The Diabetic Foot: A Historical Overview and Gaps in Current Treatment

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Significance: The number of patients with diabetes is rapidly increasing around the world. A large percentage of this population can be expected to develop diabetic ulcers. The economic, social, and public health burden of these ulcers is enormous. It is a common problem that is tackled every day by many healthcare workers throughout the world.

Recent Advances: Many pioneers contributed to the good standard of care we have today when treating diabetes and its complications. Current treatment of diabetic foot ulcers involves a multidisciplinary team approach, controls the underlying disease, and treats the wounds using debridement, different wound dressings, and redistributes pressure off the wound.

Critical Issues: Since the discovery of the association between diabetes and gangrene of the foot 160 years ago, there have been developments and milestones that are the base of our treatment today. However, with all the modern wound treatment available today, there is a group of patients with hard-to-heal ulcers who do not seem to respond to the regular treatment.

Future Directions: It is clear that more research has to be done to improve techniques that will enhance wound healing in chronic wounds. Innovative techniques will be discussed and outlined in this article.

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SCOPE AND SIGNIFICANCE

SINCE THE DISCOVERY of the association between gangrene of the foot and diabetes 160 years ago, many achievements have been made in treating diabetic foot ulcers. Ulcers as a complication of diabetes is common practice: hospitals around the world treat patients with diabetic ulcers on a daily base.

which the treatment options are very limited. Innovative wound treatment is developed worldwide, but evidence in this field is difficult to find, since controlled studies are few and the majority are of poor methodological quality. It is clear that more research needs to be done to provide evidence that will change protocols for routine care that are used in hospitals today.

TRANSLATIONAL RELEVANCE

Diabetic ulcers are a serious health problem. Many hospitals have large outpatient clinics where they treat patients with chronic diabetic ulcers. Although the treatment of diabetic ulcers has developed greatly over the past one and a half century, the treatment of chronic diabetic ulcers remains a significant problem in

CLINICAL RELEVANCE

The management of chronic foot disease in patients with diabetes remains a major therapeutic challenge for doctors throughout the world. Patients with chronic diabetic ulcers have to deal with pain, infection, hospital stays, and amputations. For patients and their families, this results in a poor quality of life. For the

community, it results in large healthcare expenditures, which could be reduced if a proper, evidence-based treatment for these chronic ulcers would exist.

DISCUSSION

Recognition of the diabetic foot ulcer and great medical discoveries

Halfway through the 19th century the problem of diabetic foot ulcers was described for the first time. It was Marchal de Calvi in 1852 and Thomas Hodgkin in 1854 who realized that there was an association between diabetes and gangrene of the foot.^{1,2} At that point in time, it was common to treat ulcers by prolonged bed rest, although it was noticed that the wounds would return once the patient started to mobilize again. Frederick Treves (1853–1923) was an extremely talented surgeon, famous for performing the first appendectomy in 1888. He suggested a different approach for the treatment of ulcers, using sharp debridement of callus after application of linseed poultices to soften the callus. After debridement, an antiseptic cream would be applied to the thin fresh pink epidermis. Once the patient started mobilizing again he instructed the patient to wear a thick pad of felt plaster over the healed ulcer to reduce pressure and prevent recurrence of the wound.³ At the end of the 19th century therefore, Treves had established three important principles in the treatment of ulceration of the foot: sharp debridement, off-loading pressure, and education about foot care and footwear.⁴

One of the landmark medical discoveries of the 20th century was the isolation of the internal secretion of the pancreas at the University of Toronto by Frederick Banting and his companions. The introduction of therapeutic insulin following that discovery allowed patients affected by the disease to live an almost normal life. Before insulin therapy, gangrene followed diabetic coma as a cause of death in patients with diabetes.⁵ After the discovery of insulin, it became apparent that insulin was not a cure for diabetes; although it decreased the proportion of patients dying from diabetic coma, the proportion of patients dying from foot disease increased significantly.⁶

The introduction of insulin caused patients to live longer, but they experienced complications that had not been seen before.⁷ This caused an enormous increase in the workload at hospitals throughout the world. Elliot Joslin, MD (1869–1962), a famous American diabetologist noticed this increase in workload and established the first hospital foot clinic at the New England Deaconess

Hospital (Boston, MA) in 1928.⁸ He was also the founder of the multidisciplinary team approach in the treatment of diabetic foot ulcers. In the clinic at Deaconess Hospital, he assigned one graduate nurse and two pupil nurses to educate patients and extended the teamwork with chiropodists outside the hospital.⁹

The discovery of penicillin by Scottish scientist Alexander Fleming in 1928¹⁰ led to a more conservative approach to surgery. It also made primary suture a safer option, shortening the time required to heal and producing a better scar. In those patients who still needed a major surgery, it contributed to a reduction in mortality of almost half.⁴ For example, at Deaconess Hospital, the mortality for major amputations fell from 11.6% in the years 1923–1943 to 6.6% in 1944–1949.^{11,12}

Another important achievement of the 20th century was the ability of revascularization and limb salvage. Frank Wheelock (1919–2006) was the first American surgeon responsible for the end-to-side femoral popliteal bypass graft.¹³ Emphasis on foot preservation became increasingly important and resulted in the development of distal revascularization to restore foot perfusion.¹⁴ Angioplasty was initially described by an interventional radiologist Charles Dotter in 1964. In January of that year, he successfully dilated a superficial femoral artery in an 82-year-old patient. Toward the end of the 20th century, the angioplasty technique was developed further and it became possible to revascularize distal arteries down to foot arteries. It was found to be a safe and effective method for limb salvage in patients with diabetes.¹⁵

The 21st century: a high standard of care

The Infectious Diseases Society of America (IDSA) developed a clinical practice guideline for the diagnosis and treatment of diabetic foot infections. The information provided in this guideline was gathered from leading hospitals and universities around the world. It was published for the first time in 2004 in the October issue of *Clinical Infectious Diseases*. The primary purpose of this guideline was to help reduce the medical morbidity, psychological distress, and financial costs associated with diabetic foot infections.¹⁶

The guideline recommends treatment of diabetic foot ulcers with surgical debridement, redistribution of pressure off the wound, and a selection of dressings that allow a moist wound environment and control excess exudation. Furthermore, it encourages revascularization of the leg if necessary, stimulates the use of antibiotics, and active search for osteomyelitis.

Revascularization. Diabetes is one of the risk factors for peripheral arterial disease (PAD). The vascular state of a patient with a diabetic ulcer should always be investigated. Several large studies have shown that PAD is present in up to 50% of the patients with a diabetic foot ulcer. This could range from mild disease with limited effect on wound healing to severe ischemia with a high risk of amputation.¹⁷ Early detection and treatment of PAD is important in limb salvage. It is alarming, however, that the Eurodiale cohort shows that less than 50% of the patients with diabetes and an ankle brachial pressure index <0.5 underwent adequate vascular evaluation and subsequent revascularization. This proves that there is still room for improvement in the delivery of care.¹⁸ Patients who underwent successful revascularization appear to do better than those who undergo major amputation, half of whom are dead within 3 years.¹⁹ There are currently no randomized controlled trials directly comparing open with endovascular revascularization in patients with diabetes and an ischemic foot ulcer. This means that more research is needed, not only to differentiate between the revascularization options but also to determine the right indication and timing for treatment.

PAD is more difficult to treat in patients with diabetes than in patients who do not have diabetes. The atherosclerotic lesions in patients with diabetes are often multilevel with a high prevalence of long occlusions.²⁰ This, combined with severe arterial calcification, increases the technical challenges of revascularization (open or endovascular). Furthermore, patients with diabetes often have other comorbidities such as neuropathy, renal failure, and the presence of abnormalities in coronary and cerebral arteries, which makes it difficult perform revascularization in time.

Treatment of infection. Patients with diabetes who develop infection with their ulcers need urgent antibiotic treatment. The most common pathogens in acute, previously untreated, superficial infected foot wounds in patients with diabetes are aerobic gram-positive bacteria, particularly, *Staphylococcus aureus* and beta-hemolytic streptococci (group A, B, and others). Infection in patients who have deep limb-threatening infection or chronic wounds is usually caused by a mixture of aerobic gram-positive, aerobic gram-negative (e.g., *Escherichia coli*, *Proteus* species, *Klebsiella* species), and anaerobic organisms (e.g., *Bacteroides* species, *Clostridium* species).²¹ The antibiotic regimen should therefore at least have anti-staphylococcal coverage, but which antibiotics should be used

depends on the severity of infection, the duration of the ulceration, and the allergies of the patient.²² The aim of antimicrobial therapy is to cure the infection, not to heal the wound. Extended treatment with antibiotics increases the risk of drug-related toxic effects and development of antibiotic resistance.²³

When dealing with infected ulcers, the attending clinician should obtain material for a wound culture when possible. Specimens are preferred to wound swabs, because they provide more sensitive and specific results.²⁴ Other good cultures can be obtained by aspirating pus or other fluids from the wound. Furthermore, it is useful to use a permanent marker to mark the edge of the cellulites around the ulcer. In the next hours to days, the cellulites can be closely monitored using the permanent marker as a landmark; when the cellulites increase (rapidly) beyond the permanent marker line, the antibiotics used are probably not covering all the specific bacteria in the wound. The severity of the infection can be demonstrated by obtaining a blood sample from the patient (C-reactive protein, complete blood count, and inflammatory markers).²⁵

One of the most difficult problems of infected ulcers is the possibility of developing osteomyelitis. Osteomyelitis can be difficult to diagnose. If the bone is visible in an ulcer, osteomyelitis could be present. This could be evaluated using the probe-to-bone test and radiological imaging. Plain radiography is one of the most common choices for radiological imaging because it is readily available and cheap. However, for the diagnosis of osteomyelitis, plain radiography has relatively lower sensitivity (40–60%) and specificity rates (60–90%) than magnetic resonance imaging (MRI) and nuclear medicine scintigraphy studies. Therefore, plain radiography is mainly used for the evaluation of major structural changes.²⁶ MRI is currently considered as the best modality for the evaluation of soft tissue and bone marrow changes associated with the diabetic foot.²⁷ The sensitivity and specificity of MRI for the detection of osteomyelitis are high, making it useful as a diagnostic instrument.²⁸ The downside of MRI is that it is expensive and not readily available in every hospital. Osteomyelitis can be the underlying problem of a hard-to-heal ulcer and should be treated first before closure of the wound is attempted. Treating osteomyelitis involves surgical resection of all infected bone, although some studies suggest that long-term antibiotic treatment can also be effective.²⁹

Wound dressings. The wound healing in patients with diabetes is impaired by both intrinsic

and extrinsic factors. Extrinsic factors include repeated trauma to the foot, mechanical stress as well as neuropathy, and ischemia as a result of vascular disease.³⁰ Intrinsic factors affecting healing of the wound include hyperglycemia and an altered immune function. Patients with a lower HbA1C experience faster wound healing of foot ulcers than patients with a higher HbA1C, thereby emphasizing a clinical correlation between hyperglycemia and impaired wound healing.³¹ In diabetic ulcers, an altered pattern of cytokine appearance in the wound environment may contribute to delayed wound healing.³²

For a diabetic ulcer to heal, off loading of pressure, surgical debridement, correction of hyperglycemia, the use of antibiotics, and revascularization are indispensable. Wound dressings alone cannot be used to treat a diabetic ulcer, they must be seen as an addition to all the above. There are many different types of wound dressings, all aimed at creating a neutral wound environment. This include the use of simple wet gauzes, calcium sodium alginate dressing (Kaltostat®), hydrofiber wound dressing (Aquacel®), or any other form of noninvasive treatment. Different clinics will use different dressings throughout the world. There is little evidence to support the choice of any one dressing or wound application in preference to any other in an attempt to promote healing of (chronic) ulcers of the foot in patients with diabetes.³³

Topical negative pressure. Topical negative pressure wound therapy is a technique that was developed during the 1990s. It is a vacuum dressing, attached to a pump, which encourages excess fluids to leave the wound and promotes wound healing. The use of this method is now widely accepted and can also be used safely in the treatment of the diabetic foot.³⁴ Topical negative pressure is mainly used after surgery and debridement of the diabetic foot; it is not recommended when treating an infection. There is also no evidence at this time that it encourages wound healing in the hard-to-heal diabetic ulcer.

Chronic diabetic ulcers, the need for innovative treatment and more research

Although the IDSA guideline provides an excellent starting point for the treatment of many patients with diabetic foot ulcers, there is no recommendation as to how to treat patients with chronic, hard-to-heal ulcers (Fig. 1). Ulcers are considered chronic when they do not show any clinical improvement during a period of 3 months.¹⁶ Chronic diabetic ulcers are considered as a large

Figure 1. Typical chronic ulceration in a patient with diabetes. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

health burden, not only for the patient as an individual (pain, infection, hospital stay, amputations) but also for healthcare expenditures in general.³⁵ In the United States alone, 6.5 million people are affected by chronic wounds (responsible for over 25 billion dollars of health expenditure costs). This number includes not only patients with diabetic ulcers but also pressure ulcers and venous ulcers.³⁵ It is estimated that in developed countries, 1–2% of the general population will develop a chronic wound in their lifetime.³⁶ It is expected that the number of patients with diabetes will increase over the next decade. The population in general will become more obese, also the elderly, increasing the number of patients with diabetes. Up to 25% of the patients with diabetes will develop an ulcer in their lifetime.³⁷ The exact number of patients who are dealing with hard-to-heal diabetic ulcers is not known. It is a considerable percentage of the patients who suffer from diabetes, since the specialized outpatient clinics of our hospitals are flooded with patients every day.

If a diabetic ulcer fails to heal, despite good wound care, the wound management should be reevaluated. This should include ensuring adequate perfusion of the leg and foot and addressing infection, especially osteomyelitis. One should also take a biopsy of a wound when the healing time is prolonged; a malignancy could be the cause of the nonhealing ulcer.¹⁶ Once all underlying problems of wound healing have been addressed, other adjunctive treatments could be considered.

At this moment in time, there is little evidence, other than the recommendations of the IDSA guideline, for which treatment to use when treating

Table 1. *Different recommended approaches, including level of evidence*

<i>Treatment</i>	<i>Diabetic Ulcers</i>	<i>Chronic Diabetic Ulcers</i>
Debridement	Recommended (2A)	Recommended (2A)
Redistribution of pressure	Recommended (1A)	Recommended (1A)
Different wound dressings	Recommended (2A)	Not enough evidence
Antibiotics	Treatment of aerobic gram-positive bacteria (2A)	Broader treatment required (2A)
Topical negative pressure	Not when treating an acute infection (4)	Not enough evidence
Hyperbaric oxygen treatment	Some evidence (5)	Not enough evidence
Platelet-rich plasma	Not enough evidence	Not enough evidence

chronic ulcers in patients with diabetes. The outcome of management of these chronic ulcers is poor and there are many uncertainties regarding the optimal approach to the management of these ulcers. For these reasons, the International Working Group of the Diabetic Foot (IWGDF) has issued guidelines and reviews to inform protocols for routine care and highlight areas that could be considered for further study.³³ Analysis of this evidence is difficult: the number of controlled studies is small and the majority are of poor methodological quality. When reviewing the literature, one finds a variety of different approaches and innovative methods to treat hard-to-heal diabetic ulcers. The most important gap in current treatment is, however, the lack of evidence in the treatment of chronic ulcers. In the following paragraphs, different aspects of wound treatment are listed, which should at least be considered when treating patients with chronic diabetic ulcers.

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy (HBOT) involves breathing pure oxygen in a pressurized room. In a HBOT room, the air pressure is raised up to three times higher than atmospheric pressure. Under these conditions, the lungs can gather up to three times more oxygen than would be possible breathing pure oxygen at normal air pressure. The blood carries the oxygen throughout the body, stimulating the release of growth factors and stem cells, which promote healing. Furthermore, HBOT reduces tissue edema by vasoconstriction in nonischemic tissue.³⁸ The treatment of diabetic foot ulcers is accomplished with daily treatment sessions ranging from 90 to 120 min at a time. Five to 15 min are required for compression and decompression. Recent studies have shown that HBOT can be a useful addition in the treatment of hard-to-heal diabetic ulcers.³⁹ In the past, small, prospective series dominated the publications on HBOT. Recently, a well-designed, randomized, double-blind,

placebo-controlled trial showed that healing rates increase significantly in the HBOT group.⁴⁰ Again, more evidence needs to be gathered to define the population most likely to benefit from this therapy.

Platelet-derived growth factors. Platelets play two essential roles in the wound healing process: hemostasis and the initiation of wound healing. After platelet activation and clot formation, growth factors are released. In ordinary blood, the number of platelets is $\sim 200,000/\mu\text{L}$. In contrast, platelet-rich plasma (PRP) has a concentration of at least five times that amount.⁴¹ Autologous PRP consists of a fibrin scaffold derived from the patient's blood, together with cytokines, chemokines, and growth factors.⁴² The exact mechanism of action remains unknown. It is thought that PRP stimulates wound healing by molecular and cellular induction of normal wound healing responses, similar to that seen with platelet activation.⁴³

Autologous growth factors from concentrated platelet suspensions have been used to treat wounds for years. The first article on platelet-derived wound healing was published more than 25 years ago. Since then, many studies with platelet suspensions have been published. However, the study design, population, clinical outcome, and methodological quality vary between citations, making conclusions difficult. A recent systematic review shows that there is scientific evidence regarding favorable outcomes of the use of PRP for the treatment of diabetic ulcers.⁴⁴ There is one major reason for the limited use of platelet-derived products. The cost of harvesting autologous platelets is high.

There are many more methods to enhance wound healing (use of larvae, bioengineered skin, electromagnetic stimulation, ultrasound, and other therapies). Evidence for these therapies is very thin and not investigated further for this review (Table 1).

SUMMARY

Since the recognition of the association of gangrene of the foot and diabetes, many achievements have been made to treat foot ulcers and infections. The multidisciplinary approach is encouraged in every hospital involved in treating diabetic foot ulcers. However, more than one and a half centuries later, there is still no cure for hard-to-heal diabetic ulcers. There are some promising methods that need to be investigated further and will

hopefully tackle this health burden in the years to come.

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In this article, some highlights and milestones in the approach of the treatment of diabetic foot were discussed. It is difficult to include all of the people who have played a major role in this. The author would like to express her regrets in advance for any abbreviation or omission of any individual in this article. No funding sources were used for this article.

AUTHOR DISCLOSURE AND GHOSTWRITING

This work did not require the approval of an Ethics Committee. The author has no financial involvement in any (commercial) associations that might have a conflict of interest with this article. The content of this article was expressly written by the author listed. No ghostwriters were used to write this article.

TAKE-HOME MESSAGES

- Medical discoveries over the past one and a half centuries have led to a high standard of treatment of diabetic ulcers worldwide.
- A multidisciplinary approach for the treatment of diabetic ulcers is indispensable.
- Every patient with a diabetic ulcer should have their vascular status reviewed.
- The treatment of patients with chronic diabetic ulcers is a slow and tedious process, which involves time and effort from both the patients and clinicians. Due to this slow healing process, the costs of treatment of chronic wounds are high.
- More evidence for the treatment of chronic diabetic wounds is required; the treatment options that are readily available now are not aimed at chronic wounds.

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Abbreviations and Acronyms

HbA1c = glycated hemoglobin, which identifies average plasma glucose concentration
 HBOT = hyperbaric oxygen therapy
 IDSA = The Infectious Diseases Society of America
 IWGDF = International Working Group of the Diabetic Foot
 MRI = magnetic resonance imaging
 PAD = peripheral arterial disease
 PRP = platelet-rich plasma