitant conditions
Adverse effects of therapy

to healing of chronic wounds, as correction of impediments to healing generally leads to healing. Conversely, if an impediment is not recognized and corrected, the wound is unlikely to heal.

Age

Age has been associated with impaired healing, as there are differences in healing in the fetus, child, adult, and the elderly. Fetal wound healing occurs without an inflammatory response.² Wound healing and contraction occur more rapidly in childhood than in adulthood. As adulthood progresses, dermal vascularity decreases, collagen density decreases, the basement membrane flattens, fragmentation of elastin occurs, and the number of mast cells decreases. As people age, the entire healing process occurs more slowly, including the inflammatory response.³

Although the elderly experience these physiological changes, their rate of healing remains within a normal range or only slightly delayed in the absence of chronic disease.⁴ Yet the elderly are more likely to have chronic illnesses, such as cardiovascular disease, pulmonary disease, and diabetes, and because of this association, age is often noted as a cofactor in impaired healing. Differentiating which dimensions of impaired healing in the elderly are due to concomitant disease and which are due to aging is the subject of ongoing research.

Low Oxygen and Perfusion

Low oxygen levels and *decreased perfusion* are often related to impaired healing, as well as increased risk of infection. Oxygen is needed for

collagen formation; the rate and quality of collagen are decreased when sufficient oxygen is not present. Angiogenesis (replacement of injured blood vessels) and epithelization are similarly impaired in hypoxic wounds. In addition, hypoxia inhibits resistance to infection. When neutrophils and macrophages ingest foreign material and microorganisms, more oxygen is consumed than during their resting state. Lack of sufficient oxygen slows leukocyte activity, decreases superoxide release and, therefore, bacterial killing, and often is associated with wound infection.^{5,6}

Although *hemoglobin* carries much of the oxygen content in the blood, dissolved oxygen is most important for wound healing, because wounds depend on diffusion from relatively scarce capillaries for oxygenation. Thus, anemia does not result in impaired healing unless the anemia is severe (hematocrit < 18%). Wound oxygen tension is not decreased when subjects are anemic as long as the subjects have adequate circulating intravascular volume.⁷ Cardiac output increases to compensate for the decreased oxygen content, and that, combined with decreased viscosity, increases wound blood flow sufficiently to increase wound temperature by 1.5°C to 2°C and to maintain normal wound oxygen. Clinical studies have confirmed and extended these early findings: levels of hydroxyproline, a major component of collagen, are not decreased in subjects with anemia.^{8,9} Data indicate that anemia is not a cofactor in impaired healing unless the anemia is sufficient to impair cardiac output or the patient does not have sufficient circulating volume.

Smoking tobacco clearly impairs wound healing via several mechanisms. The triad of nicotine, carbon monoxide, and hydrogen cyanide from smoking are thought to interact to produce deleterious effects.¹⁰ Nicotine acts as a potent vasoconstrictor, increases platelet adhesiveness, and enhances the risk of microvascular thrombosis and ischemia. Carbon monoxide binds with hemoglobin and aggravates the situation, reduces available sites for oxygen carrying, and lowers oxygen saturation. Hydrogen cyanide inhibits the enzyme systems necessary for oxidative metabolism and the cellular transport of oxygen. Thus, a major adverse effect of smoking is the creation or worsening of wound hypoxia.¹¹

Hypovolemia (ie, the lack of adequate intravascu-

lar volume) has also been associated with impaired healing.^{12,13} With hypovolemia, circulating volume is insufficient to transport oxygen and nutrients to the tissues; if the state is prolonged, cellular activities needed for healing are diminished. Unfortunately, even supplemental oxygen does not increase tissue oxygen levels when tissues are hypoperfused.¹² Hypovolemia that is clinically obvious (eg, hypoxemia, thirst, decreased urine output, or hypotension) is treated with supplemental fluid. A more difficult situation occurs when subclinical hypovolemia or underhydration is present. Subclinical hypovolemia is defined as the presence of decreased intravascular volume with no overt clinical signs and symptoms. Subclinical hypovolemia can be detected by measuring capillary refill time at the forehead (< 3 sec) or prepatellar knee (< 5 sec) or by measuring cutaneous (skin) oxygen levels, a more precise, though more complex and expensive, method.

Subclinical hypovolemia has been well documented in the surgical population. In examining the effects of various levels of inspired oxygen on tissue and wound oxygenation, researchers found tissue hypoxia in a subset of the study sample.¹² Treatment with a bolus of fluid resolved the hypoxia, and the authors concluded that subclinical hypovolemia had been present. It is important to note that no signs or symptoms were present that would have allowed the clinician to diagnose the hypovolemia. Follow-up studies showed that fluid titration based on subcutaneous oxygen levels led to higher tissue oxygen levels and greater quantities of hydroxyproline being synthesized in surgical patients in the early postoperative period than when fluid was administered based on a traditional fluid formula.¹³ In the chronic wound population, subclinical hypovolemia has been identified in pilot work with elderly nursing home residents with pressure ulcers.¹⁴ Fluid administration for subclinical hypovolemia, however, has potential deleterious effects. Although inadequate hydration is much more common than fluid overload, care must be taken to maximize intravascular volume without causing fluid overload. Vasoconstriction caused by pain, psychophysiologic stress, or cold cannot be overcome by fluid administration. Thus, cold and vasoconstricted patients are at higher risk of fluid overload. Conversely, patients who are warm and well perfused will tolerate high volumes of fluid

infusion, resulting in higher tissue oxygen levels and lower infection rates.⁵

Malnutrition

Either **inadequate intake of nutrients** or **pre-existing malnutrition** has the potential to delay healing or result in infection. While most wounds heal regardless of nutritional status, severe protein-calorie malnutrition or specific nutritional deficits that are symptomatic can impair healing.¹⁵ Providing adequate nutrition to all persons with injuries should be a therapeutic goal so that wound healing can occur within an optimal environment.⁵

Most wound healing abnormalities are associated with protein-calorie malnutrition rather than depletion of a single nutrient.¹⁶ Nonetheless, **inadequate quantities of specific nutrients** can impact healing. Deficiencies of protein result in decreased fibroblast proliferation, reduced proteoglycan and collagen synthesis, decreased angiogenesis, and disrupted collagen remodeling. Protein requirements increase with healing. Provision of arginine and glutamine supplements (nonessential amino acids) has produced mixed results. Of these, arginine has shown the most significant wound healing effects, specifically increasing the inflammatory response in patients with diabetes.¹⁶ Recent intake rather than remote intake of nutrients is more important in supporting collagen deposition and healing.

With **insufficient carbohydrate intake**, body protein is catabolized for energy. Protein, thus, is diverted from repair to provide the glucose needed for cellular maintenance. This adaptation process is especially important in fighting infection, as leukocytes require glucose for phagocytosis. **Fat inadequacy** is seen only in prolonged starvation or severe hypermetabolic states, and deficiencies of the fat-soluble vitamins (A, D, E, and K) may develop in these situations. Lack of vitamin A can result in an inadequate inflammatory response, while an excess of it may cause an excess inflammatory response; both impair healing.¹⁶ **Thiamine (B1) deficiency** results in decreased collagen formation, while pantothenic acid (B5) deficiency results in decreased tensile strength and fewer fibroblasts. Inadequate vitamin C may result in lysis of collagen exceeding synthesis, meaning new wounds may have delayed

collagen formation, and old wounds may breakdown. Levels of vitamin E in excess of the recommended 100 IU daily may result in retardation of healing and fibrosis.

Zinc, iron, copper, and manganese are needed in small quantities for normal collagen formation. Data strongly suggest that zinc deficiencies impair healing, and repletion in states of deficiency returns healing to its normal rate. Supplementing those with normal zinc levels has not been shown to augment healing. Zinc deficiencies are seen in the elderly as well as those with chronic metabolic stress, excessive wound drainage, and persistent diarrhea. Regarding copper, impaired healing has been seen with decreased copper stores, although somewhat more rarely. Iron deficiency is primarily a problem in infants and may impair collagen formation. Severe iron deficiency also results in impaired healing because of its role in hydroxylation of proline and lysine to make collagen. Of these mineral deficiencies, iron deficiency is most often detected and treated.¹⁶

Most studies that examine nutrition and chronic wounds address the pressure ulcer population.¹⁷ Review articles indicate that research has not demonstrated a cause-and-effect relationship between nutritional status or intake and the development or healing of pressure ulcers. Nonetheless, provision of adequate nutrition, especially protein, is important in optimizing host status to tissue tolerance and healing of existing ulcers. Additionally, data indicate that nutritional deficiencies are present in a portion of venous ulcer patients.¹⁸ Further work is needed to confirm these findings.

Bioburden

Bioburden, the metabolic load imposed by bacteria on tissue, is often a cofactor in impaired healing.^{19,20} Wounds that have impaired healing are more susceptible to infection, and infected or heavily contaminated wounds demonstrate impaired healing. **All wound surfaces are contaminated** with bacteria, yet it is rare that the organisms on the wound surface cause the infection. Nonetheless, contamination is important, because the organisms compete with new tissue for nutrients and oxygen, and their byproducts are deleterious to the normal physiological balance of the healing wound. Overall, contamination pre-

disposes the patient to delayed healing and sets up an environment for infection to develop.

Wound infection is present when microorganisms invade tissue. Diagnosis usually is based on clinical signs, ie, the presence of pus, warmth, pain, erythema, and induration. In immunocompromised persons and those with neuropathy, often the only sign of infection is a change in sensation around the wound. Also, in some chronic wounds, poorly granulating tissue may be a sign of infection.²⁰ Wound infection in the elderly presents as decreased cognitive function or functional status, requiring the provider to investigate to find the source of the problem.¹⁴

Wound culture is performed to identify the specific organism(s) and identify an antibiotic to which the organism(s) is(are) sensitive. **Qualitative** wound cultures are not useful in diagnosing wound infection, because all wounds are contaminated to some degree. **Quantitative** culture (either of a tissue biopsy or a carefully obtained swab) may be more reliable but is not available at most hospitals. A wound that contains $\geq 10^5$ organisms per gram of tissue is unlikely to heal without treatment because of excessive bacterial burden. The exception to this criterion is with beta hemolytic streptococcus where fewer organisms (10^3 organisms per gram of tissue) are required to produce infection.^{19,20}

Host resistance and the local environment are important in determining whether a contaminated wound becomes infected. Normal, healthy tissue is resistant to microorganisms. In fact, contamination by a small number ($\leq 10^2$) of organisms per gram of tissue will activate leukocytes and has been seen as a factor that supports rather than impairs healing.¹⁴

Local environmental factors that contribute to bacterial proliferation and the development of impaired healing include the presence of devitalized tissue, dirt in the wound, an abscess distant from the site of the injury, and a hematoma or large wound space.²⁰ Super-infection from contamination, regardless of whether from stool, urine, or another wound site, is also associated with infection in pressure ulcers.¹⁷

Old Tissue

Old tissue is a factor recently recognized as an impediment to healing. In studies of recombinant

growth factors, debridement of old tissue from chronic wounds was shown to enhance healing.²¹ This supports clinical experience that radical debridement of tissue is essential to effective treatment of chronic wounds. While the exact mechanism by which old tissue impairs healing is not entirely understood, debridement involves removal of senescent fibroblasts, inflammatory cells, and old scar tissue, implicating these factors in the impairment. It is not clear, however, exactly when tissue converts to “old” tissue; further research should clarify this issue.

Excess Pressure

Pressure, shear, and friction are cofactors in all types of chronic wounds. They are most often associated with **pressure ulcers**¹⁷ but also are significant factors in the majority of chronic wounds. Little documentation exists to support this triad as contributing to chronic wounds, but clinical experience supports these as important factors in impaired healing. In the **venous ulcer population**, this problem is seen in the shear and friction that occur when compression stockings or bandages are utilized. Friable epithelial tissue may be disrupted under the stocking or bandage, especially along the previously intact skin of the shin, over the bony prominences of the ankle, and around the edge of the ulcer. Shear and friction occur most often during stocking application or removal and with ambulation. Clinically, this problem is most often seen in the elderly who have limited strength and manual dexterity. Often, coexisting arterial disease is present in the patient with venous ulcers. Inappropriate application of compression stockings and/or bandages may result in additional damage due to ischemia.

In persons with **neuropathic ulcers**, it is well accepted that excess pressure that is not perceived and that continues beyond tissue tolerance causes damage and prevents repair.⁵ In the pressure ulcer population, data show that low pressures for long periods of time or high pressures for short periods produce pressure ulcers.¹⁷ Controversy exists over what level of pressure causes vessel occlusion that leads to ischemia and necrosis.

Psychophysiological Stress

Stress has been identified as a potential cofactor in impaired healing. The proposed mechanism

is through stimulation of the sympathetic nervous system, with the outflow of vasoactive substances and subsequent vasoconstriction. Increased cortisol levels also have been implicated, as steroids are known to impair wound healing. The major stressors that have been investigated in this category are **psychological stress, pain,** and **noise**. Stress has been linked with pressure ulcer development in patients transferred from acute care to long-term care, using cortisol as an objective measure of stress. Although the numbers are small, and the ulcers are not severe, data show that subjects with higher cortisol levels developed ulcers, while subjects with lower cortisol levels did not develop ulcers. Relaxation and guided imagery also are related to healing in persons with wounds. Stress, measured with cortisol levels, and inflammation were reduced with relaxation and imagery. These data suggest that available therapies might be used to decrease the sympathetic nervous system response to stress and thus support healing in persons with wounds.²² Further research is needed to establish the direct effect on healing.

Intuitively, **pain** is thought to be an important issue in the development and healing of chronic wounds. For example, a recent large database study found that the presence of pain upon admission to a nursing home was associated with pressure ulcer development within the first 6 months after admission. Data do not indicate, however, if pain is a cofactor in healing impairment.²³ Pain reduction using transcutaneous electrical nerve stimulation (TENS) and music has been shown to be effective in reducing pain in persons with open wounds.²² Unfortunately, healing was not an outcome measure when evaluating these treatments. It would seem logical that a reduction in pain would mitigate vasoconstriction thus increasing wound perfusion and supporting wound healing. Whether this is true remains to be established.

Noise is another stressor that results in a systemic cardiovascular response that may affect repair. Noise has been shown to increase epinephrine levels and later *in-vitro* leukocyte function. In addition, intermittent noise has been shown to decrease healing in an animal model.²² However, studies have not specifically addressed this issue in the chronic wound patient population.

Concomitant Conditions

A myriad of concomitant conditions is associated with impaired healing. Major conditions include *peripheral vascular disease, diabetes mellitus, pulmonary disease, cardiac disease, conditions that result in immunocompromise*,^{4,5} and *specific treatments*, including *surgery*.²⁴

Persons with *vascular disease* are at risk for impaired healing. In arterial disease, the cause is accepted as tissue hypoxia due to arteriosclerotic disease. In venous disease, back pressure from venous hypertension and edema is thought to contribute to impaired healing. *Persons with diabetes mellitus* are at risk for impaired healing. Glucose control is essential for normal healing, and high glucose levels are often seen in diabetes, especially during periods of physiological stress and repair. High glucose levels result in impaired leukocyte function and increased risk of infection. Diabetes also appears to reduce growth factors and growth factor receptors in wounds. Lack of sensation is a serious problem in the more advanced states of diabetes where Charcot foot and neuropathy occur. When persons lack normal protective sensation, initial damage may occur without the person being aware of it. In addition, an existing wound may be exacerbated by excess pressure and mechanical or thermal damage in persons who lack sensation.⁴ Unfortunately, it is common to see persons with multiple concomitant conditions, such as a person with a venous leg ulcer and coexistent arterial disease and diabetes.

Immunocompromised patients include persons who are HIV-positive, those with cancer, the malnourished, those receiving immunosuppressive agents, and the aged. Persons who are immunocompromised are unable to mount an adequate inflammatory response or the response is delayed. With immunocompromise, all phases of healing are delayed, and patients may be at risk for infection or wound disruption.²²

Adverse Effects of Treatment

Iatrogenic effects of therapy also may result in impaired healing. Thus, treatment for pathologies may be a cofactor in healing impairment. Examples of such treatments are *radiation therapy, chemotherapy, steroid therapy*, and *anti-inflammatory drugs*.²²

Radiation disrupts cell mitosis at the time of

the treatment and has ongoing effects for the individual's life. These include obliterative arteritis and fibrosis that result in woody, hypoxic skin that does not heal well after injury. The dose and dose rate, along with the patient's genetics, determine the extent of damage and the speed at which it occurs. Bone marrow is the organ most sensitive to radiation exposure. The effects of radiation are seen immediately in terms of the number and various circulating cell types. Recovery depends on the dose of radiation and the half-life of the various cells.

Chemotherapy is designed to interrupt the cell cycle. It affects cells while they are dividing. This is accomplished in most anticancer drugs by damaging DNA or preventing DNA repair. Hormonal anticancer agents prevent binding of hormones, while others antagonize receptors to inhibit tumor growth. The primary effects of chemotherapy on healing are experienced during the treatment period and immediately after treatment.

A newly introduced form of cancer treatment is the use of *antiangiogenic agents (eg, bevacizumab)*, which block new blood vessel formation around the tumor by binding to a particular growth factor. Although these agents have the potential to impair wound healing, the pathway for wound angiogenesis and tumor angiogenesis appears to be somewhat different, and these agents have not caused the wound healing problems many anticipated.²⁵

Steroids impair all phases of healing by suppressing the inflammatory response, reducing immunocompetent lymphocytes, decreasing antibody production, and diminishing antigen processing. Clinical signs of inflammation are suppressed. If steroids are administered at the time of injury, their impact is greater than if they are administered several days after injury because of their effect on the inflammatory response that accompanies the initial injury. When the initial inflammatory response is decreased, all subsequent phases of healing are delayed, and the risk of infection is increased. Other medications, such as nonsteroidal anti-inflammatory agents, phenylbutazone, and vitamin E, disrupt the normal healing process. Their effects are primarily anti-inflammatory and, thus, are seen early after injury.⁵

Conclusion

Healing in individuals with chronic wounds is a complex process. One cannot simply dress the wound and expect healing to occur. It is important to assess the individual for the presence of each of the potential cofactors described in this chapter. Typically, evaluation of cofactors for impairment is integrated into the initial history and physical and should be an integral part of the ongoing holistic patient assessment. Early identification of the cofactors for impaired healing allows the practitioner to make a differential diagnosis, initiate appropriate referrals, and develop a comprehensive plan of care. Management of local and systemic cofactors that impact repair will mitigate their adverse effects and facilitate healing of chronic wounds.

Take-Home Messages for Practice

- A thorough history is the basis for determining factors present that may impair healing.
- It is important to assess the scientific evidence for the manifestation of specific factors on healing for patients with wounds.
- Current scientific knowledge about the mechanisms by which specific cofactors impair healing should be utilized when evaluating patients with wounds.

Self-Assessment Questions

1. Factors associated with impaired healing are:
 - A. Warm temperature and low perfusion
 - B. Warm temperature and high perfusion
 - C. Cold temperature and high perfusion
 - D. Cold temperature and low perfusion
2. Factors that contribute to impairment in healing due to infection are:
 - A. Albumin of 4.5 g/dL
 - B. Abscess distant from the wound
 - C. 10^3 organisms per gram of tissue
 - D. Healthy tissue
3. Anemia is a risk factor for impaired healing when:
 - A. People are smokers
 - B. Diabetes mellitus is present

- C. Intravascular volume is low
- D. Chemotherapy is utilized

Answers: 1-D, 2-B, 3-C

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Wound Healing Impairment. Impaired wound healing is a major issue for our societies as it confers pain, suffering, psychological stress and loss of quality of life on many millions of people and is associated with huge costs to health care providers and insurers [1]. From: Advanced Drug Delivery Reviews, 2018. Related terms: Complication. Inflammation. Neoplasm. Diarrhea. Acute wounds in normal, healthy individuals heal through an orderly sequence of physiologic events. Some individuals have one or more factors that contribute to. Some individuals have one or more factors that contribute to impaired wound healing, which can lead to chronic nonhealing wounds and ulcers or can complicate the surgical course. The risk factors associated with impaired wound healing due to patient factors, underlying disease, and disease treatments are reviewed here. Wound mechanisms, normal phases of wound healing, and wound classification as well as the clinical evaluation and management of wounds are discussed elsewhere. **FACTORS IN WOUND HEALING** The complexity of wound healing makes it vulnerable to interruption at many levels. Factors that affect physiologic responses and cellular function can potentially influence wound healing. This section will briefly highlight the effect several factors have on wound healing. **Local Factors.** Several local factors can greatly influence wound healing. Wound neutrophil activity has been demonstrated to be impaired at lower oxygen tensions identified in wounds. Low temperature, low pH, and elevated glucose concentrations also limit leukocyte function.²⁶ Fibroblasts exposed to longer periods of hypoxia may not participate in the formation of the extracellular matrix, thus delaying healing.²⁷ Chronic wounds, however, do not follow this sequence of events and can challenge the most experienced clinician if the underlying factors that are impairing wound healing are not identified. The purpose of this article is to present recent information about factors that impair wound healing with the underlying pathophysiological mechanism that interferes with the response to tissue injury. These factors include co-morbidities (diabetes, obesity, protein energy malnutrition), medications (steroids, non-steroidal anti-inflammatory drugs or NSAIDs, anti-rejection medications), oncology interventions. Wounds that don't heal within 30 days are considered chronic. Wounds that become chronic generally stall in one or more of the phases of wound healing. Here are 10 of the most common factors affecting wound healing in chronic wounds: 1. **Age of Patient.** Studies have shown that people over the age of 60 may have delayed wound healing due factors associated with physical changes that occur with advanced age. In addition to multiple existing comorbidities, there is decrease in the body's inflammatory response, a delay in angiogenesis and the process of epithelialization is slower. Some visible changes to the skin are related to the alteration in melanocytes, such as age spots, as well as drier skin due to a decreased function of the sebaceous glands.