Updates in Diabetic Wound Healing, Inflammation, and Scarring

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Abstract

Diabetic patients can sustain wounds either as a sequelae of their disease process or postoperatively. Wound healing is a complex process that proceeds through phases of inflammation, proliferation, and remodeling. Diabetes results in several pathological changes that impair almost all of these healing processes. Diabetic wounds are often characterized by excessive inflammation and reduced angiogenesis. Due to these changes, diabetic patients are at a higher risk for postoperative wound healing complications. There is significant evidence in the literature that diabetic patients are at a higher risk for increased wound infections, wound dehiscence, and pathological scarring. Factors such as nutritional status and glycemic control also significantly influence diabetic wound outcomes. There are a variety of treatments available for addressing diabetic wounds.

Keywords
- diabetes
- wound healing
- inflammation
- scarring

Recent studies regarding its prevalence and burden show that diabetes remains a significant problem. According to the Centers for Disease Control, in 2018, there were 34.2 million Americans with diabetes and an additional 88 million with prediabetes leading to a staggering $237 billion in annual medical costs.[1] Diabetic wounds, including foot ulcers, affect up to 25% of the diabetic population.[2] Treatment of these wounds is expensive, generating at least one-third of the total cost of treating diabetes and its complications.[3]

Diabetes is associated with several pathological changes that contribute to poor wound healing. Chronic hyperglycemia damages vasculature and hinders proper blood perfusion. Diabetic patients also often exhibit peripheral vascular disease and neuropathy, making wound detection difficult. Diabetic wounds are characterized by excessive inflammation, decreased angiogenesis, disrupted keratinocyte migration, and decreased fibroblast proliferation.[4] Together, these changes result in increased wound complications in diabetic patients, including infections, wound dehiscence, and non-healing wounds that become chronic.

Impact of Diabetes on Wound Healing

Normal wound healing is a complex process that proceeds through overlapping phases: inflammation, proliferation, and remodeling. The inflammatory phase is characterized by hemostasis and the infiltration of various immune cells. The proliferative phase is characterized by robust angiogenesis and reepithelization.[5,6] The proliferation phase ends with wound maturation and remodeling, ultimately resulting in a scar.[6] Diabetes disrupts almost all of these healing processes.[4]

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Inflammation in Diabetic Wounds

Compared with nondiabetic wounds, diabetic wounds have a longer inflammatory phase of wound healing. This extended proinflammatory state delays wound healing and can lead to the formation of a chronic wound.[7] In the inflammation phase of normal wound healing, the first macrophages to arrive (M1) are phagocytic and proinflammatory. They are eventually replaced by M2 macrophages that are anti-inflammatory, synthesize extracellular matrix (ECM), and promote angiogenesis.[8] In diabetic wounds, macrophages produce excessive proinflammatory cytokines.[9] Additionally, the inflammatory macrophage does not readily transition to the anti-inflammatory macrophage in diabetic wounds.[8]

Neutrophils also contribute to inflammation by releasing cytotoxic enzymes, inflammatory mediators, and free radicals that further oxidative stress. Oxidative stress leads to further tissue damage and delayed pathological healing in diabetic wounds.[10] Neutrophils produce excessive extracellular traps, or neutrophil extracellular traps (NETs), that target microorganisms. In diabetic wounds, NET production is upregulated, perpetuating an inflammatory state that hinders wound healing. Other molecular changes that contribute to excessive inflammation in diabetic wounds include micro-ribonucleic acid (miRNA). Although miRNA involved in healing was observed at the same levels in uninjured diabetic and nondiabetic skin, it was expressed differently once wounded, suggesting that miRNA also contributes to dysregulated inflammation.[8] Dysregulation of transcription factors[9] and epigenetics[11] further contribute to pathological inflammation in diabetic wounds.

Several studies in both diabetic and human models indicate that sustained inflammation is one of the main reasons for impaired healing in diabetic wounds. Prolonged inflammation delays the healing process, increasing the risk of chronic wounds. It is also associated with pathological scars, including hypertrophic[12] and keloid scars.[13] In diabetic mice models, reducing inflammation by inducing the transition from M1 to M2 macrophages, increased levels of several prohealing growth factors, thereby improving wound healing.[14] Thus, curbing inflammation during the healing process is crucial to minimize scarring in diabetic patients.[10]

Angiogenesis in Diabetic Wounds

Reestablishing blood supply is a crucial part of proper wound healing, and mostly occurs in the proliferation phase.[15] In uninjured skin, basal levels of proangiogenic factors, most notably vascular endothelial growth factor (VEGF), and antiangiogenic factors, such as Ang-1 and pigment epithelium-derived factor, are responsible for maintaining quiescent vasculature. When an injury occurs, the resulting hypoxic state stimulates the production of proangiogenic factors and the inhibition of antiangiogenic factors. Later, as wound healing progresses into the remodeling phase, vascular maturation factors, such as platelet-derived growth factor (PDGF), are necessary for vasculature pruning and maturation.[6]

In diabetic wounds, insufficient angiogenesis is one of the biggest contributors to poor wound healing, and occurs through several mechanisms. First, diabetic wounds have a deficit of necessary proangiogenic factors, possibly due to fewer macrophages that produce them.[5] Additionally, antiangiogenic factors are upregulated, while capillary maturation factors are downregulated. miRNAs, known to silence angiogenic genes, and matrix metalloproteinases also contribute.[16] In the later stages of wound healing, deficits in vascular maturation factors impair the maturation, regression, and stabilization of the newly formed capillary bed. This deficit in maturation factors delays progression of the healing process, increasing the risk of the wound becoming chronic or recurring.[5] Changes in diabetic vasculature and deficient oxygen delivery also impairs leukocyte migration into the wound, increasing the risk of infections.[17]

Scarring in Diabetic Wounds

The resolution of normal wound healing involves maturation, remodeling, and the formation of a scar. During this phase, excess collagen degrades, wound contracture occurs, and a scar is formed.[6] The scar results from the collagen and ECM produced by fibroblasts.[10] New cutaneous scars are different from the original tissue in a few ways: there are no hair follicles or sebaceous glands, and the collagen fibers are more densely packed.[18] In diabetes, it has been demonstrated that healing results in a scar characterized by lower collagen synthesis as well as changes in its structure compared with healthy scars. These changes result in a scar that has a reduced ability to contract and an increased density of collagen, both of which result in a scar with lower tensile strength and are detrimental to proper wound healing.[19] This poor contraction of diabetic wounds can be attributed in part to fibroblasts in diabetic wounds that are refractory to proliferate and have reached a senescent state. Without adequate wound contraction, diabetic wounds depend more on granulation and reepithelialization to heal, thus leading to poor tolerance of diabetic scars matrix to tensile forces and shear stress.[20]

Diabetes and Postoperative Wound Healing Complications

As described above, diabetic patients have significantly higher rates of various wound complications including infections, dehiscence, and scarring. Patients with diabetes have increased rates of surgical site infection across most surgical specialties, even when directly compared with elevated glucose postoperation. This suggests that diabetes increases the risk of infection through other mechanisms in addition to hyperglycemia.[21] Additionally, common comorbidities, such as obesity, significantly increase the risk of superficial and deep incisional surgical site infections.[22]

Following abdominal panniculectomies, diabetic patients have significantly higher rates of complications including wound dehiscence, infections, higher rates of reoperation, readmission, sepsis, and a longer postoperative hospital stay.[22] In abdominal wall reconstructions, diabetic patients are at a higher risk for infection of the standard mesh reinforcement technique used.[23] In breast reconstruction, diabetes has been associated with nipple-areolar complex

ischemia, dehiscence, and increased flap necrosis, leading to delayed wound healing.[24] In aesthetic breast surgery, diabetes has been associated with surgical site infection and other complications.[25] Diabetic patients undergoing augmentation mastopexy have higher complication rates.[26] In another examination of aesthetic surgeries of the face, body, and breast, diabetes increased the risk of infection. Interestingly, this same study found that cosmetic surgeries performed on the body had significantly higher rates of wound complications than those on the face or breast. However, the reason for this location-based difference in diabetic wounds remains unclear.[27] For surgeries of the hand, diabetes has been associated with wound healing complications including delayed wound healing, infection, and, depending on the operation, even postoperative stiffness.[28] This was found in trigger finger releases and is contested in carpal tunnel releases.[29–31] In facial fracture repairs, diabetic patients had longer hospitalizations and a greater risk of infection.[32]

Nutritional Status and Diabetic Wounds

Nutritional status is a significant predictor of wound healing outcomes.[33] In type 2 diabetic patients, nutritional status is a significant independent predictor of infections and overall healing outcomes in surgical wounds. Poor nutritional status is also directly associated with more severe wounds, as characterized by nutritional status (subjective global assessment) and Wagner grades, a commonly used scale to evaluate the severity of diabetic ulcers.[34]

Wound healing is a catabolic process, and therefore requires increased nutrition. In diabetic patients, wound healing is further driven to catabolism because diabetes leads to lower levels of anabolic hormones and more inflammatory cytokines that increase insulin resistance.[35] Additionally, diabetic patients are predisposed to malnutrition due to metabolic changes such as hyperglycemia, a negative nitrogen balance, increased resting energy expenditure, and protein loss.[34] Compared with an uninjured state, diabetic patients with wounds have reduced lean body mass, a predominance of fat catabolic processes, and ongoing protein loss due to microalbuminuria.[33] Combined, these mechanisms make it clear that the importance of nutrition is even greater in diabetic wound healing than in normal wound healing.

Nutritional status in diabetic patients can be improved by evaluating what macro- and micronutrient deficiencies exist, an evaluation of the degree of wasting of lean body mass, and incorporating a diet that meets these needs.[33] Supplementation of whey protein can help cutaneous wound closure by restoring proinflammatory and anti-inflammatory cytokine levels similar to that of nondiabetic wounds.[36]

Reduced baseline skin integrity is another significant contributing factor to poor diabetic wound healing. Uninjured diabetic skin is characterized by several changes including reduced thickness of the dermal layers and disorganized collagen. Diabetic skin accumulates significantly more advanced glycation end products (AGEs), which are pathogenic molecules that induce oxidative stress and contribute to skin stiffness and aging.[37] Taken together, these various changes in diabetic skin set up patients for poorer wound healing when an injury does occur. In diabetic mice models, the pathogenic effects of dietary AGEs were even more detrimental when wounded resulting in sustained inflammation and delayed healing.[38] Since diabetic patients already have elevated endogenous AGE production, it is important to restrict the dietary intake of additional AGEs during wound healing. Diabetic patients with wounds should take extra care to avoid foods high in AGEs (fats and meats) and modify food cooking and processing methods, such as avoiding frying, grilling, or roasting, to generate fewer AGEs.[39]

Glycemic Control in Diabetic Wounds

The normal perioperative stress response involves the secretion of glucagon, epinephrine, and cortisol, which work through counter-regulatory pathways and can lead to perioperative glycemic dysregulation. In diabetic wounds, these changes are more pronounced and detrimental to healing. Thus, it follows that specialty-specific guidelines recommend that plastic surgeons have an established process to screen for poor glycemic control, improve preoperative glycemic control, and ensure glycemic control is maintained in the postoperative phase.[25] Careful monitoring and adjusting the patient's diabetic treatment is important even in patients with preoperative controlled glycemia.[40]

Hemoglobin A1C (HbA1c), reflecting average glucose levels for the past few months, is a measure of chronic glycemic control. The American Diabetes Association recommends that diabetics keep their HbA1c below 7%.[41] Several studies corroborate the strong association between high HbA1c and poor wound healing outcomes. In a recent retrospective study of open, primary carpal tunnel release, diabetic patients with a HbA1c of 7.8% or above were at the highest risk for postoperative wound complications including slower healing, superficial infection, and unresolved carpal tunnel symptoms. This same study also found that compared with blood glucose levels, HbA1c is a stronger predictor of wound complications.[42] In another retrospective study of almost 500 various noncardiac surgeries, diabetic patients with a HbA1C below 7% had significantly fewer wound infections.[43]

There are several factors that can influence perioperative glycemic control and stratify wound healing outcomes. Psychosocial factors such as depression, stress, and lack of social support are strongly linked to poor glycemic control.[44,45] Another factor is the patient's diabetic treatment. An analysis of nearly 40,000 patients undergoing breast, hand/upper and lower extremity, abdominal, or craniofacial procedures found that compared with noninsulin-dependent diabetic patients, insulin-dependent patients are at a higher risk for wound dehiscence, infection, and longer hospital stays.[46] Postoperative glycemic control may also be influenced by the nature of the medical procedure itself. In abdominal subcutaneous fat reductions, abdominoplasties were found to reduce HbA1c levels more than bariatric surgeries at a 12-month follow-up in obese patients with type 2 diabetes.[47]

Treatments in Diabetic Wounds

The current standard of care for diabetic wounds involves debridement, controlling blood glucose and infections, patient education, and various other treatments to aid wound healing.[48] Although there are plenty of treatments that have demonstrated success in diabetic wound healing, there is little research comparing the effectiveness of different treatments.

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT), also known as vacuum-assisted closure, uses a vacuum pump to establish evenly distributed negative pressure to the wound. The negative pressure provides a moist environment conducive to healing, increases the clearance of bacteria and debris, promotes blood perfusion, increases granulation, and stabilizes the wound bed.[10] The International Consensus recommends NPWT for a variety of different wounds including those from trauma or reconstructive surgeries such as flaps and grafts.[49] It also recommends NPWT treatment be used in nonischemic diabetic wounds based on significant evidence that NPWT heals a higher proportion of wounds compared with non-NPWT.[50]

Platelet-Rich Plasma

Platelet-rich plasma (PRP) therapies consist of highly concentrated platelets which naturally secrete growth factors, cytokines, and interleukins to aid tissue regeneration. PRP is becoming increasingly common for a variety of applications. However, PRP has mixed results in diabetic wounds. A recent meta-analysis of studies on PRP treatment in diabetic foot ulcers (DFUs) found that PRP significantly improved the likelihood of complete healing, reduced the volume of the wound, and reduced healing times. The same meta-analysis found that PRP did not significantly affect wound complications or recurrences, but did significantly reduce adverse events.[51]

Growth Factors

Growth factors are endogenous signaling proteins that promote wound healing by stimulating angiogenesis, mitogenesis, granulation, remodeling, and reepithelization.[52,53] As mentioned previously, diabetic wound healing is hindered by deregulated growth factors. Notable growth factors that have successfully aided wound healing in nonhuman models are platelet-derived growth factors (PDGF), vascular endothelial growth factors (VEGF), and fibroblast growth factors (FGF). The only growth factor therapy that is currently approved for clinical use by the Food and Drug Administration (FDA) is PDGF in the treatment of DFUs.[54]

Cellular Dermal Regeneration Templates

Cell-based dermal regeneration templates have become increasingly effective and common to aid wound healing. However, few studies exist comparing the differences in mechanisms of action and outcomes between diabetic and nondiabetic wound healing. Amniotic and placental membrane templates function as extracellular matrices and take advantage of native growth factors, fibroblasts, epithelial cells, and mesenchymal stem cells (MSCs). Various amniotic and placental templates (e.g., Grafix, Epifix, AmnioExcel, NEOX) on the market have been shown to reduce healing time, adverse effects, wound infections, and dehiscence by aiding epithelialization in diabetic patients.[55]

Acellular Dermal Matrices

The International Consensus defines dermal matrices as acellular scaffolds that function as a collagen structure for tissue repair.[56] Dermal matrices (e.g., Integra, Graft-Jacket RTM, PriMatrix) function as a scaffold that supports fibroblast and endothelial cell infiltration, and eventually are replaced by host ECM in wound healing. Because they lack cellular components, dermal matrices have a significantly reduced risk of antigenic response in the patient. A review of 17 different primary studies of dermal matrix treatments in DFUs found that dermal matrices promote significantly faster and more complete healing.[48]

Repurposed Medications

Using existing diabetes medications can independently aid in diabetic wound healing. The advantage of existing FDA-approved medications is that it is more cost-effective and convenient to repurpose them for wound healing. Some of the medications that are supported by strong evidence to possess wound healing benefits include dipeptidyl peptidase 4 inhibitors (DPP-4i), statins, phenytoin, and metformin.[57] DPP-4is, such as sitagliptin and linagliptin, are antidiabetic medications that may minimize scar formation by reducing excessive production of ECM.[58] In human diabetic subjects following median sternotomies, DPP-4is reduced the risk of hypertrophic scarring and keloids by almost half.[59] However, certain medications have been implicated in disrupting wound healing including anticonvulsants, steroids, antibiotics, angiogenesis inhibitors, and nonsteroidal anti-inflammatory drugs.[6]

Stem Cell Therapies

Mesenchymal stem cells (MSCs), often from adult bone marrow or blood, are an effective treatment for a variety of different wounds including diabetic ones. A review of preclinical and clinical studies of MSC therapies in diabetic wounds found that MSCs can greatly accelerate healing by reducing inflammation, increasing angiogenesis, and improving cell migration. This same review also found evidence that endogenous MSCs in diabetic patients may have impaired functionality. Therefore, allogeneic MSCs may be a better treatment option than autologous MSCs, despite a higher risk for an immune response.[60]

More recently, induced pluripotent stem cells (iPSCs), have demonstrated the ability to significantly improve vascularization, blood perfusion, granulation, and reepithelialization in diabetic mice models. iPSC therapies are based on dedifferentiating any adult somatic cell via the introduction of certain transcription factors. iPSCs can then redifferentiate into any cell from all three germ layers. Furthermore, iPSCs may have greater potential than MSCs for future autologous patient-specific stem cell therapies.[4,61]

Debridement

The International Consensus recommends that chronic diabetic wounds be first debrided, followed by adjunct therapy.[62] Debridement is the removal of substances inhibiting proper healing such as hyperkeratotic epidermis, necrotic tissue, bacteria, and other foreign debris.[63] Debridement serves to decrease bacterial burden, increase the wound bed's responsiveness to adjunct therapies, and obtain quality cultures for continued treatment.[53] There are several methods of debridement including physical (sharps or surgical), enzymatic, biological, and autolytic.[64] Surgical debridement may be the quickest and most commonly utilized approach in diabetic wounds. Enzymatic debridement is another commonly used method and relies on chemical agents derived from various microorganisms. A systematic review found that enzymatic debridement promotes wound healing in DFUs.[65] One study found that enzymatic debridement may result in greater wound area reduction and less pain compared with mechanical debridement.[66]

Other

Human skin allografts and substitutes (e.g., Theraskin, Graftskin, Dermagraft, OrCel) are often utilized to cover exposed wounds and have also demonstrated significantly faster and better wound closure compared with control treatment (usually saline gauze) in DFUs.[55] Various nitric oxide treatments in diabetic wounds have been shown to improve granulation, angiogenesis, and wound closure.[67] Hyperbaric oxygen therapy is another approach that may improve healing in diabetic patients.[68] Direct glycemic control via local insulin therapy can significantly improve outcomes. In full-thickness diabetic wounds from necrobiosis, trauma, and postneoplasm resections, insulin administration was found to significantly improve vascularization, fibrosis, and the mean temperature of the wound.[69]

Conflict of Interest
None declared.

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