REVIEW ON DIABETIC FOOT ULCERS ITS PATHOGENESIS, EPIDEMIOLOGY AND EMERGING TREATMENTS

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Abstract

Diabetic foot complications aren't exactly a hot topic. Diabetic nephropathy, heart attack and stroke aren't as common as diabetic foot complications although they are still the most common complications of diabetes. As a result of diabetic foot infections and lesions, the majority of diabetics are hospitalised and require long-term hospitalizations. In the case of diabetic foot ulcers (DFUs), which can lead to amputations of the limb, as well as significant social, psychological, and economic effects. A DFU can develop in up to 25% of diabetic people throughout the course of their lives, and more than half of those patients become infected. As a result, in order to avoid undesirable results, infection and ulcer recovery must be carefully managed. Doctors and patients alike should be aware of the latest developments in DFU treatment. An overview of the current assessment and treatment options for DFUs is provided here in order to assist clinicians in making educated decisions, including molecular and regenerative medicine; energy-based antimicrobial therapies; plant extracts; antimicrobial peptides; growth factors; devices; and nanomedicine.

Keywords: *Diabetic foot ulcers, Antimicrobial activity, Neuropathy, Therapeutic treatment*

Introduction

When it comes to sickness, diabetes is among the oldest. The Ebers Papyrus, which dates back to 1500 B.C., outlines the disease's symptoms and offers therapy. In Chronicles II, an instance of gangrene of the feet, which may have been caused by diabetes, is mentioned[1].

Diabetic neuropathy, the insensitive foot, and foot ulcers were found by British surgeon Pryce more than a century ago. he said[2]. "It was apparent that the underlying cause of the perforating ulcer was peripheral nerve degeneration and that diabetes itself played an active role in the causation."

Diabetic ulcers are the major cause of lower limb amputations in the United States[3-5]. Diabetic foot issues can be prevented or diagnosed early by family physicians. Understanding the key risk factors for amputation in diabetic feet necessitates regular evaluations and rigorous preventative maintenance. Peripheral artery occlusive disease, diabetic neuropathy, and structural foot deformity are the most common causes of ulcer formation. For individuals at risk for foot ulcers, a thorough physical exam, supported by monofilament neuropathy testing and noninvasive testing for vascular insufficiency, can be used to accurately classify patients who currently suffer from ulcers or other diabetic foot problems. In order to reduce the likelihood of an injury leading to the formation of an ulcer, patients must be educated about correct foot hygiene, nail care, and footwear. In order to increase communication between primary care physicians and subspecialists in the field of diabetes, it is important to adhere to a systematic approach to diagnosis and classification. As a result of this collaborative approach, lower limb amputations due to diabetes may be reduced[6].

During the 6–18 months following the initial evaluation of the illness, 60–80 percent of foot ulcers will heal, 10–15 percent will remain active, and 5–24% will eventually lead to limb amputation[7].

More than half of non-traumatic amputations are caused by diabetes, and 85 percent of these cases are preceded by an ulcer on the foot. Following an amputation, the death rate rises from 13 to 40 percent at one year to 39–80 percent at five years. In addition, 50 percent of those who have had an amputation will experience foot ulcers and infections on the opposite side within the first 18 months after the amputation. In the three to five years following the initial amputation, a startling 58% of patients will require a contralateral amputation[8].

As the majority of diabetic amputations are followed by foot ulceration, it is critical that measures be taken to avoid this complication. There is a strong correlation between diabetic foot issues and nephropathy; retinal disease; Ischemia of the cardiovascular system; and cerebrovascular disease. A multidisciplinary approach is more likely to help these patients, as they face some of the most difficult challenges[9]. In this paradigm, a multidisciplinary team of doctors, including a plastic and orthopaedic surgeon, an endocrinologist (diabetologist), a microbiologist, a senior physiotherapist, and a podiatrist, works together to provide the patient with the best possible care. Rapid decision-making based on fresh clinical information is made possible by daily contact among the team's members. The network aids in the formulation of treatment plans by streamlining the process of making critical decisions. Implementing a multidisciplinary team approach has also been shown to be effective in decreasing the frequency of major amputations.

Pathogenesis

Ischaemia or neuropathy symptoms may be more common. Both are existent, but they don't exist in isolation from one another. However, the clinical appearance is the result of a combination of these factors.Most diabetic foot lesions are caused by peripheral neuropathy. Most people who are admitted to the hospital with diabetic foot ulcers do so as a result of an injury that was painless. As seen in Figure 1, the many paths that might lead to wound infection, gangrene, and amputation are shown[10].

The precise incidence of PN cannot be determined. The prevalence of clinical neuropathy is estimated to be between 10 and 20 percent in most investigations. However, after 25 years of diabetes, this percentage may rise to as high as 50%. Peripheral neuropathy and the insensate foot are the primary causes of diabetic foot ulcers, however unpleasant sensations are common in people with PN. Painful symptoms are common in individuals with PN regardless of the presence or absence of foot ulcers, according to a series of studies. The insensitivity of a diabetic patient's feet doesn't mean they can't have uncomfortable symptoms. 33 percent of those with foot ulcers reported experiencing pain. As a result, both painful and non-painful PN may exist at the same time in the same patient. Patients with a diabetic foot ulcer that was previously painless should be aware that if the ulcer suddenly becomes inflamed, it could be a sign of a more serious infection.

Peripheral neuropathy has a significant impact on the diabetic foot because it reduces feeling, making the foot vulnerable to even minor injuries. Even the smallest and most inconspicuous skin breach can serve as a point of entrance for microorganisms. Amputation is necessary if an infection is not successfully treated[11].

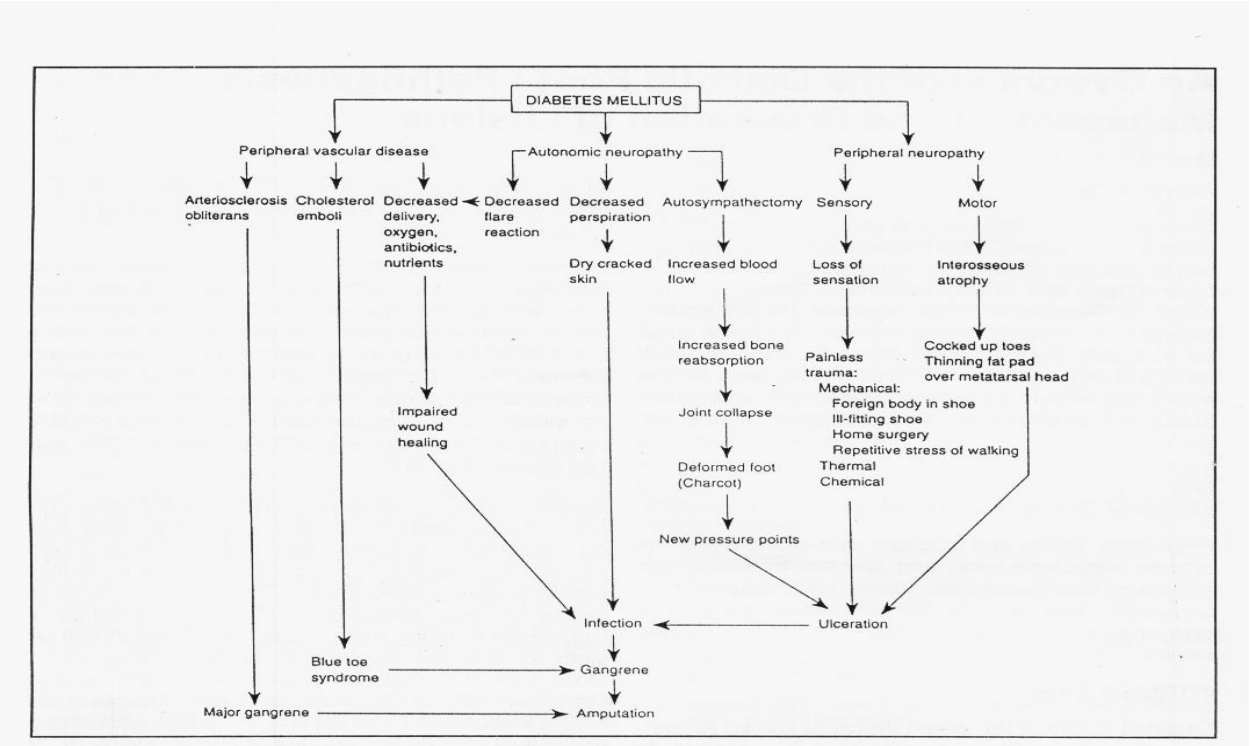

Fig 1: Pathogenesis of Diabetic Foot Ulcers

Neuropathy

More than 60% of the time, diabetic neuropathy is the underlying cause of foot ulcers. Neuropathy is a common complication of hyperglycemia-induced metabolic disorders. One of the most frequently cited modes of action is the polyol pathway. Aldose reductase and sorbitol dehydrogenase are two enzymes that have a role in the development of neuropathy when blood sugar levels are elevated. The intracellular glucose is transformed into sorbitol and fructose as a result. To maintain proper neuronal conduction, myoinositol synthesis is reduced as a result of the sugar product buildup. As a further complication, the conversion of glucose into a molecule necessary for the detoxification of reactive oxygen species (ROS) and the synthesis of nitric oxide vasodilator is depleted by this chemical conversion[12]. Vasoconstriction and an increase in nerve cell oxidative stress lead to ischaemia, which increases the risk of nerve cell damage and death. Oxidative stress and hyperglycemia cause nerve cell proteins to be glycated in an abnormal way, resulting in further nerve damage and ischaemia. Eighty percent of instances of diabetic polyneuropathy are distal symmetric length-dependent, despite the fact that diabetics are at risk for a wide range of neuropathies[13]. According to research, the metabolic abnormalities associated with diabetes make peripheral nerves more susceptible to long-term compression, which results in diabetic neuropathy. One possible explanation for this behaviour is the conversion of glucose to sorbitol, which elevates intraneural water content osmotically. Consequently, it has a low tolerance for variations in its diameter when it passes through fixed anatomical features. Since swelling puts the nerve within its anatomical "tunnel," it is at risk of being compressed, leading to an embolism, which results in distal nerve ischaemia and a decrease in blood flow[14]. The accumulation of advanced glycation end products (AGEs) in the intraneural space, produced by elevated levels of serum glucose, slows axoplasmic protein trafficking for repair and signal transduction. If these processes are combined, the ability of a neuron to communicate with its end-organs, such as muscles or skin mechanoreceptors, will be hampered. Symmetric and length-dependent effects on the lower limbs occur first in asymmetric and length-dependent ways[15].

The nervous system's motor, autonomic, and sensory components are all affected by diabetic neuropathy. When the intrinsic foot muscles are injured, there is an imbalance in the affected foot's flexion and extension[16]. Eventually, these irregularities lead to skin breakdown and ulceration as a result of atypical bone prominences and pressure points on the foot. Autonomic neuropathy impairs the function of the sweat and oil glands. As a result, the skin on the top of the foot becomes dry and more susceptible to tears and infection. The absence of sensation in peripheral neuropathy increases the risk of ulceration[17]. Since the injury is so severe, it is difficult for patients to determine whether or not their lower legs have been damaged. Furthermore, as a result of recurrent pressure and shear pressures from ambulation and weight-bearing, the wound often goes untreated[18].

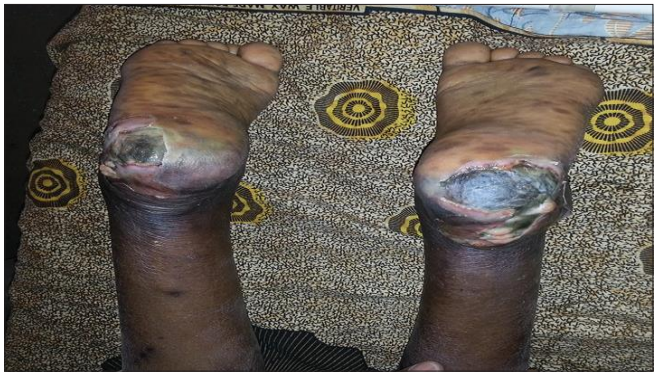

Fig 2 : Feet affected Neuropathy leading to ulceration

Vascular Disease

Foot ulcers can be caused by peripheral artery dysfunction in as much as 50 percent of the cases. The tibial and peroneal arteries of the calf are frequently affected. Peripheral artery endothelial damage and smooth cell abnormalities result from a long-term hyperglycaemic condition. Constriction occurs as a result of a decrease in endothelium-derived vasodilators. Because of the increased thromboxane A2 production due to diabetes-induced hyperglycemia, there is an elevated risk of plasma hypercoagulability[19]. Additionally, changes in the vascular extracellular matrix may contribute to arterial stenosis. Other risk factors for peripheral artery disease in diabetes patients include smoking, hypertension, and hyperlipidemia. As a result, diabetics are at greater risk of developing occlusive vascular disease, which can lead to ischaemia in the lower extremities and ulcers [Fig 3].

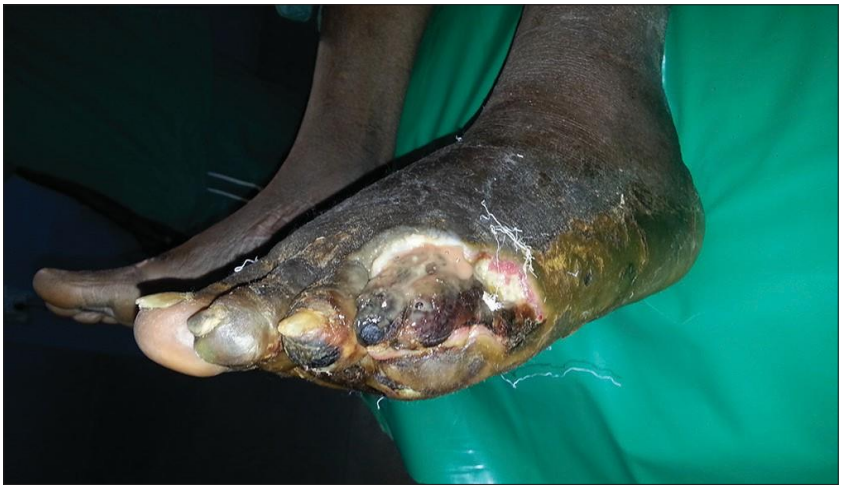

Fig 3 : Foot affected by Peripheral arterial disease

Management Therapeutic Approaches of Diabetic foot ulcers

Patients with DFIs may have their feet or legs amputated, as well as die in extreme cases. Ischemia in combination with an infected DFU is one of the most difficult challenges in treating DFUs. A buildup of germs in the wound can lead to shock and systemic inflammation (SIR), highlighting the importance of infection treatment for patients with DFUs[20]. Treatments range from topical and oral to intravenous, depending on the severity

of the illness and the patient's response to treatment. When all symptoms have subsided and laboratory results have returned to normal, a course of antibiotics must be resumed. The wound should be evaluated often throughout the course of infection therapy in order to determine the efficacy of the medication. As can be seen from Table S1, the antibiotic regimen used in DFIs is extensive (Supplementary Materials)[21].

Debridement

The eradication of the bacterial biofilm and necrotic tissue from the foot ulcer necessitates infection treatment. In addition to providing tissue for microbiological culture, the wound healing process is facilitated. In order for the wound to heal, necrotic tissue accumulates surrounding it. Debridement helps wound healing by removing necrotic tissue, despite the fact that necrotic tissue prevents the formation of new tissue[22]. For debridement and wound cleansing, Isotonic saline solutions are widely used in conjunction with antibiotic therapy (0.9 percent NaCl). The bio-burden of plantar neurotrophic ulcers can be reduced by removing the hyperkeratotic margins of these ulcers. Every seven to 14 days is the ideal interval for this procedure. Debridement treatments that are both active and autolytic are used in the clinic. The removal of necrotic material from the wound bed by means of manual treatments such as surgical debridement frequently results in bleeding in the wound. Using a forceful jet of water, hydro-surgical debridement is able to remove dead tissue. In outpatient settings, ultrasonic-assisted debridement is convenient. An irrigation fluid and a low-frequency pulse are employed in this treatment[23].

Dressings

Its principal role is to shield the wound from infection and environmental exposure, as well as to increase the area's dampness so that new tissue can grow and autolytic debridement can take place. Autolytic debridement accelerates the breakdown of necrotic tissue by endogenous proteolytic enzymes. Some of the existing dressing types include films, hydrogels, acrylics, hydrocolloids, calcium alginates, hydrofibers, and foams. High secretions demand absorbent dressings in contrast to dry wounds, which require moisture balancing dressings[24].

Hydrogels

Hydrogel dressings' insoluble component material contains water-binding copolymers. The matrix can absorb exudates from the wound to maintain it wet. Hydrogel dressings may be more effective for repairing DFUs than other types of dressings, according to some research[25].

Alginate Dressings

Alginate products are made from seaweed (such as sodium alginate, potassium alginate, or calcium alginate). Like hydrogels, these absorb wound exudate and keep the wound wet. Studies and meta-analysis have demonstrated that basic contact dressings and silver hydrocolloid dressings are not different[26].

Acrylics

Water vapour permeability is an inherent characteristic of the dressing. In addition to the fact that it has a low capacity for absorption, it is tough to get rid of[27].

Hydrocolloids

The hydrophilic carboxy components of this dressing are bound to the hydrophobic methylcellulose by a polyurethane film. Autolytic debridement is aided by these long-lasting, self-adhesive components. During the removal process, the wound may be disturbed and allergic responses may ensue[28].

Foam Adhesive

This glue, composed of absorbent polyurethane with various pore sizes, can be used to apply silver and ibuprofen to the wound. However, the skin around foam adhesives is irritated, which is a disadvantage[29].

Hydrofibers

Hydrofibers are made up of sheets of carboxymethylcellulose. Two advantages are the high capacity of the absorbent and the ease with which it may be removed. Nonetheless, a second layer of defence is required. '

Topical Antimicrobials

A topical antibiotic isn't advised for chronic wounds due to the lack of moisture balance maintenance and autolytic debridement. It is important to use topical antimicrobials that have low toxicity to the host tissue when applying them topically. This section details some of the topical antiseptics and antimicrobials that can be used for DFIs[30].

10% Solution of Povidone Iodine

As an antimicrobial, povidone iodine can penetrate the bacterial biofilm and help wound healing. Two to four weekly assessments are carried out and used for two to four weeks. It is possible to develop hypothyroidism and tissue toxicity from long-term use, on the other hand.

Chlorhexidine

Antibacterial and wound-healing properties are provided by this substance. However, cartilage tissue may be damaged[31].

Systemic Antibiotic Therapy

Systemic antibiotic therapy is required when there is evidence of localised, progressive, or systemic infections. Antimicrobial treatment is influenced by a variety of factors, including a microbiological culture, clinical symptoms, body structures implicated, and a patient's immunocompetence. After obtaining bacterial culture results, broad-spectrum antibiotics are taken first, followed by a more targeted medication. An intravenous antibiotic may be given if the infection is severe, not responding, spreading, or if osteomyelitis is thought to be significant. Oral antibiotics can be used to treat staphylococci and streptococci. Adding a second antibiotic if the first fails to control the infection is done. Methicillin-resistant

infections should be treated with preventative measures. The treatment of MRSA may be explored for patients who have previously been infected with Staphylococcus aureus if the infection is resistant to antibiotics or if the prevalence of infection is high. To treat a minor illness, a single course of antibiotics is typically sufficient; for a more serious infection, a course of two to three weeks of antibiotics is usually required. As a broad-spectrum antibiotic, Cibacillin/Tazobactam, Piperacillin/Tazobactam, and Amoxicillin/Clavulanic Acid are among the most commonly prescribed drugs[32].

DFU Emerging Therapies

Drugs

The availability of new treatments for DFUs that deviate from the standard of care for ulcer healing is increasing. Examples of these treatments include growth factors, inflammatory modulators, plant extracts, blood products, biologic therapy, wound negative pressure, hyperbaric oxygen therapy, and skin substitutes." But these therapies are not alternatives for standard diabetic foot care, and should not be utilised as a substitute. Below, we'll go into greater detail about a few innovative treatments[33].

Ciprofloxacin Loaded Calcium Alginate Wafer

A calcium alginate wafer containing ciprofloxacin has already been developed.. Applying this wafer directly to the site of the wound was the method used in this study. An initial quick release of medication was followed by a sustained medication release in the dressings, which were found to be effective against both Gram-positive and Gram-negative bacteria. The dressings were also found to be biocompatible (>85% cell viability over 72 hours) with human adult keratinocytes[34].

WF10 (Immunokine, Nuvo GmbH)

It contains 4.25 percent chlorite, 1.9 percent chloride, 1.5 percent chlorate, and 0.7% sulfurate in a sodium cation solution in WF10, which is distributed in 1:10 aqueous solution. When chronic inflammation is to blame for symptoms such as proctitis or cystitis, the chlorite ion is an effective treatment. WF10's potential to stimulate macrophage phagocytic activity by stimulating the myeloperoxidase–hydrogen peroxide–halide pathway results in an increased immunological response[35]. In a study by Yingsakmongkol, WF10 was utilised in conjunction with standard treatment for severe DFUs. Patients with neuropathic ulcers had an excellent or fair prognosis, according to the results of this study.

Pirfenidone (PFD)

PFD can be used to treat idiopathic lung fibrosis as an antifibrogenic agent. As a modulator of the extracellular matrix, PFD is essential. Prolonged use of PFD has been shown to have anti-inflammatory and antioxidant properties, as well as to reduce TNF-secretion and TNF-associated levels. An experimental study in Mexico comparing the efficacy of topical PFD + M-DDO (an antimicrobial and antiseptic agent) versus ketanserin, an antagonist of 5-HTR2 with no agonistic properties (approved for wound treatment by the Mexican Comisión

Federal para la Protección contra Riesgos Sanitarios: COFEPRIS) was conducted. Patients received either PFD + M-DDO or ketanserin for a period of six months[36].

Nitroglycerine (Isosorbide Dinitrate)

It is possible that nitroglycerine, when administered to diabetic wounds, can operate as an effective source of nitric oxide (NO), increasing blood flow and metabolic activity at the ulcer site.

Biologics

Biologicals include humans, animals, and microbes (vaccines, blood and blood components, and gene therapy). Cell-based and growth factor therapy are examples of biologics used in wound healing. Biologics are regulated by the FDA's Center for Biologics Evaluation and Research[37].

Growth Factors

As a result of growth factor injections, wound healing can be expedited. These injections include platelet-derived growth factor-BB, fibroblast growth factor-b, epidermal growth factor (EGF), VEGF, and granulocyte colony-stimulating factor (G-CSF) (G-CSF). Their usefulness is currently unproven, and they are extremely difficult to obtain. The synergistic impact of combining these components with other extracts and chemicals is sometimes employed. This recombinant DNA growth factor for wound healing has undergone significant investigation and is currently approved for use[38].

Insulin

Because insulin is a naturally occurring glucose-lowering molecule, it has been the universal treatment for diabetes since the 20th century. When it comes to DFUs, topical insulin is becoming more popular as a therapeutic agent. Many diabetics and animals who received insulin-based treatments for their chronic ulcers had outstanding outcomes. A key problem with applying topical insulin is the molecule's volatility[39].

Neuropeptides

Peripheral nerves and cutaneous neurobiology maintain a bidirectional relationship between the nervous and immune systems during normal wound healing. A condition known as diabetic peripheral neuropathy (DPN) can lead to the development of chronic wounds and ulcers. A lack of neuropeptide production by C-nociceptive fibres, which are damaged by neuropathy, has been found to hinder recovery.

Cell and Gene Therapy

Cell and gene therapy can be used to improve DFU therapies. Stem cells, keratinocytes, and fibroblasts have all been examined in the treatment of chronic wounds. Stem cell therapy can increase blood flow in limbs that are ischemic. As of now, there is no evidence that this method is effective for the treatment of chronic wounds. There were good results in studies using autologous stem cells, mesenchymal marrow cells, and bone marrow-derived mononuclear cells for DFU healing[40].

- **Stem Cells**

Stem cells have the ability to self-renew and specialise into a wide range of cell types. Bone marrow (BM) and mesenchymal stem cell (MSC)-derived mononuclear cells are examples of stem cell therapies (MSC). Progenitors in MSCs are multipotent and can differentiate into a range of cell types. MSCs embedded in a collagen matrix were used to study DFU healing in a mouse model. The healing rate of MSC-treated mice was found to be greater than that of the control animals[41].

- **Fibroblast Cultures**

As a graft substitute, dermal fibroblasts were used to generate three-dimensional dermis substitutes for non-ischemic ulcers, which were successfully treated. Fibroblasts (Apligraf®, GraftSkin) were studied and found to be in good health. As a result, more study is needed to improve and clarify the situations for these innovative medicines[42].

- **Grafting (Bioengineering)**

DFUs with higher activation rates can benefit from grafting to address skin defects. External wounds that only affect the skin and not the soft tissues, muscles, joints, or bones of the body can be treated using grafting[43].

- **Bovine Fluid Collagen**

It is a highly refined fibrillar bovine collagen fluid. Collagen found in bovine fluid collagen is unique from that found in biological scaffolds because it is fibrillar, rather than cross-linked (that is, non-cross-linked collagen). A fluid version of the collagen scaffold, the wound fluid matrix is the most advanced form of the collagen scaffold. The wound tunnels, on the other hand, are difficult to treat because of their irregular design[44].

Honey

Since ancient times, honey has been used to cure a variety of chronic skin diseases. Wounded and burned skin can benefit from the antibacterial, antioxidant, and anti-inflammatory properties of honey. Treating DFUs with honey has gained a lot of attention over the last several decades, and various research have analysed the various qualities of honey to cure the various phases of DFUs. Honey has been shown to aid in the healing process in animal tests. Researchers determined that honey dressings are safe despite the absence of high-quality evidence, but further research is needed to determine their true value[45].

Ozone Therapy

In response to the lack of oxygen in wounds caused by DFUs, ozone therapy was proposed, which is supplied in various formulations, such as ozonized oils (for example, sunflower or olive oil), as well as a mixture of oxygen and ozone, administered directly to the lesion. Antibacterial characteristics and a method to activate distinct endogenous growth factors boost wound healing when applied directly to chronic wounds. However, over use of this medicine can lead to undesirable outcomes[46-48]. Previous studies have shown that intracellular ozone injections can help treat patients with severe gangrene and DFUs. The patient had to switch to a new treatment in order to avoid unpleasant side effects[49]. It was

thus unable to evaluate if ozone therapy for the treatment of DFUs was useful. After a clinical case demonstrated that ozone therapy was being utilised inappropriately in patients with advanced DFUs, more research and training are needed [50].

Conclusion

In diabetic patients, foot ulcers are more prone to occur than in those who do not have the illness. Deformity and ulceration are side effects of uncontrolled hyperglycemia for an extended period of time. The feet of diabetics should be inspected at least once a year in order to rule out any potential ulcers. Individual ulceration risk and examination findings should be used to guide treatment recommendations. If ulcers are present, appropriate debridement, off-loading, and dressings should be applied. Wound cultures should also be utilised to determine the presence of infections, as well as their results being used to help guide treatment. If a patient shows signs of ischemia, they should be assessed to see if revascularization is an option. People who have experienced serious injuries can benefit from complementary and alternative therapy. There are numerous therapies (biological, devices, pharmaceuticals, etc.) being tested in order to treat chronic wounds caused by diabetes, which are a global health problem and a considerable burden on the quality of life of patients. Maintaining good care for standard DFU therapies should not be abandoned. In this study, wound healing was observed to be faster when PDGF was administered. Wound healing has been improved through stem cell therapy and the use of natural products like honey, which has biological antibacterial action.

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