



# A Review: Matrix Metalloproteinase-9 Nanoparticles Targeted for the Treatment of Diabetic Foot Ulcers

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**Abstract:** Diabetes foot ulcers are a leading cause of death in diabetic individuals. There are very few medicines and treatments that have received regulatory clearance for this indication, and numerous compounds from various pharmacological classes are now in various stages of clinical studies for diabetic foot ulcers treatment. Multiple risk factors contribute to diabetic foot ulcers, including neuropathy, peripheral artery disease, infection, gender, cigarette smoking, and age. The present difficulties in diabetic foot ulcers treatment are related to bacterial resistance to currently utilized antibiotics. Inhibition of the quorum sensing (QS) system and targeting matrix metalloproteinase-9 (MMP-9) are promising. This study focuses on the difficulties of existing treatment, current treatment technique, and novel pharmacological targets for diabetic foot ulcer. The electronic data base search diabetic for literature on foot ulcers treatment was carried out using Science Direct, PubMed, Google-Scholar, Springer Link, Scopus, and Wiley up to 2021. Becaplermin, a medication that targets MMP-9, glyceryl trinitrate, which inhibits the bacterial quorum sensing system, probiotic therapy, and nano technological solutions are just a few of the novel pharmaceuticals being developed for diabetic foot ulcers treatment. A combination of therapies, rather than one particular agent, will be the best option for treatment of Diabetes foot ulcer since it is multifactorial factors that render occurs of diabetic foot ulcer.

**Keywords:** diabetic foot ulcer, gangrene, probiotics, antimicrobial peptide

## Introduction

Diabetes mellitus (DM) is a long-term metabolic disorder characterized by hyperglycemia.<sup>1</sup> According to the World Health Organization's global diabetes report,<sup>2</sup> the global prevalence of diabetes was 422 million in 2014, with the highest trend in the Eastern Mediterranean region, increasing from 5.9% in 1980 to 13.7% in 2014, with the global prevalence expected to creep up to 592 million by 2035. The World Health Organization defines diabetic foot (DF) as

the foot of a diabetic patient that has the potential risk of pathologic consequences including infection, ulceration, and/or destruction of deep tissues associated with neurologic abnormalities, various degrees of peripheral vascular disease, and/or metabolic complications of diabetes in the lower limb.<sup>2</sup>

Early identification of the at-risk foot should be given high clinical priority in order to avoid the development of foot ulcers.<sup>3</sup>

## Epidemiology

Zhang et al found that Belgium has the greatest prevalence internationally in a recent systematic review and meta-analysis of data from various continents

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(16.6%)<sup>4</sup> The global prevalence of DFU was 6.3%, with type 2 diabetes having a greater prevalence (6.4%) than type 1 diabetes (5.5%). Belgium has the highest prevalence (14.8%), followed by Canada and the United States (13.0%). North America has the greatest continental prevalence (13%) of any continent. Africa accounted for 7.2%, Asia for 5.5%, and Europe for 5.1%.<sup>5</sup> According to study by Degu et al, in Ethiopia the prevalence of diabetic foot ulcers in Addis Ababa, Jimma, Gondar, Bahir dar, Mekele, Arba Minch, and Dessie, is 1.36%, 25.76%, 13.62%, 21.22%, 12.28%, 14.87% and 1.85% respectively.<sup>6</sup>

In addition, studies by Mariam et al at the University of Gondar Referral Hospital on the Prevalence of Diabetic Foot Ulcer and Associated Factors among Adult Diabetic Patients who attend the Diabetic Follow-Up Clinic showed the same results (13.6%).<sup>7</sup> Non-healing foot ulcers are the cause of about 85% of lower extremity amputations. A diabetic person's lifetime risk of having a foot ulcer might be as high as 25%. Lower limb amputations are 15 times more common in diabetes individuals than in non-diabetics.<sup>8</sup>

## Etiology and Risk Factors

DFUs are caused by a number of interconnected causes, the most frequent of which are peripheral neuropathy and Peripheral Arterial Disease (PAD). As a result, DFUs are often categorized as neuropathic, neuroischaemic, or ischaemic ulcers. Since the 1990s, the prevalence of neuroischaemic and ischaemic ulcers has increased from about one-third of patients to become the most prevalent aetiology of DFUs.<sup>9,10</sup> This is most likely owing to increasing knowledge of the significance of ischaemia in DFUs and their negative consequences, however it might also be due to improved diagnostic techniques, which has implications for diagnostic criteria recommendations.<sup>10,11</sup> During diagnosis, 70–83% of diabetes patients with severe soft-tissue infections are polymicrobial.<sup>12</sup> Furthermore, as compared to acute wounds, chronic DFUs have unusually high Matrix metalloprotease (MMP) levels, which promotes tissue degradation and eventually hinders normal healing processes.<sup>13</sup>

## Gangrene in Diabetics

Diabetes and long-term smoking both raise the risk of gangrene.<sup>14</sup> Gas gangrene, a rare consequence of diabetic foot ulcers, can occur in people with these persistent non-healing lesions.<sup>15</sup> Gangrene is produced by

a reduction in blood flow to the afflicted tissues, which results in cell death owing to a hypoxic environment and cellular damage caused by Advanced Glycation End Products.<sup>16</sup>

## Wound Healing Process in Diabetes Mellitus and in Normal Wound Healing

In healthy people, wound closure consists of several sequential processes: rapid hemostasis, which involves platelet aggregation to form the platelet plug; inflammation, which involves neutrophils, Macrophages, and mast cells releasing proinflammatory cytokines; and wound contraction, which occurs when inflammation decreases, angiogenesis occurs, keratinocytes and fibroblasts migrate, and wound contraction occurs.<sup>17,18</sup>

Diabetes mellitus (DM) affects wound closure processes, beginning with a reduction in fibrinolysis and an imbalance of cytokines, which produces a change in wound closure.<sup>18</sup> Hyperglycemia also limits angiogenesis and cell migration, resulting in inadequate re-epithelialization; similarly, fibroblasts' poor synthesis of extracellular matrix (ECM) contributes to the problem of insufficient wound healing.<sup>19,20</sup>

During wound-induced hypoxia, vascular endothelial growth factor released by macrophages, fibroblasts, and epithelial cells phosphorylates and activates endothelial nitric oxide synthase in the bone marrow, resulting in an increase in NO levels and the mobilization of bone marrow EPCs to the circulation. SDF-1a, a chemokine, increases EPC homing to the site of damage, where they engage in neovasclogenesis. Gallagher et al<sup>20</sup> demonstrate that in a diabetic mouse model (right), eNOS phosphorylation in the bone marrow is reduced, limiting EPC mobilization from the bone marrow into the circulation. They also reveal that SDF-1a expression is reduced in diabetic wound epithelial cells and my fibroblasts, which inhibits EPC homing to wounds and hence restricts wound healing. The authors go on to show that inducing hyperoxia in wound tissue (through HBO treatment) activated multiple NOS isoforms, raised NO levels, and improved EPC mobilization to the circulation. These findings imply that HBO treatment coupled with SDF-1a administration might be a promising therapeutic approach for accelerating diabetic wound healing, either alone or in conjunction with established clinical procedures.<sup>21–26</sup>

## Current Approach to the Diabetic Foot Ulcers Management Wound Dressing

Before putting a sterile dressing, the wound should be cleaned with an antiseptic solution. Antiseptics have a larger spectrum of activity and various targets, including bacteria, fungus, viruses, and protozoa.<sup>27</sup> The applications and indications for antiseptics vary; nevertheless, their use as preventive anti-infective agents for open wounds such as lacerations, abrasions, burns, and chronic ulcers has been a source of considerable debate for some years.<sup>28</sup> Povidone-iodine, chlorhexidine, alcohol, acetate, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), boric acid, silver nitrate, silver sulfadiazine, and salt are the most widely used antiseptic solution items in clinical practice today. In order to facilitate the removal of a dressing, the moisture of the material should be adequate enough to prevent adherence to the surrounding skin. In the case of dry DFUs, the use of hydrogel has been suggested.<sup>29,30</sup>

## Antimicrobial Peptides

Antimicrobial peptides (AMPs) are host defense peptides because they have properties of both the innate and adaptive immune systems, which are found in nearly all species. AMPs are short polypeptides with an amphipathic structure and a cationic property (usually no more than 60 amino acids). Most AMP serve as the initial line of defense against the spread of a wide range of pathogens, including bacteria, fungus, viruses, and protozoan parasites.<sup>31–33</sup> Most AMPs are now utilized in clinical trials, and they are used to treat a variety of human ailments, including diabetic foot ulcers. For example, the Neuprex medicines (RBPI 21) are designated as orphan medications by the FDA. Despite the fact that the degree of toxicity of Neuprex is unclear, research on a topical route for its administration are being examined.<sup>34</sup> A recent study of accessible patent information on the therapeutic application of AMPs from 2003 to 2015 showed that the majority of the claimed AMPs were described not only as strong antibiotics, but also as efficient modulators of inflammation or neutralizers of pathogenic toxin.<sup>35</sup>

## Phenytoin

Phenytoin promotes improves healing through several mechanisms, including stimulation of fibroblast proliferation, improvement of granulation tissue formation, reduced collagenase activity, inhibition of glucocorticoid activity,

and direct or indirect antibacterial activity via inflammatory cells and neovascularization.<sup>36</sup>

Heparin is extensively praised for its beneficial effects on local tissue microcirculation and oxygenation by inhibiting thrombin production and improving fibrin gel porosity. This greatly promotes fibrinolysis, demonstrating its use in DFUs. Aside from its significant anti-thrombotic benefits, heparin is also reported to be viable in vitro, encouraging heparin sulfate synthesis in endothelial cell cultures.<sup>37</sup>

## Growth Factors

PDGF is a mitogenic bioactive substance that induces the differentiation of undifferentiated mesenchymal cells into mature tissue, resulting in the creation of new cells and an increase in wound healing. Furthermore, platelets have the potential to stimulate tissue migration and angiogenesis from a pre-formed vascular bed, as well as provide vascular endothelial synthesis with a last boost by causing vasodilation.<sup>38</sup> Defective IGF expression in DM patients' dermal fibroblasts has been demonstrated, and this may be responsible for the delayed wound healing observed in this population. Some wound healing therapies continue to target variables that promote tissue IGF.<sup>39</sup>

## Anti-Diabetic Drugs and Diabetic Foot Ulcers

### Insulin

Maintaining normoglycemia with adequate food and/or anti-diabetic medications is one of the most effective strategies of preventing diabetes complications. Insulin intravenous injection was observed to improve DFU healing at a reported healing rate of 30.3%.<sup>40</sup> It is referred to as a physiological glucose-lowering agent. The use of dermal insulin administration as a healing agent in DFUs has lately been a source of concern.<sup>41,42</sup>

### Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 is a large-scale enzyme that causes the inactivation of GLP-1 and GIP cretin hormones. In T2DM,<sup>43</sup> DPP-4 inhibitors are oral medications authorized by FDA which block dipeptidyl peptidase and improve the flow of incriminated hormones while providing glycemic control and enhanced cell activity of islet. DPP-4 inhibitors, such as sitagliptin, vildagliptin, and anagliptin, are used to treat diabetes by lowering blood glucose levels. Some medicines, such as Exendin-4, are glucagon-like peptide-1 (GLP-1) receptor agonists produced from the saliva of

the Gila monster, a huge poisonous lizard located in the United States' South Western area; it is dermal application of this drug expedited DFU wound healing in experimental animals with or without the addition of adipose-derived stem cells.<sup>44,45</sup>

### Use of Enzymes in Diabetic Foot Ulcers

Urokinase, also known as Urokinase-type plasminogen activator (uPA), is a serine protease that is released and produced by keratinocyte cells. Mostly expressed during wound healing by migrating keratinocytes.<sup>10,46</sup> Patients with DFU showed rapid improvement in clinical signs and symptoms following a continuous, 96-hour infusion of Urokinase via the femoral artery, according to a limited trial of 6 patients. This can be attributed to the restoration of collateral blood flow in and around the site.<sup>47</sup>

### Use of Stem Cells in Diabetic Foot Ulcer

Stem cells such as adipose-derived stem cells and endothelial progenitors cells imported from bone marrow or other sources can generate blood vessel and extracellular matrix cell precursors in DFUs.<sup>48,49</sup> These progenitor cells can be implanted into the wound to stimulate the creation of new cells in the wound region.<sup>50</sup>

### Natural Products

Several investigations reported the benefits of plants, such as Aloe vera, Salvia miltiorrhiza, Mimosa tenuiflora, Alchemilla vulgaris, Angelica sinensis, and Moringa oleifera which are used in a wide range of cosmetic products, such as ointments, creams, and gels. Moringa oleifera has been shown to reduce DFU wound size, improve tissue granulation, and significantly reduce the levels of a multitude of cytokines including, but not limited to, TNF- $\alpha$ , IL-6 and VEGF.<sup>51,52</sup>

Honey contains antibacterial, antioxidant, and anti-inflammatory properties that help to cure wounds and burns while causing no harm. In recent years, therapy with honey has sparked considerable interest as an alternative treatment for DFUs, with several research evaluating various characteristics of honey to treat DFUs at various stages.<sup>53,54</sup> A recent study compared honey dressings to conventional saline solution dressings and discovered that honey dressings were more efficient in terms of healing time and number of wounds cured after 120 days.<sup>55</sup>

## Challenges to Current Treatment for Diabetic Foot Ulcer

The primary treatment problems associated with DFU are believed to be diabetic foot infections and delayed wound healing.<sup>56</sup> Because probiotics have the capacity to boost the immune system, have anti-inflammatory properties, and therefore might accelerate the wound healing process, the concept of probiotic consumption is fascinating and important in light of the rising worldwide antimicrobial drug resistance concerns.<sup>57,58</sup> According to WHO, 60% of bacteria are becoming resistant to key antibiotics, and in the next years, all diseases will acquire 100% drug resistance. One explanation for greater adaptability of bacteria to antibiotics may be self-medication as well as continuous administration. Rigorous research operations are continuing to discover other means of treating illnesses caused by these microbes.<sup>59</sup> A new method, such as probiotics and phage treatment, can remove harmful microorganisms and perhaps enhance the healing process.<sup>60</sup>

### Bacteriophages

Bacteriophages are viruses that identify and reproduce in bacterial cells. Bacteriophages contain capsid protein heads that transport and protect the virus's genetic material.<sup>61</sup> Depending on the virus, the genetic material can vary in size, organization (circular, linear, or segmented), and structure (ssDNA, dsDNA, ssRNA, dsRNA). Bacteriophages are very host specific and will only attack particular strains based on the bacteriophage utilized and the target proteins that aid in bacterial host attachment.<sup>62</sup> So far, phages have been shown to be effective in treating bacterial diseases such as cerebrospinal meningitis, skin infections caused by *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, and *E. coli*, among others, as well as cystic fibrosis, eye infections, neonatal sepsis, urinary tract diseases, and cancers.<sup>63</sup> According to Khalifa et al, the Myoviridae bacteriophage EFLK1 was effectively identified against the phage-resistant strain of Vancomycin-resistant *Enterococcus faecalis* V583.<sup>64,65</sup> Because of genetic supremacy, even phage resistant bacteria can be destroyed by other phages from the same host in this research. Ryan et al suggested that bacteriophage T4 and antibiotic cefotaxime combined therapy can eradicate the biofilms of *E. coli* and even alone phage therapy can clear the *E. coli* biofilm.



## Probiotics Therapy

Probiotics are among these new agents which are widely used and extensively studied for their health promoting effects.<sup>66</sup> Probiotics are either a single strain or a combination of various organisms, and they are capable of strengthening immune systems, producing anti-inflammatory activity and improving wound healing following inflammatory cell buildup at the wound site.<sup>67</sup> Recent randomized controlled trials experiments have demonstrated that certain intestinal bacteria, like *Lactobacillus* and *Bifidobacteria*, inhibit cariogenic streptococci and *Candida Spp*, have positive effects in their oral action.<sup>68</sup>

## Amputation

Amputation above the ankle is frequently a problem or need for a patient with infected DFUs and PAD. The five-year death rate following a diabetes-related amputation is up to 60%, which is greater than the mortality rate for some cancers.<sup>68</sup> Patients at high risk for ulceration and those who have had an amputation for a DFU should be evaluated by a DFU expert team one to three times each month. At each visit, the patients' feet should be examined, and the need for a vascular assessment should be determined.<sup>69</sup>

## New Drug Targets for Diabetic Foot Ulcer

Inhibition of quorum sensing system for Treating Chronic Wounds.

## Role of Quorum Sensing (QS) Mechanism in Inhibiting Wound Healing

The QS-System is a two-component system composed of an enzyme that catalyzes the signal molecule (auto inducer) synthesis reaction and a receptor molecule that binds to the signal molecule (for example, acyl-homoserine lactone, AHL, and cyclic peptides) and regulates the transcription of many genes in addition to that encoding the signal molecule.<sup>70</sup>

Because the bacterial QS system is required for biofilm development in chronic wounds, it is an important target for anti-biofilm treatment. Because the QS system is reliant on signaling by auto inducer chemicals, blocking these would prevent coordinated virulence action. Gram-positive and Gram-negative bacteria have a wide range of QS systems.<sup>71</sup> The capacity of glyceryl trinitrate (GTN) to

suppress QS-based biofilm development in *P. aeruginosa* burn infections was investigated.<sup>72</sup> GTN is a wound healing and antibacterial agent that has been authorized by the FDA. It is used in ointments for treating anal fissures and for inhibiting *plank tonic Candida albicans* when used at a concentration 0.15% to 0.3%. GTN was found to inhibit biofilm formation by *P. aeruginosa*.<sup>73,74</sup>

## Targeting Matrix Metalloproteinase 9 (MMP-9) in Diabetic Foot Ulcers

Wound healing can be hampered by stress. Cortisol, a steroid hormone, is increased during stress and chronic inflammation, and it slows wound healing.<sup>75</sup> Elevated MMP-9 levels have been linked to higher cortisol levels in individuals with coronary artery disease. Prostaglandin E2 has been shown to increase cortisol release and to activate MMP-9. The increased activity of matrix metalloproteinase (MMPs)<sup>76</sup> is one of the culprits in the recalcitrance. MMPs are categorized in several ways, including their preferred substrates, such as gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8, and MMP-13), and stromelysins (MMP-3 and MMP-10). The first generation of MMPs were broad-spectrum zinc chelators with low bioavailability, prompting the development of a second generation of orally bioactive broad-spectrum inhibitors. The medication becapermin Gelatinase activity was reduced, but collagenase activity was unaffected; active MMP-9 was reduced, while active MMP-8 was unaffected.<sup>77</sup>

Treatments for DFUs that do not specifically target MMPs can have important effects on MMP expression and activity. As MMP-9 has long been of interest in wound healing, most studies have focused on the effects on this proteinase in particular (Table 1).

## Nano Biotechnology Solutions for Wound Healing and Healing Diabetic Wounds

Debridement was not performed with Nano scale treatments. Pectins found in hibiscus flowers bond to heavy metal ions. Heavy metal ions have a strong affinity for these pectins. Some red spinach extracts can be utilized for heavy metal and toxic metabolite bio-chelation because they have an unusual structure that binds harmful species.<sup>85</sup> The particle sizes of the bioactive forms produced from the extracts range from 35nm to 200nm, with a peak at 100nm.<sup>86</sup>

**Table I** Summary of the Matrix Metalloproteinase-9 Treatment Articles That Were Previously Published and Included Studies in the Review, 2021

Treatment	Study Material	Method of MMP Measuring	Effect on MMPs	Reference
Vacuum-assisted closure (VAC)	Human chronic wound fluid	Gelatin zymography	Reduced MMP-9 and MMP-2	[78]
VAC	Human chronic wound fluid	ELISA	Reduced MMP-9/TIMP-1 ratio, no change in MMP-9	[79]
Mesenchymal stem cells (MSC)	Mouse model of diabetic wounds	Gelatin zymography, quantitative PCR	Reduced MMP-9 activity and expression	[80]
N-acetyl cysteine	HaCat cells treated with MGO	Western blot	Reduced MMP-9 expression	[81]
Manuka honey wound dressing	Human DFU patient wound fluid	ELISA	Increased MMP-9 expression (no improvement on ulcer healing)	[82]
Becaplermin	Mouse model of diabetic wounds	In-situ zymography and batimastat affinity resin coupled proteomics	Decreased gelatinase activity, no effect on collagenase activity; decreased active MMP-9, no effect on active MMP-8	[83]
Acclerastide	Mouse model of diabetic wounds	Batimastat affinity resin coupled proteomics	Increased active MMP-9, no effect on active MMP-8	[84]

**Abbreviations:** ELISA, enzyme-linked immunosorbent assay; DFU, diabetic foot ulcer; MMP-8, matrix metalloproteinase-8; MMP-9, matrix metalloproteinase-9; PCR, polymerase chain reaction; VAC, vacuum-assisted closure; MGO, methylglyoxal; HaCaT, cultured human keratinocyte (cells); THMM-1, tissue inhibitor matrix metalloproteinase-1.

## Conclusion

Diabetic foot ulcer (DFU) is a significant complication of diabetes, complicating the lives of millions of diabetic individuals. Despite the medical community's extensive understanding of DFU, there is still a continuing effort to discover the most appropriate therapy for this debilitating illness; one that is not only cost effective, but also safe to give.

Because DFU is caused by a mix of variables, a combination of treatments, rather than a single drug, will be the best option for therapy. The use of anti-diabetic medicines such as insulin, exendin-4, and DPP-4 inhibitors holds a lot of promise because this class of treatments targets the source of the problem, hyperglycemia and MMP-9 were observed in mouse and human diabetic wounds using a batimastat affinity resin and proteomics. MMP-9 was shown to play a detrimental role in diabetic wound healing, whereas MMP-8 was beneficial. A new class of selective MMP-9 inhibitors shows clinical promise for the treatment of DFUs. Normal glycemia aids in the correction of the underlying issues that contribute to the formation of DFU, and so serves as both a preventative strategy and a facilitator of wound healing in DFUs.

## Author Contributions

All authors made a significant contribution to the work reported, that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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