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REVIEW ARTICLE

Factors That Impair Wound Healing

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Abstract The body's response to tissue injury in a healthy individual is an intricate, sequential physiologic process that results in timely healing with full re-epithelialization, resolution of drainage, and return of function to the affected tissue. 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 (radiation, chemotherapy), and life style habits (smoking, alcohol abuse). Successful treatment of any chronic wound depends upon identification and management of the factors for each individual.

Introduction

The body's response to tissue injury in a healthy individual is an intricate sequential physiologic process that results in timely healing with full re-epithelialization, resolution of drainage, and return of function to the affected tissue. Chronic wounds, however, do not follow this sequence of events and stall in some phase of wound healing, usually inflammation, without progression to the next phase. The lack of progression may be a result of inability to recruit the necessary cells, the lack of "materials" to build the tissue needed to fill and/or cover the wounded area, or pathological cellular dysfunction as a result of harmful products introduced into the body.

While the principles of standard wound care (including debridement, treating infection, moisture appropriate dressings, and off-loading or pressure-redistribution if indicated) are applicable to all wounds, identification and treatment of the impeding factors is a necessary part of the patient assessment and plan of care. These factors can be classified into the following categories: co-morbidities, medications, oncology interventions, and life style habits.

Co-morbidities

Diabetes

Diabetes is present in 8.3% of the United States' population and is becoming an increasingly prevalent issue in modern-day health care.[1] One complication of diabetes is ulceration of the foot secondary to neuropathic

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involvement.[2–5] Peripheral neuropathy leads to decreased protective sensation and foot deformities.[2] The deformities then lead to a redistribution of pressure during gait and can result in ulceration at high pressure areas.[2,3] Further, autonomic neuropathy results in trophic changes to the skin which can leave it vulnerable to cracking and breakdown, thus increasing the risk of infection.[2,3]

For patients with wounds of other etiologies (e.g. surgical incisions, pressure ulcers, or infected wounds) diabetes with poorly-controlled blood sugars results in cellular dysfunction that impedes all phases of wound healing. During hemostasis, there is decreased platelet-derived growth factor (PDGF) receptor expression on endothelial and epithelial cells, resulting in delayed transition to inflammation.[6] An increase in the number of wound-activated macrophages (WAMs) causes increased and prolonged expression of inflammatory cytokines, thereby prolonging the inflammatory phase.[7,8]

The proliferative phase is affected by impaired fibroblast signaling resulting in poor granulation tissue formation,[9,10] fibrotic extracellular matrix resulting in stalled keratinocyte migration and delayed re-epithelialization,[11] elevated metallomatrix proteinases and reactive oxygen species (ROS) resulting in ECM instability,[12] and altered sensitivity to VEGF resulting in decreased angiogenesis and poor vascularizaiton.[4] Table 1 lists the values recommended for diabetes markers in order to facilitate healing and prevent complications to all systems.

Peripheral arterial disease is a common complication of diabetes and can lead to peripheral ischemia. Decreased blood flow to an area of ulceration results in reduced oxygenation, nutrition, and healing rates.[3] Not only is there a decreased supply of blood to the lower extremities in diabetes, but also an altered blood composition. In a recent study by Tiaka et al, a decreased amount of antioxidant enzymes in the blood and a high rate of lipid peroxidation were shown to be associated with prolonged inflammatory states and chronic diabetic ulcers.[5] Therefore, increased oxidative stress found in diabetes could perpetuate non-healing diabetic foot ulcers.

Table 1 Recommendations for Glycemic Control for Patients with Diabetes

	HbA1c	Fasting Plasma Glucose	Postprandial Plasma Glucose
ADA	<7%	90–130 mg/dL	<180 mg/dL
		5–7.2 mmol/L	<10 mmol/L
ACE	6.5%	<110 mg/dL	<140 mg/dL
		<6.1 mmol/L	<7.8 mmol/L

ADA – American Diabetes Association. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Available at: http://care.diabetesjournals.org/content/35/6/1364.full.pdf+html; Accessed 04.05.13.

ACE – American College of Endocrinology. Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient — 2013 Update. Available at: https://www.aace.com/files/publish-ahead-of-print-final-version.pdf; Accessed 04.05.13.

Management of diabetic foot ulcers is widely varied and dependent on the patient and the severity of diabetes. Treatments involve revascularization via vascular surgery, off-loading utilizing casting or orthotics, and re-oxygenation with hyperbaric oxygen therapy. Also, statins are shown to improve ulcer healing rates in patients with peripheral arterial disease due to the cholesterol-lowering effects.[2] One treatment goal for a diabetic ulcer is conversion of the ulcer from a chronic wound to an acute healing wound via the principles of debridement, off-loading, and moisture balance. Moist dressings and debridement can restore a balanced environment to facilitate wound healing and closure, while off-loading will reduce harmful mechanical forces on the ulcer so that healing may occur.

Due to diabetic neuropathic deformities, off-loading of the ulcerated area is necessary to equalize plantar pressure and facilitate healing. Total contact casting is the gold-standard for off-loading and allows the patient to remain ambulatory.[13] A study by Ganguly et al compared treatment with total contact casting versus treatment with conventional dressings alone in patients with diabetic foot ulcers.[14] This study revealed that the total contact casting group had a statistically significant higher rate of wound closure as compared to the conventional dressings group. A more recent study by Kashefsky and Marston used total contact casting along with cryo-preserved human fibroblast-derived dermal substitute on 15 patients with diabetic foot ulcers. The authors compared the results to previously published rates of healing with total contact casting alone and found a reduced time to wound closure with dermal substitute use.[15] The average healing rate of the 15 wounds was 23.7days $\pm$ 16.3 days, and the average number of dermal substitute applications was 2.1. In addition, there was no correlation between ulcer duration or location on the foot; there was a correlation between healing time and ulcer size. The results suggest there may be benefits to a combination of total contact casting with advanced dermal substitutes; however, further research is necessary as this study had a small sample size.

Hyperbaric oxygen therapy (HBOT) is another method of assisting in diabetic ulcer healing and closure. HBOT is shown to improve tissue hypoxia, enhance proliferation of fibroblasts and blood vessels and reduce inflammation and infection.[5] A randomized controlled study by Londahl et al included 94 diabetic patients with a Wagner grade 2–4 foot wound of more than 3 months duration. The end point was full ulcer healing. The treatment group had a healing rate of 52% (25/48); the placebo group, 29% (12/42), $P = 0.03$.[16] Systematic reviews have concluded that HBOT reduces the chance of amputation (odds ratio 9.992, 95% CI).[17,18] An extensive review of the benefits of HBOT in the treatment of diabetic wounds, including healing rates, amputation reduction, and quality of life is provided by Tiaka et al.[5] Although the results of HBOT are promising, the treatment

cost remains high and more established guidelines for treatment protocol and patient selection are necessary.

Obesity

Obesity is prevalent in one third of the United States' adult population.[19] A major concern of obesity is the increased workload of the heart to supply oxygenated blood to body tissues. If the heart is unable to perfuse these tissues, ischemia can occur and thus contribute to necrosis and impaired wound healing.[20] An obese person has a tendency to hyperventilate because the diaphragm is unable to fully descend due to the large amount of adipose tissue. Hyperventilation and decreased chest expansion then result in decreased vital capacity and decreased oxygenation of blood, thereby negatively impacting tissue oxygenation.[17] If tissue near a wound is not adequately oxygenated, fibroblasts cannot form collagen and oxygen-dependent cellular repair processes cannot occur.[17,21]

Once an obese patient develops a wound, the risk for infection is higher partly due to the avascularity of the surrounding adipose tissue.[17,18] Avascularity decreases the body's ability to defend against infection because the lack of oxygen prevents neutrophils from effectively phagocytizing bacteria, thus increasing the bacterial load of the wound.[17] Decreased blood supply to the wound prevents the necessary cells, e.g. neutrophils and macrophages, from reaching the wound site to protect against infection.

On a cellular level, researchers have shown that obesity can impair wound closure via the effects on circulating blood cells. Normally, vasculogenic progenitor cells (PC), derived from adult bone marrow, respond to peripheral injury by traveling through the circulatory system to the wound site and contributing to wound angiogenesis. In a recent study by Wagner et al, PCs of 25 non-diabetic and obese subjects (BMI $>$ 30) and 17 non-obese subjects (BMI $<$ 30) were harvested, cultured, and assessed for their ability to adhere, migrate and proliferate.[22] PCs of obese subjects were significantly less adherent to collagen, had significantly decreased ability to migrate, and were unable to proliferate effectively. As a result, Wagner et al demonstrated that obesity is associated with impaired vasculogenic PC function which results in delayed wound closure.

Increased body habitus of obese patients often causes limited mobility and inability to optimally reposition oneself or provide adequate hygiene or nail care. These patients may need to rely on caregivers to help reposition and off-load high pressure areas in order to prevent pressure-related injuries. Increased adipose tissue will not protect high pressure areas but instead makes the area more vulnerable because of the avascularity of adipose tissue.[17] Skin folds are prevalent on obese patients and can provide a moist environment for bacteria to thrive, as well as lead to ulceration from skin on skin friction.[17,18] The Braden Scale, used to assess risk for pressure ulcers, considers many factors including moisture, mobility, friction and shear. In a study by Drake et al utilizing the Braden Scale, the prevalence of a pressure ulcer among patients with a BMI less than 40 was 12.5% versus 26% in patients with a BMI greater than 40.[23] When effects of BMI were controlled for, patients with a Braden Scale score of 16 or less were 6 times more likely to develop a pressure ulcer when compared to patients with a score of more than 16. This study concluded that either a BMI greater than 40 or a Braden Scale score of 16 or less was a statistically significant independent predictor for development of a pressure ulcer.

Protein Energy Malnutrition

Malnutrition is a common problem in the elderly population and can result in delayed wound healing. Protein intake can result in decreased collagen production, angiogenesis and fibroblast proliferation, all of which negatively impact wound healing. In addition, ingested proteins are metabolized into amino acids and peptides that serve as enzymes, hormones, cyotokines, growth factors, and components of antibodies. Inadequate numbers of these protein substances impedes both tissue maintenance and wound healing.

Insufficient protein intake can be assessed utilizing hematological markers such as albumin and pre-albumin or total lymphocyte count. Other diagnostic tools, namely the Rainey MacDonald nutritional index (RMNI) or the Mini-nutritional assessment (MNA), are useful in assessing risk or presence of protein malnutrition. A study by Guo et al utilized the RMNI, MNA and total lymphocyte counts to assess the impact of protein levels on wound healing for 207 patients status post hip fracture surgery.[24] The authors determined that total lymphocyte count levels and MNA scores were significantly predictive for determining a patient's risk of delayed wound healing.

Protein malnutrition is important to assess for patients with chronic wounds of all etiologies. Forty-one patients with chronic venous insufficiency ulcers underwent a wound evaluation and nutritional assessment at both baseline and 12 weeks after start of care.[25] These patients were compared to a control group of 43 patients attending an outpatient dermatology clinic. Protein deficiency, marked by a serum albumin level less than 35 g/L, was independently related to increased wound size at 12 weeks follow-up. Also, researchers found that wound complications, such as infection or hospitalization, were associated with the presence of an inflammatory syndrome, as evidenced by the C-reactive protein level. Therefore, protein deficiency has a large impact on chronic wounds and can be associated with a poor prognosis.

Nutritional support and replacement therapy may be necessary for patients experiencing a non-healing wound or for patients undergoing surgery (see Table 2). One randomized controlled trial by van Anholt et al assessed the effects

Table 2 Nutritional Requirements for Wound Healing

	Calories[a]	Protein[b]
Normal (at rest)	20–25 kcal/kg/day (age dependent)	0.8 g/kg/day 60–70 g
Post-operative/ill/injured	30–50% above normal	1.2–2 g/kg/day
Large open wounds, burns		2–2.5 g/kg/day
Malnourished	50% above normal	1.5 g/kg/day plus Anabolic agent[a]

[a]Demling RH. Nutrition, anabolism, and the wound healing process: an overview. *Eplasty*. 2009;9:65–94.
[b]Huckleberry Y. Nutritional support and the surgical patient. *American Journal of Health-System Pharmacy*. 2004;61:7.

of a high-protein arginine-based nutritional supplement on the healing of stage III or IV pressure ulcers in 43 patients who normally would not be given nutritional support (22 experimental or ONS and 21 control subjects).[26] The patients were given a nutritional supplement or a non-caloric control product three times every day in addition to their normal diet and standard wound care treatment. The ONS group had statistically significant accelerated rates of wound healing (0.26 cm^2/d in the first 3 weeks) compared to the control group (0.14 cm^2/d in the first 3 weeks). In addition the ONS group required fewer dressing changes and required less time for care than the control group. Thus, nutritional supplementation could lead to decreased costs for treatment of wounds as well as increased rates of closure.

Medications

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have a depressant effect on wound healing while simultaneously decreasing the granulocytic inflammatory reaction.[27,28] NSAIDs inhibit the production of PGE2, an inflammatory mediating prostaglandin, and can thereby reduce pain.[24] The suppression of PGE2 also occurs with excessive wound scarring and therefore NSAIDs may increase scar formation, especially if they are used during the proliferative phase of healing.[24] NSAIDs have an anti-proliferative effect on blood vessels and skin, thereby delaying healing rate.[29] NSAIDs may be prescribed post soft-tissue injury or post-surgery to assist with pain control management and to diminish inflammation; however, due to their negative effects on wound healing, their use is controversial.

Platelets, inflammatory cells, fibroblasts and epithelial cells produce nitric oxide (NO), partially in response to inflammatory cytokines that are released with injury. Subsequently nitric oxide assists in angiogenesis and inflammation mediation. If the nitric oxide enzymes necessary for this cascade are inhibited by either medication or disease, wound healing is impaired.[30] Kaushal et al attempted to determine if by linking NO to ibuprofen, the anti-inflammatory effect could be retained while preventing its negative impact on healing.[23] The study compared ibuprofen alone with ibuprofen linked to NO on incisional wounds of rats. Ibuprofen linked to NO encouraged collagenation and epithelialization, as well as promoted wound contraction.[23] The results suggest that ibuprofen with NO may prevent the healing depressant effect of NSAIDs while maintaining the anti-inflammatory effects.

Another study by Krischak et al, analyzed the effects of NSAIDs on incisional wound healing after surgery using a rat model. Of 20 rats given incisions, 10 rats were given the NSAID diclofenac and 10 rats were given a placebo. Histologically, although all wounds closed, the rats treated with NSAIDs had a significant reduction in fibroblasts, thereby inhibiting proliferation.[25] Therefore, the results suggest that short-term use of NSAIDs after surgery is beneficial for its analgesic effect, but that patients with chronic wounds or diabetes could be more dramatically affected by NSAID's effect on fibroblast inhibition.[25] Thus, in these conditions, NSAIDs should be used with caution.

Steroids

Steroids are used in diagnoses such as asthma, cancer, or autoimmune disorders. An example of a commonly used steroid is dexamethasone, an anti-inflammatory drug and immunosuppressant glucocorticoid. Despite the beneficial effects of glucocorticoids in rheumatoid arthritis and bronchospasms, the anti-inflammatory and immunosuppressant actions of these steroids can result in delayed healing.[31,32] Another at-risk patient population is transplant recipients who are placed on anti-rejection medications (e.g. Prednisone and Cellcept) after transplant surgery. The negative impact on wound healing results from the tendency of steroids to impede wound contraction and decrease tensile strength.[27]

Glucocorticoids are known to have dermal effects that can impact wound healing, including inhibition of fibroblast proliferation and decreased collagen production. To further assess the effects of glucocorticoids on the epidermis, Stojadinovic et al utilized human keratinocytes to determine the effects of dexamethasone on genes that are expressed in skin.[26] Of the 12,653 total genes analyzed,

6285 (49.7%) were suppressed by the application of dexamethasone. Further, gene inhibition resulted in downregulation of interleukin signaling, cytoskeletal remodeling, and keratinocyte proliferation, thus affecting the inflammatory and proliferative phases of wound healing. Matrix metalloproteinases (MMPs), enzymes that assist in degradation of the extracellular matrix and keratinocyte migration, and vascular endothelial growth factor C (VEGfC), a factor supporting angiogenesis, were also suppressed with glucocorticoid use.

Cortisol, another glucocorticoid, is released during the stress response and can increase blood glucose, inhibit the immune system, decrease bone formation and impede wound healing. One prospective study by Ebrecht et al analyzed 24 male non-smokers with a small punch biopsy wound and assessed their perceived stress via the Perceived Stress scale (PSS) and a General Health Questionnaire (GHQ).[33] The questionnaires, along with multiple saliva samples for cortisol, revealed a significant correlation between increased stress and cortisol levels with impaired wound healing.

A study by Feeser et al assessed the effects of androstenediol (AED), an immune-regulating hormone and metabolite of the adrenal steroid DHEA, on steroid-induced immunosuppression.[27] Mice were injected with methyl prednisolone to elicit immunosuppression and given full thickness wounds. Wound contraction rates were measured and the mice that received steroids and AED had accelerated wound closure rates versus the mice that did not receive AED but had steroids. (Wounds in the AED group were 16 ± 11 percent of original size on day 12 as compared to 46 ± 24 percent in the control group.). Therefore, introduction of AED allowed for a reversal of steroid-induced immuno-suppression. Further studies are needed to assess these effects in a clinical human population and to determine how AED may affect immunosuppressed patients with wounds.

Patients who have a history of long-term steroid use are also at risk for developing drug-induced diabetes. Therefore, when treating a patient who is taking steroids, assessing for hyperglycemia may also reveal undiagnosed diabetes which may also be affecting the wound healing potential.

Oncology Interventions

Radiation

Ionizing radiation does not solely target the cancerous tissue it was meant to irradiate. The radiation beam also affects the surrounding tissues (such as the epithelium that it passes through in order to reach the malignant cells) by destroying the DNA and preventing cell replication needed for tissue injury. Actively dividing cells, such as tumor or epithelial cells, are the most prone to radiation damage. As a consequence, radiation-induced damage to the epithelium can result in skin breakdown, lower tensile strength, atypical fibroblasts and delayed healing rates.[34] During radiation therapy, overall toxicity is limited by fractionating the cumulative dose over an extended period of time. This protocol is practiced because surrounding tissues have a dose-dependent response to radiation therapy, thus lower amounts of exposure will improve the tissue response to treatment. Tissue damage can occur more than 6 months after radiation therapy is completed and can result in erythema, swelling, moist or dry desquamation and ulceration. Further delayed effects can include fibrosis, capillary bed telangiecstasia, and skin necrosis.[29]

Radiation therapy can occur before or after tumor excision, but either situation has been shown to result in wound complications. One study by Jagetia et al utilized a mouse model to assess the effects of various levels and durations of gamma radiation on full-thickness excision wounds. The researchers also tried to determine if curcumin (an antioxidant and radioprotective agent that has been shown to have beneficial effects on rheumatism, skin disease, and inflammation) would have beneficial effects on wound contraction when administered before radiation.[35] As shown in prior studies, ionizing radiation produced a dose-dependent delay in wound contraction and prolonged the healing process. However, mice that were given curcumin had a significant decrease in wound healing time for doses of 10, 20, and 40 Gy as measured at 5, 10, or 20 days (e.g., for 10 Gy, 18.6 ± 0.46 days mean healing time for the experimental group compared to 20 ± 0.55 days for the comparable control group). The mice that were given curcumin also had increased collagen, DNA, and nitric oxide synthesis. The authors propose that this natural product could be utilized to enhance healing rates in place of more costly treatments.

Radiation injuries can develop months or years after radiation treatment itself has ceased. Late radiation tissue injuries have shown improved outcomes with hyperbaric oxygen therapy (HBOT). A recent Cochrane review evaluated 11 randomized controlled trials (669 participants) that studied the effect of HBOT versus no HBOT on late radiation tissue injuries. The review suggested improved healing outcomes with HBOT on late radiation tissue injuries to the head, neck, anus and rectum.[36] The authors suggest that further research is needed to determine optimal patient selection and timing of therapy, as well as cost-effectiveness.

Chemotherapy

Chemotherapy, like radiation therapy, targets rapidly dividing cells and results in impaired tumor growth; however, it also impairs wound healing. Many chemotherapeutic agents can be utilized in cancer treatment, including adriamycin and bevacizumab. The chemotherapeutic drug's

main effects on wound healing include delayed inflammatory phase of healing, decreased fibrin deposition and collagen synthesis, and delayed wound contraction. Gulcelik et al studied the effects of adriamycin, a wide-spectrum anthracycline group chemotherapeutic agent with many known side effects, on abdominal wound healing in 5 treatment groups of 24 rats. The researchers also analyzed the effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) injected into the wounds to determine if it would improve dermal wound healing.[37] The treatment group of adriamycin-treated rats that received the GM-CSF injection had improved wound healing rates compared to rats that did not receive GM-CSF (as measured by mean bursting of the incision and hydroxyproline concentrations at the wound margins). GM-CSF is normally used in the treatment of chemotherapy-related neutropenia, but also has beneficial effects on chronic venous ulcers, pressure ulcers and incisional wounds.

Another chemotherapeutic drug, bevacizumab, targets VEGF and impairs angiogenesis to slow the progression of metastatic breast cancer, colon cancer, and non-small cell lung cancer.[38] However, bevacizumab has negative effects on wound healing secondary to its anti-angiogenic properties which decrease its ability to carry nutrients, oxygen and important cells to the wound site. These effects can result in surgical complications such as dehiscence, surgical site bleeding or infection. A review of the current literature determined that patients should wait 6–8 weeks after bevacizumab use before electing to have surgery in order to avoid wound healing complications. Also, even after surgery, patients should wait at least 28 days to resume use of bevacizumab in order to limit wound complications.

As detailed above, the timing of bevacizumab treatment is crucial to avoid wound complications. One retrospective study by Erinjeri et al looked at 1108 patients treated with bevacizumab and the timing of when the patients received chest wall port placements.[39] 120 of these ports required explants secondary to wound complications and dehiscence. A higher rate of dehiscence occurred when patients had a shorter period of time (<14 days) between bevacizumab treatment and port placement. Overall, the literature recommends that timing of bevacizumab usage must be considered in relation to when surgeries occur in order to prevent detrimental wound healing complications.

Life-style Habits

Smoking

Smoking is most associated with its effects on lung tissue and the increased risk of cancer; however, smoking also has a detrimental influence on wound healing. Nicotine, an alkaloid poisonous substance present in all tobacco products, reduces cutaneous blood flow by vasoconstriction, stimulates release of proteases that may accelerate tissue destruction, suppresses the immune response and leads to an increased risk of infection.[1] Tobacco altogether slows collagen production, weakens scar tissue, and leaves healed tissues more susceptible to risk of recurrent injury.[40] These effects can alter all phases of wound healing, thereby resulting in inefficient and slower closure of wounds.

During the initial phase of hemostasis, the clot chemical composition is altered in smokers in regard to cytokines, chemo-attractants, and growth factors[41]; however, smoking also enhances the formation of a clot via platelet activation and increases release of blood fibrinogen. This increased concentration of fibrinogen could be attributed to damage from oxidative processes on vascular endothelial cells.[36] Although there is faster clot formation, the inflammatory phase of healing is delayed and neutrophil cell count is increased.[36,42] As a result, there is a decreased chemotactic responsiveness and migratory capacity of cells, as well as an increased release of proteolytic enzymes. These enzymes, in combination with reduced protease inhibition, can lead to connective tissue degradation.[36] In a study of 48 smokers and 30 non-smokers with full thickness biopsy punch wounds, Sørensen et al determined that inflammation and fibroblast proliferation were delayed in smokers.[37] The smokers were also randomized to continued smoking or abstinence groups after 1 week. The abstinence group had increased inflammatory cell infiltration and macrophages in the wound.[37]

The proliferative and remodeling phases of healing are also affected by smoking. In the proliferative phase, a decrease in collagen synthesis and deposition may impair wound angiogenesis.[36] Also, while the effects of smoking on the inflammatory phase can be reversed by smoking cessation, the effects on the proliferative phase cannot be reversed.[37] Not only may angiogenesis be affected by smoking, the formation of new epithelium and epidermis is affected as a result of reactive oxygen species and toxins in tobacco smoke that can cause vascular endothelial injury and impaired migration of neutrophils and monocytes.[36] Tobacco smoke also contains carbon monoxide which preferentially binds to hemoglobin over oxygen and thereby impedes oxygen delivery to healing tissue.[36]

Specifically with surgical wounds, researchers found a higher risk of adverse events occurred with smoking. These adverse events included tissue flap necrosis, wound dehiscence, and surgical site infections, as well as long-term complications such as fistulas or incisional hernias.[36] A study by Manassa et al of 132 patients who underwent abdominoplasties revealed 53.8% of patients smoked and these patients had a statistically significant higher rate of wound healing complications and wound dehiscence compared to non-smokers.[43]

Smokers who are undergoing elective surgery need to be advised of the increased risk of impaired healing and the need to cease smoking prior to surgery, as well as the strong

Table 3 Effects of Smoking and Alcohol Abuse on the Healing Phases

	Inflammation	Proliferation	Remodeling
Smoking	Impaired leukocyte activity Decreased macrophages Decreased neutrophil bactericidal activity Decreased IL-1 products	Decreased fibroblast migration Decreased wound contraction Decreased epithelial regeneration Decreased extracellular production Increased proteases	
Alcohol abuse	Decreased neutrophil chemokines with decreased neutrophil infiltration Decreased IL-8 and TNF-α Decreased monocyte function Decreased macrophage response to microbes	Decreased endothelial cell response Decreased angiogenesis Increased tissue hypoxia Impaired cell signaling	Decreased production of Type 1 collagen Increased level of MMP-8 Degradation of epithelial ECM Decreased tensile strength of skin

recommendation of not smoking after surgery. This is especially critical in patients who have peripheral vascular disease with lower extremity wounds where hypoxia is already a factor in reduced healing potential. Smoking cessation programs are available through organizations such as the American Cancer Society, and are highly recommended for any patient who is having difficulty with wound healing.

Alcohol Intake

While the effects of smoking on wound healing are universally accepted and discussed with patients, the effects of excessive alcohol intake on wound healing are just coming to be recognized as problematic. Patients who have a history of alcohol abuse have higher hospital-acquired infection rates and increased incidence of dehisced infection surgical incisions.[44]

The mechanisms of alcohol intake that impair wound healing include increased insulin resistance and higher blood sugar levels.[45] In addition, alcohol abusers tend to have poor eating habits with higher risk of protein energy malnutrition. The results include decreased inflammatory and immune responses to tissue injury, decreased fibroblast migration and angiogenesis, and decreased Type I collagen production and weaker scar tissue during remodeling. Thus there is slower healing and increased risk for recurrence with any mechanical force.

Wound healing is inhibited in the inflammatory, proliferative, and remodeling phases by the mechanisms listed in Table 3. Studies have shown that acute ethanol intoxication has a detrimental effect, not just chronic abuse.[46,47] In summary, there is a decrease in the inflammatory and immune responses to injury that result in both delayed healing and increased risk of infection, decrease in fibroblast migration and angiogenesis during the proliferation phase, and decreased Type 1 collagen production with concurrent increase in protease activity during the remodeling phase resulting in weaker extracellular matrix.[48] The clinical presentation will be slower healing with a tendency to recur with any mechanical force.

Summary

Even in the best of conditions, wound healing is an intricate process that requires timely communication of cellular and acellular components to complete the process in order to restore optimal function of both the injured tissue and the individual patient. Any pathophysiologic interruption in the process results in delayed or halted healing and presents conundrums that result in frustrating and expensive care and therefore does not achieve patient and provider goals. An astute clinician will explore all aspects of the patient medical history, psychosocial habits, potential undiagnosed disorders, and medications to determine the cause of wound chronicity and to develop the optimal plan of care.

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