Review Article

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Diabetic Pedal Osteomyelitis and Its Treatment

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Diabetes is a fast-growing chronic metabolic disorder that is widely associated with foot ulcers. The major challenge among these ulcers is wound infections, altered inflammatory responses, and a lack of angiogenesis that can complicate limb amputation. The foot, because of its architecture, becomes the part most prone to complications and the infection rate is higher mainly between the toes due to the humid nature. Therefore, the infection rate is significantly higher. Wound healing in diabetes is a dynamic process usually delayed due to poor immune function. Diabetes-related pedal neuropathy and perfusion disturbances can lead to a loss of sensation in the foot. This neuropathy can further be a risk factor for ulcer development due to repetitive mechanical stress that later might get infected by the invasion of microorganisms extending to the bone and causing an infection called pedal osteomyelitis. This review details the pathophysiology, the biomaterials aiding in the infection cure and regeneration of bone along with their limitations, as well as their future prospects.

Key Words: *Osteomyelitis; Ulcer; Biocompatible Materials*

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INTRODUCTION

Diabetes mellitus is a world-wrecking chronic metabolic disorder emerging as a major health issue globally characterized by a hyperglycemia state. This may lead to a compromise in the microvascular and macrovascular supply of blood.[1] Due to the decrease in blood flow, the immunity is compromised and hence the body is incapable of defending itself from invading pathogens. The various pathogens that invade are bacterial as well as viral, fungal, and protozoal.[2] These infections are quite prevalent in diabetic patients owing to the humidity and lack of cleanliness, especially between their toes.[3] The nerve damage in diabetes affects the sensory fibers that lead to the loss of the protective sensation of pressure, pain, and heat. The motor fibers are also impaired leading to muscle weakness followed by atrophy and paresis. Lastly, the autonomic fibers are also damaged resulting in vasodilation and reduced sweating causing skin integrity loss and making the site vulnerable to further microbial invasion.[4] The infections are polymicrobial in nature which includes aerobic gram-positive cocci, gram-negative rods, the fungus, and also the anaerobic organisms. The majority of ulcers heal without any reoccurrence while nearly 20% of the ulcers which are neuro ischemic will lead to limb amputation within 18 months.[5] There is an increased risk ratio associated with age and diabetes duration for the development of ulcers that leads to amputation.[4] Also the prevalence is found to be higher in elderly males as compared with the other population.[6] However life-threatening complications such as gangrene and amputation can be mitigated by proper glycaemic control, proper dressing, debridement of wounds, and surgery. Diabetic ulcers are critical when it takes a longer time to get diagnosed, ultimately making it a deep-seated wound. This initially starts with skin tissue degradation along with cellular layer exposure slowly invading the underlying bone tissue causing an infection called osteomyelitis.[7]

Osteomyelitis is an inflammatory process that is associated with the destruction of the bone by invading microorganisms. The infection mostly is confined to a single portion of the bone or sometimes involves various regions such as the periosteum, cortex, and marrow.[3] Osteomyelitis is usually suspected if the ulcer healing does not occur in 6 weeks with the persistence of bone infection and impaired immunity. The inflammatory responses are also impaired enabling the microorganisms to adhere to the sequestrum causing biofilms. These biofilms consist of

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poly-microbial communities with highly persistent phenotypes which resist the host responses.[8] Osteomyelitis of the foot may affect any bone but the most commonly affected bone is the forefoot which has the best prognosis followed by the midfoot while the least affected area is the hindfoot.

Fig. 1 explains hyperglycemia (etiology) which is the triggering factor for the development of ulceration which later gets infected and invades the underlying bone causing bone infections (pathology). The diagnosis could be made based on the depth of the ulcer such that if it is deeper than (>3 mm) they are commonly associated with bone involvement. The other detection is done through the "probe-to-bone test" (PTB) in which a sterile blunt probe is probed through the ulcer area and if it reaches the bone surface the test is positive. In x-ray imaging of the foot, the periosteal thickening with erosion of the cortical bone causing osteolysis and bone sequestration are noted. The combination of PTB with the X-ray improves the specificity and sensitivity of the diagnosis.[9] The approaches for treatment at various stages of the infection are discussed starting from proper blood glucose control to debridement and amputation.[10]

PATHOPHYSIOLOGY OF DIABETIC PEDAL OSTEOMYELITIS

Diabetes is a condition that is characterized by a hyperglycaemic state over a prolonged duration. The complications associated with diabetes are due to uncontrolled blood glucose levels. Plantar hyperkeratosis occurs when the area of the sole is put under too much pressure and excessive pressure triggers the keratin production in excess. This results in the thickening of the skin leading to foot ulcers and fissures through which the infection encroaches the bone underneath shown in Fig. 2.[11]

Fig. 1 and Fig. 2 were created with software from BioRender.com. The bacteria reaches the bone through contiguous spread from the nearby infected soft tissue and adheres subsequently to the components of the bone matrix.[12] The infections of the diabetic foot, as mentioned

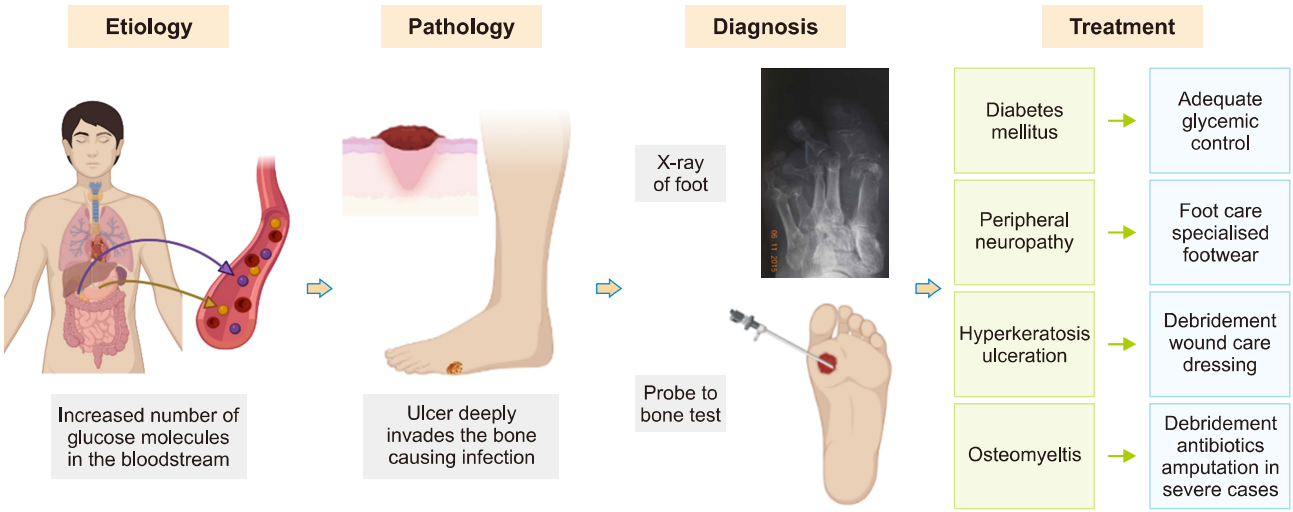

FIG. 1. Depicts the cause for the development of foot ulcers which subsequently turns into a bone infection that can be diagnosed by X-ray or probe to bone test and the treatment at various stages that finally leads to osteomyelitis are briefly given.

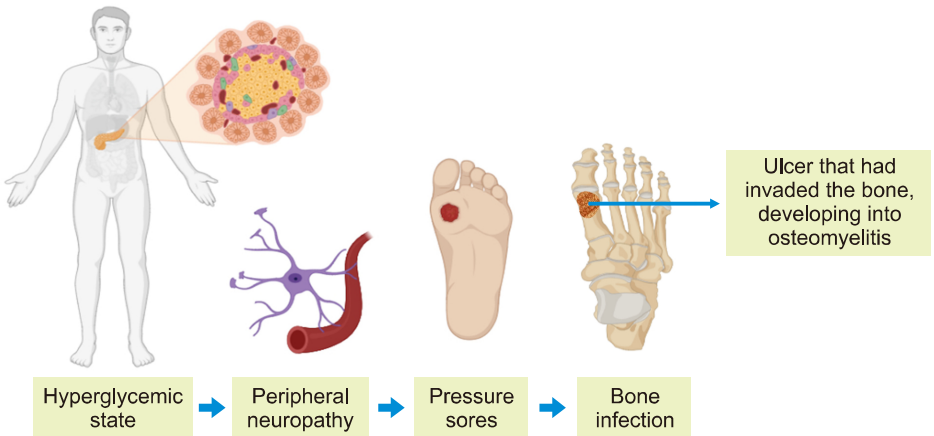

FIG. 2. Showing the diagrammatic representation of the pathophysiology of diabetic pedal osteomyelitis.

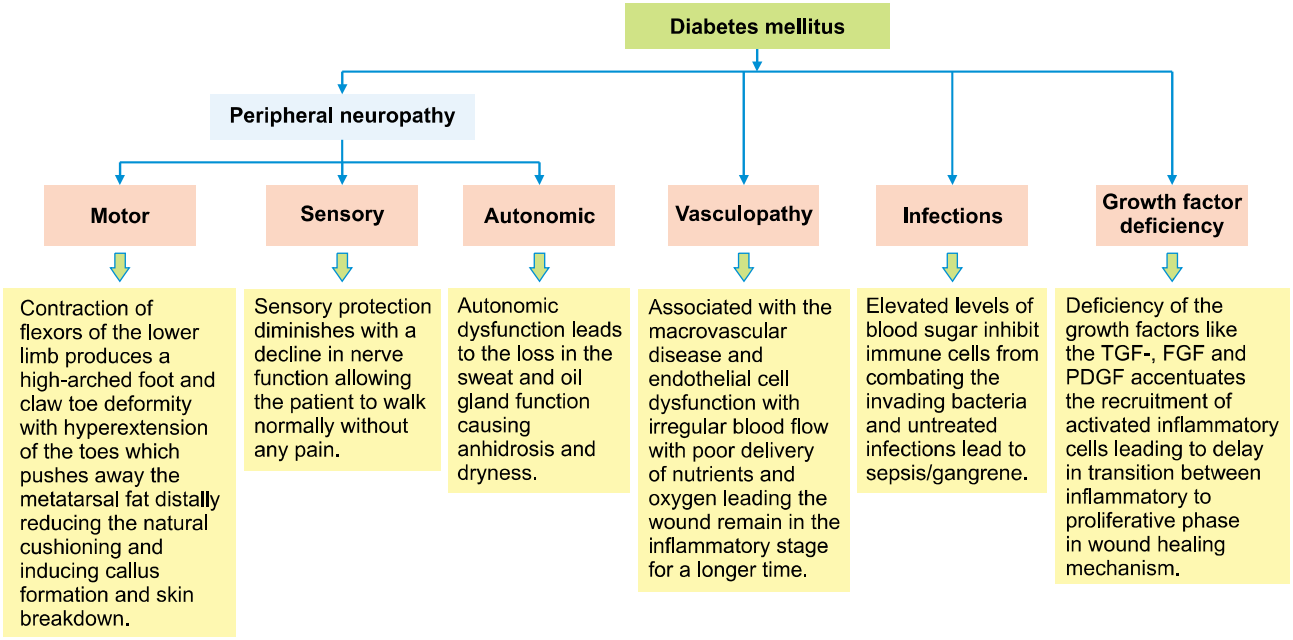

FIG. 3. The flowchart explains the various mechanisms involved in diabetic pedal osteomyelitis.

above, are due to the invasion of the host tissue by micro-organisms that begin with ulcers due to a split in the cutaneous envelope. Then it results in soft tissue infection that invades the deep underlying bone causing contamination firstly of the cortex and then the marrow. The infection is mostly polymicrobial and the major organism reported is *Staphylococcus aureus*. The other organisms include *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus sp*.[13] Several kinds of fungus, *Candida parapsilosis*, *Candida tropicalis*, *Trichosporon asahii*, *Candida albicans*, and *Aspergillus species*, were the commonly associated isolates.[14]

The most common mechanism is peripheral neuropathy leading to intrinsic muscle atrophy which disturbs the anatomy causing hammer toe development and also high-pressure zones on the sole, mainly at the toes. There is decreased sensation owing to neuropathy which can cause skin injury due to repeated trauma with walking, finally leading to atrophy and the protective plantar fat pads dislocation. The multiplex of mechanisms involved with various complications in diabetic foot osteomyelitis is listed in Fig. 3.[15]

The ulceration associated with the foot infections exaggerate the risk of amputation of the foot by 50% being one of the most dreadful outcomes in diabetic foot patients. The anatomy of the foot is unique such that the infection is potentially complicated at this site.[16] The sheath, tendons, structure compartment, and neurovascular bundles are prone to favor the proximal spread of the infection.[17] The wound healing in diabetes ulcers takes a longer duration to heal due to the deficiency of the growth factors like the TGF-β, FGF, and PDGF. The deficiency of these factors accentuates the activated inflammatory cells recruitment leading to a delay in the transition between inflammatory to the proliferative phase in wound healing mechanism.[18,19]

Patients with chronic hyperglycemia tend to have lipid peroxidation product accumulation. Iron metabolism is also impaired leading to a free ion presence in the plasma. A new type of cell death known as ferroptosis due to the iron overload intracellularly and iron-dependent lipid peroxides accumulation is also responsible for wound healing delay in diabetic ulcers. The decline in glucose metabolism in diabetic patients causes the ulcer wound to remain in a hyperglycaemic state with an increase in mitochondrial reactive oxygen species production that leads to lipid peroxidation activation causing cellular dysfunction and death.[20]

The other factors predisposing to these delays in wound healing in diabetic patients are detailed in Fig. 4. The lack of adhesion of neutrophils owing to the microcirculatory defects causes inflammatory phase prolongation and delays the healing cascade in diabetes. The fibroblasts that activate the secretion of the growth factors become resistant to endogenous cytokines and growth factors.[18]

Diabetes is associated with impaired angiogenesis and the hyperglycaemic state induces vascular damage by increasing intracellular oxidative stress. The chronic hyperglycemic state causes insulin-independent transporter downregulation. This leads to the exposure of high amounts of glucose to the cells resulting in reactive oxygen species generation by the polyol pathway, advanced glycation end-products pathway, and hexosamine pathway. The hyperglycemia-induced ROS formation is accomplished by superoxide anion overproduction through the electron transport chain of the mitochondria along with an over-

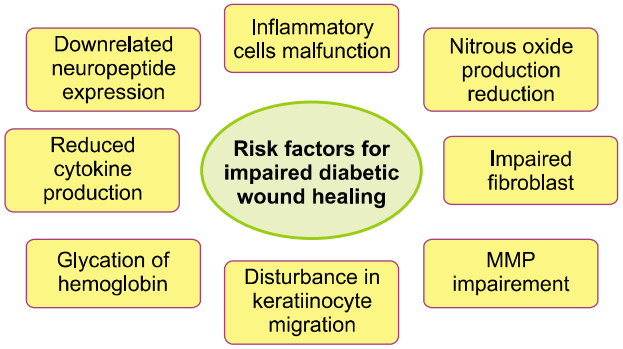

FIG. 4. Showcases the various factors responsible for delayed wound healing in diabetes.

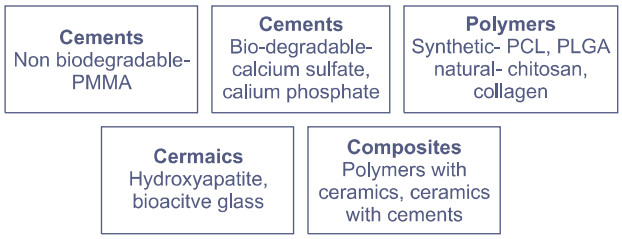

FIG. 5. Lists the biomaterials commonly used in diabetic pedal osteomyelitis.

production of nitrous oxide. The ROS formation induced by hyperglycemia finally leads to endothelial dysfunction and atherosclerosis.[21] Macrophages that are required for wound healing have been shown to have an altered function in diabetic patients. In normal patients during wound repair, the macrophage changes from a proinflammatory phenotype to a pro-reparative phenotype that later supports the tissue regrowth. Whereas in the case of diabetic wounds, the macrophages which are the important source of VEGF and the other pro-angiogenic mediators become deficient and lead to decrease in angiogenesis at wound site. Apart from the reduction in the pro-angiogenic stimulus, diabetes is also associated with alterations in the anti-angiogenic factors at the wound site. The anti-angiogenic factor PEDF that has a negative impact on the wound healing outcome is increased in cases of diabetic patients. The vascular maturation pathway Ang1/Ang2/Tie2 complex deficit is seen in diabetic wounds. Also, the ratio of Ang1 to Ang2 is reduced thereby disturbing the capacity of the diabetic wound vasculature progression to a matured phenotype. The microRNAs that generally regulate the angiogenesis in a wound repair are expressed differentially in cases of diabetes. The platelet-derived growth factor (PDGF) that encourages the capillary maturation by recruiting and nurturing pericytes is also perturbed in a diabetic wound. The prostaglandin E2 necessary for vasodilation and angiogenesis is impaired which develops the peripheral arterial disease. In addition to all these, there is also a decline in the endothelial progenitor cells (EPC) produced by the bone marrow in a diabetic state. This in turn decreases the vascularity baseline and hinders wound angiogenesis with reduction in the production of angiogenic sprouts and tubes in ischemic models. Without the proper functioning of these cells, the processes such as the granulation formation, collagen deposition, and the capillary growth are impaired in the wound area. All these factors contribute greatly to vascular pruning and maturation delay in diabetic wounds thereby leading to chronicity or recurrence of wounds due to lack of well-perfused vascular bed.[22]

BIOMATERIALS USED FOR DIABETIC PEDAL ULCERS AND OSTEOMYELITIS TREATMENT

The treatment of pedal osteomyelitis is usually done using the incorporation of antibiotic beads or sponges that are locally placed following the debridement of the infected bone and soft tissues. The commonly used bio-materials in practice for the treatment of osteomyelitis are listed in Fig. 5.[23] The antibiotic beads are made from PMMA (polymethyl methacrylate) which is a non-biodegradable material. The biodegradable materials used are calcium phosphate and calcium sulfate. A technique proved to be efficient in treating osteomyelitis is the local incorporation of antibiotics into the infected site after local debridement which has been shown to reduce the morbidity of the local site. The antibiotic gentamicin-incorporated PMMA beads fabricated on a surgical wire for local site loading after debridement of the infected bone was shown to have a good outcome in pedal osteomyelitis.[24] To treat diabetic foot infections ciprofloxacin incorporated sponge-based lyophilized hydrogel having two polyelectrolytes that are oppositely charged using poly cyclodextrin citrate and chitosan which yielded a sustained release and reduced the risk of systemic toxicity by local administration.[25]

Liposomes loaded with the hydrophobic drugs in the double layer of phospholipid and the hydrophilic drug encapsulated within the aqueous core served as a potent antimicrobial drug delivery agent for diabetic foot infections.[26] The use of bioactive glass in osteomyelitis potentiates cellular proliferation and improved angiogenesis by effectively bonding to the living tissue creating a stable interface while being coated with the nanocrystalline hydroxyapatite. The material S53P4 which is similar to bioglass initially releases sodium from the surface causing an alkaline surrounding and later releases calcium, silicon, and phosphorous imparting elevated osmotic pressure and inhibiting the bacterial adhesion and colonization to the surface. Thus, rendering both anti-bacterial activities as well stimulating bone synthesis by being a sterile osteoconductive material, the use of bio-glass demonstrated an 80% healing rate and a shorter healing time.[27]

Chitosan bandages incorporated with ciprofloxacin and fluconazole were able to release drugs in a sustained manner for about two weeks and were proven to be cytocompatible. The high swelling ability along with the porosity

of these chitosan bandages was able to uptake the wound exudate and prevented the maceration of the peri-wound area.[28] Nanotechnology has played a significant role in treating osteomyelitis by introducing ceramics like hydroxyapatite, tricalcium phosphate, and silicate Bio glass attributed to their high compressive strength and biocompatibility. Ceramics namely HA, TCP, and phosphate bio-glass hold various applications with good compressive strength and hardness and are used in orthopedics. The nano grain-sized HA is a well-known osteoconductive material for graft substitute in bone having the structural similarity with that of the natural minerals present in the bone aiding in the tight bond formation with the nearby local tissue. Nano-phase HA possesses improved cytocompatibility than that of micron-sized HA. Nano-sized calcium phosphate particles are one of the native minerals found in the bone. Synthetically made calcium phosphate nanoparticles are used widely in practice for delivery of the antibiotic in bone treatment as they are bioactive and osteoconductive and help in bone growth additionally.

Metallic nanoparticles, namely silver, hold good microbicidal efficiency and are often used in bandages and wound dressings, especially in cases of diabetic foot polymicrobial infections reducing the complications such as chronic infections or amputations. Recently, carbon nanotubes have been used to deliver antibacterial effects by modification of their surfaces. The scaffold made from the cylindrical structure of a carbon nanotube can be loaded with antibiotics and osteocytes, rendering an anti-bacterial effect as well as bone regeneration.[29] Calcium phosphate cement incorporated with gentamycin was formed as an efficient delivery system and as an effective bone filler in the debrided space and facilitated bone formation in diabetic patients having chronic osteomyelitis.[30] Antibiotic-impregnated cement spacers using premixed gentamycin PMMA (polymethylmethacrylate) along with vancomycin have been found to accommodate and fill the void following bone debridement and bone resection in diabetic foot osteomyelitis.[31] Despite the compromised vascular support because of atherosclerosis and vessel occlusion in the diabetic foot, the use of PMMA antibiotic-loaded cement rendered high concentrations of antibiotics locally over a sustained period serving as adjunctive therapy in foot osseous infections.[32] A self-adaptive hydrogel fabricated using a phenylboronic acid group of chitosan and a hydroxyl group of polyvinyl alcohol which was multifunctional with self-healing properties and desferrioxamine incorporation proved to accelerate angiogenesis in a diabetic wound healing process.[33]

LIMITATIONS OF THE CURRENT METHOD

The treatment strategies currently opted for are good enough for a narrow period of the microbial-free zone. Although, these strategies sometimes result in improper wound healing and recurrence of bone infection, and mainly antimicrobial resistance development due to an inadequate supply of antibiotics to the targeted site. The disadvantage of PMMA bone cement beads is that it is non-biodegradable in vivo and so requires revision surgery for the removal of the bead after the elution of the antibiotics.[34] Although it gives structural support and is being used as a temporary skeletal spacer and cement for the orthopedic fixation of the implants it does not contribute to bone regeneration.[35] The issue with the calcium sulfate beads is the rapid elution of the drug leading to a high concentration of antibiotic in the site of incorporation due to a burst release and also cannot be used in treatments requiring sustained drug delivery as it has got quick resorption. The drawback of using hydrogel formulations in wound dressing with excessive exudates is insufficient efficiency due to the less absorptive nature of the hydrogel thereby reducing the interest in choosing them as the delivery mode.

DISCUSSION

Osteomyelitis is extremely challenging to treat because the treatment not only needs to tackle the infection but also restore the lost bone as well. Currently, bone- regenerative biomaterials are a hot topic for treatment as they are efficient enough in delivery of the antibiotics in a sustained manner locally overcoming systemic toxicity. They also ensure that the released dose of the drug is above the minimum bactericidal concentration for a complete infection-clear area.[34] The major drawback of combatting antimicrobial resistance is by introducing the approach of targeted drug delivery mainly in the form of nanomaterials. To mitigate the need for secondary surgery for the removal of biomaterial, biodegradable beads are being used as antibiotic delivery vehicles as well as being osteoconductive in nature. Despite all these measures to treat the infection load, the prevention of ulcer recurrence is certainly by declining the disease burden in society.[36]

CONFLICT OF INTEREST STATEMENT

None declared.

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