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Targeting Matrix Metallopeptidase 9 (MMP-9) and Role of Quorum Sensing (QS) in Diabetic Foot Ulcers

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Abstract

Diabetes-related foot ulcers (DFU) are a serious public health issue, and one of the main causes of death for diabetics is foot ulcers. Matrix metalloproteinase are crucial to both the pathophysiology of wounds and the healing process. MMPs have not previously been a focus for the treatment of DFUs due to the difficulty in differentiating between active MMPs and the two catalytically inactive forms of MMPs and the clinical failure of broad-spectrum MMP inhibitors in cancer. Managing bacterial infections by focusing on this quorum sensing (QS)-regulated process different from other management strategies. Despite the fact that the medical community has a thorough grasp of diabetic foot ulcers, research is continuously being done to find the most effective treatment for this crippling condition that is also safe to provide. Diabetic foot ulcers are brought on by a variety of factors, so a combination of therapies rather than a single medication will be the most effective course of treatment. This book chapter discusses the identification of active MMP-9 as the molecular cause of the diabetic wounds’ resistance to healing as well as the unique therapeutic strategy of inhibiting this proteinase and about role of inhibiting the quorum sensing (QS) system in the treatment of diabetic foot ulcer.

Keywords: diabetic foot ulcer, quorum sensing (QS) system and targeting matrix metallopeptidase-9 (MMP-9), antimicrobial peptide

1. Introduction

A chronic metabolic condition called diabetes mellitus (DM) is characterized by hyperglycemia [1]. Defining diabetic foot (DF) as “the foot of a diabetic patient who 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,” according to the World Health Organization [2]. To prevent the onset of foot ulcers, early identification of the at-risk foot should be given top
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clinical attention [3]. Wound healing can be negatively impacted by stress and a steroid hormone called cortisol is high during times of stress and chronic inflammation and slows the healing of wounds. The inability of diabetic foot ulcers (DFU) to heal has been reported to be substantially correlated with CYP11B1, the enzyme that catalyzes cortisol production [4]. Cortisol levels have been linked to elevated MMP-9 levels in patients with coronary artery disease, and MMP-9 is reported to be induced and cortisol production stimulated by prostaglandin E2. The enhanced activity of matrix metalloproteinase (MMPs) is one of the causes of the resistance [5]. In 1960, the family of zinc-dependent endopeptidases known as MMPs was initially identified in tadpoles. Humans have 24 distinct MMPs that have a variety of substrates and roles [6]. MMPs are categorized in part according to the substrates they prefer to break down, including the gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8, and MMP-13), and stromelysins (MMP-3 and MMP-10) [7]. MMP expression and activity may be significantly impacted by DFU treatments that do not directly target MMPs. Most research has concentrated on the effects on MMP-9 in particular because it has long been thought that this proteinase has a role in wound healing. These investigations definitely showed that MMP-9 plays a negative effect in DFU healing, while MMP-8 plays a positive role. Approximately 15% of all diabetic patients get DFU, and of those, 84% have their lower limb amputated and 6% are hospitalized for gangrene and infections that are primarily caused by multidrug-resistant (MDR) microorganisms [8]. These pathogens include Morganella morganii, Klebsiella pneumoniae, Proteus mirabilis, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus mitis, Staphylococcus aureus, and Enterococcus faecalis, which dominate and populate the foot ulcer [9]. These pathogens exhibit virulence traits such as biofilm formation and others, making antibiotic therapy ineffective against them. When bacterial colonies known as biofilms reach a certain size, they coordinate changes in gene expression via coordinated cell-to-cell communication (quorum sensing) and prepare to express additional virulent factors [10]. The development of biofilm on the skin surface of DFU is a further issue. And in DFU, biofilm is a crucial stage in the pathophysiology and it may delay recovery. Both MDR bacteria and microorganisms that produce biofilms create antibiotic-resistant conditions that cause the lesion to become chronic, infect, and, in the worst case, necessitate lower limb amputation. Managing bacterial infections by focusing on this quorum sensing (QS)-regulated process offers a novel strategy [11]. This book chapter discusses the identification of active MMP-9 as the molecular cause of the diabetic wounds’ resistance to healing as well as the unique therapeutic strategy of inhibiting enzyme proteinase and about role of inhibiting the quorum sensing (QS) system in the treatment of diabetic foot ulcer.

2. Epidemiology

A diabetic person may have a 25% lifetime risk of developing a foot ulcer and diabetes, and patients experience lower limb amputations 15 times more frequently than non-diabetics. Diabetic foot ulcer had a 6.3% global prevalence, with type 2 diabetes having a higher prevalence than type 1 diabetes (6.4 and 5.5%), respectively. The country with the highest prevalence is Belgium (14.8%), followed by Canada and the US (13.0%). Of all the continents, North America has the highest frequency (13%) by far. Asia accounted for 5.5%, Europe for 5.1%, and Africa for 7.2% [12].
From different parts of Ethiopia, Addis Abeba, Jimma, Gondar, Bahir Dar, Mekele, Arbeminch, and Dessie have higher rates of diabetic foot ulcers than other major cities (1.36%, 25.76%, 13.62%, 21.22%, 12.28%, 14.87%, and 1.85%, respectively), according to a study by Tolossa et al. [13] and Degu et al [6].

3. Etiology and risk factors

Peripheral neuropathy and peripheral arterial disease are the most frequent causes of diabetic foot ulcers out of a range of interrelated factors. Diabetic foot ulcer is hence frequently referred to as neuropathic, neuroischemic, or ischemic ulcers. Since the 1990s, ischemic and neuroischemic ulcers have become the most common cause of diabetic foot ulcer, accounting for more than one-third of all cases [14, 15]. This is most likely due to increased awareness of the importance of ischemia in diabetic foot ulcer and its detrimental effects, but it may also be related to improved diagnostic procedures, which could have an impact on recommendations for diagnostic criteria [15, 16]. Between 70 and 83% of diabetic patients with serious soft-tissue infections have polymicrobial at the time of diagnosis [17]. Additionally, chronic diabetic foot ulcer has abnormally high matrix metalloprotease (MMP) levels compared with acute wounds, which promotes tissue disintegration and eventually impedes normal healing processes [18]. Diabetes and long-term smoking both raise the risk of gangrene [19]. Gas gangrene, a rare consequence of diabetic foot ulcers, can occur in people with these persistent non-healing lesions [20]. Gangrene is induced by a decrease in blood flow to the affected tissues, which causes a hypoxic environment and cellular damage from Advanced Glycation End Products, which leads to cell death [21]. 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 [22]. Inadequate re-epithelialization is caused by hyperglycemia, which also inhibits angiogenesis and cell migration. Similarly, inadequate extracellular matrix (ECM) formation by fibroblasts contributes to the issue of inadequate wound healing [23, 24].

4. Issues with the present diabetic foot ulcer treatment

The primary treatment problems associated with diabetic foot ulcer are believed to be diabetic foot infections and delayed wound healing [25]. The idea of probiotic consumption is intriguing and significant in light of the growing concerns about antimicrobial drug resistance around the world because probiotics have the ability to strengthen the immune system and have anti-inflammatory properties, which may speed up the healing process after a wound [26]. World Health Organization estimates that 60% of microorganisms are developing resistance to important antibiotics and that all diseases will eventually develop 100% treatment resistance. Self-medication as well as ongoing administration of antibiotics could be one explanation for bacteria’s increasing tolerance to them. Thorough study is still being done to find new ways to cure disorders brought on by these bacteria [27]. Probiotics and phage therapy are innovative techniques that can eliminate unwanted germs and possibly speed up the healing process [28].
5. The current strategy for managing diabetic foot ulcers

5.1 Antimicrobial peptides

Antimicrobial peptides (AMPs), which are present in almost all animals, are host defense peptides because they possess traits of both innate and adaptive immune systems. Short-polypeptide antimicrobial peptides called have a cationic characteristic and an amphipathic structure (usually no more than 60 amino acids). The majority of antimicrobial peptides operate as the first line of defense against a variety of pathogens, including bacteria, fungi, viruses, and protozoan parasites [29]. A recent analysis of publicly available patent data on the therapeutic use of antimicrobial peptides from 2003 to 2015 revealed that the majority of the claimed antimicrobial peptides were also described as the effective modulators of inflammation or neutralizers of pathogenic toxins in addition to being potent antibiotics [3, 30].

5.2 Growth factors

Platelet-derived growth factor, a mitogenic bioactive molecule, encourages undifferentiated mesenchymal cells to develop into mature tissue, which increases the production of new cells and speeds up wound healing. Additionally, platelets have the ability to promote angiogenesis and tissue migration from a preformed vascular bed. They can also provide vascular endothelial synthesis a final boost by inducing vasodilation [31].

5.3 Antidiabetic drugs and diabetic foot ulcers

5.3.1 Insulin

One of the most efficient methods of preventing diabetes problems is to maintain normoglycemia with enough meals and/or antidiabetic drugs. A reported 30.3% improvement in diabetic foot ulcer healing was seen after receiving insulin intravenously. A physiological glucose-lowering agent is known as insulin. Recently, there has been concern over the use of cutaneous insulin administration as a healing agent in diabetic foot ulcer [32, 33].

5.3.2 Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 is a significant enzyme that deactivates the cretin hormones glucagon-like peptide-1 and glucagon-like peptide. FDA-approved oral drugs known as 43 DPP-4 inhibitors for type II diabetes mellitus block dipeptidyl peptidase, improve the flow of infused hormones, and provide glycemic control as well as increased islet cell function. By reducing blood glucose levels, DPP-4 inhibitors including sitagliptin, vildagliptin, and anagliptin are used to treat diabetes. Exendin-4, a glucagon-like peptide-1 (GLP-1) receptor agonist derived from the saliva of the Gila monster, a large poisonous lizard found in the South Western region of the United States, was applied topically on experimental animals to speed up the healing of diabetic foot ulcer wounds whether or not adipose-derived stem cells were also present [34, 35].
5.4 Use of stem cells in diabetic foot ulcer

Diabetic foot ulcer can produce blood vessel and extracellular matrix cell precursors when stem cells, such as adipose-derived stem cells and endothelial progenitor cells, are introduced from bone marrow or other sources [36, 37]. To encourage the growth of new cells in the wound area, these progenitor cells can be injected into the wound [38].

5.5 Natural products

Aloe Vera, Salvia miltiorrhiza, Mimosa tenuiflora, Alchemilla vulgaris, Angelica sinensis, and Moringa oleifera are just a few of the plants utilized in a variety of cosmetic goods such as lotions, creams, and gels. M. oleifera has been proven to drastically lower the levels of numerous cytokines, including TNF-α, IL-6, and VEGF, as well as promote tissue granulation and reduce the size of diabetic foot ulcer wounds [39, 40]. Honey has healing, non-harmful antibacterial, antioxidant, and anti-inflammatory qualities that aid in the healing of burns and wounds. As an alternative therapy for diabetic foot ulcer, honey therapy has attracted a lot of interest in recent years and several studies have evaluated the effectiveness of honey therapy for treating diabetic foot ulcer at different stages [41, 42]. A recent study compared traditional saline solution dressings to honey dressings and found that the latter were more effective in terms of healing time and the number of lesions that were healed after 120 days [12, 43].

5.6 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 [44]. The genetic material’s size, organization (circular, linear, or segmented), and structure might change depending on the virus (ssDNA, dsDNA, ssRNA, dsRNA). Based on the bacteriophage used and the target proteins that aid in bacterial host attachment, bacteriophages are very host specific and will only attack specific strains [45]. Phages have so far been found to be successful in treating bacterial illnesses including cystic fibrosis, eye infections, new-born sepsis, urinary tract illnesses, and malignancies, in addition to skin infections brought on by bacteria like P. aeruginosa, S. aureus, K. pneumoniae, and E. coli [46]. According to Khalifa et al. [47] Myoviridae bacteriophage EFLK1 was successfully identified against the phage-resistant strain of Vancomycin-resistant E. faecalis V583 and due to genetic superiority, even phage-resistant bacteria can be eliminated by other phages from the same host in this research. According to El-Shibiny and El-Sahhar [48], bacteriophage T4 and the antibiotic cefotaxime can be used in combination to treat E. coli biofilms, although phage therapy can also be used on its own to clear them [49].

5.7 Probiotics therapy

One of these novel substances that is both commonly used and thoroughly researched for its potential to promote health is probiotics [50]. Probiotics are either a single strain or a combination of several organisms, and they have the power to improve wound healing after an inflammatory cell build-up at the wound site, boost immune systems, and produce anti-inflammatory action [19–26, 42–46, 49–51].
Recent randomized controlled trial experiments have demonstrated that certain intestinal bacteria, such as Lactobacillus and Bifidobacteria, inhibit cariogenic streptococci and Candida spp., and have positive effects on their oral action [52].

5.8 Amputation

For patients with infected diabetic foot ulcer and peripheral artery disease, amputation above the ankle is commonly an issue or requirement. Up to 60% of diabetics die within 5 years of having an amputation, which is higher than the mortality rate for other malignancies [52]. A diabetic foot ulcer specialist team should assess patients one to three times each month, especially those who are at high risk for ulceration and those who have undergone an amputation for a diabetic foot ulcer. Every time a patient comes in, their feet should be checked to see whether a vascular examination is necessary [53].

6. Novel treatment options for diabetic foot ulcers

6.1 Role of quorum sensing (QS) mechanism in inhibiting wound healing

The quorum sensing system is a two-part system made up of an enzyme that catalyzes the synthesis of the signal molecule (auto inducer) and a receptor molecule that binds to the signal molecule (such as acyl-homoserine lactone and cyclic peptides) and controls the transcription of numerous genes in addition to the gene that encodes the signal molecule [54]. Because the bacterial quorum sensing system is required for biofilm development in chronic wounds, it is an important target for anti-biofilm treatment. Because the quorum sensing 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 quorum sensing systems [55]. The capacity of glyceryl trinitrate (GTN) to suppress quorum sensing-based biofilm development in P. aeruginosa burn infections was investigated [56]. The FDA has approved the antibacterial and wound-healing compound glyceryl trinitrate. When administered in ointments at a concentration of 0.15% to 0.3%, it is used to treat anal fissures and to suppress growth tonic Candida albicans. P. aeruginosa was observed to produce less biofilm when exposed to glyceryl trinitrate [5, 57].

6.2 Targeting matrix metallopeptidase 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. Elevated Matrix metallopeptidase-9 levels that 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 matrix metallopeptidase-9 [58]. One of the causes of the recalcitrance is the increased activity of the enzyme matrix metalloproteinase (MMPs). The preferred substrates of MMPs, such as gelatinases (MMP-2 and MMP-9), collagenases (MMP-1, MMP-8, and MMP-13), and stromelysins, are characterized in a variety of ways (MMP-3 and MMP-10). A second generation of orally bioactive broad-spectrum inhibitors was created as a result of the first generation of MMPIs being broad-spectrum zinc chelators with low bioavailability [59]. The medication becaplermin Gelatinase activity was reduced, but collagenase activity was
unaffected; active MMP-9 was reduced, while active MMP-8 was unaffected [60]. MMP expression and activity may be significantly impacted by diabetic foot ulcer treatments that do not directly target matrix metallopeptidase. Most researches have concentrated on the effects on this proteinase specifically since MMP-9 has long been of interest in wound healing [61].

7. Conclusion

Millions of people with diabetes struggle with diabetic foot ulcers, a serious consequence of diabetes. Despite the fact that the medical community has a thorough grasp of diabetic foot ulcers, research is continuously being done to find the most effective treatment for this crippling condition that is also safe to provide. Diabetic foot ulcers are brought on by a variety of factors, so a combination of therapies rather than a single medication will be the most effective course of treatment. The current challenges in treating diabetic foot ulcers are caused by bacterial resistance to the antibiotics now being used. Treatment options for diabetic foot ulcers include targeting matrix metallopeptidase-9 (MMP-9) and inhibiting the quorum sensing (QS) system has been emerged.

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Conflict of interest

The authors declare no conflict of interest.
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