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Review On Diabetic Foot Ulcers, Their Pathogenesis, Epidemiology,And Emerging Treatments

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Abstract:Diabetic foot complications are not exactly a hot topic. Diabetic nephropathy, heart attack, and stroke are not 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, most diabetics are hospitalized and require long-term hospitalizations in the case of diabetic foot ulcers (DFUs), which can lead to amputations of the limb and significant social, psychological, and economic effects. A DFU can develop in up to 25% of diabetic people throughout their lives, and more than half of those patients become infected. As a result, 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 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

1. 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 critical 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. A thorough physical exam, supplemented by monofilament neuropathy testing and noninvasive testing for vascular insufficiency, can effectively classify patients who currently suffer from ulcers or other diabetic foot problems for those at risk for foot ulcers. 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 essential 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 an ulcer on foot precedes 85 percent of these cases. Following an amputation, the death rate rises from 13 to 40 percent at one year to 39–80 percent at five years. Furthermore, 50 percent of those who have had an amputation will develop foot ulcers and infections on the opposite side within the first 18 months. In the three to five years following the initial amputation, a startling 58% of patients will require a contralateral amputation[8].

As most diabetic amputations are followed by foot ulceration, measures must 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 challenging challenges[9]. A multidisciplinary team of clinicians, comprising a plastic and orthopedic surgeon, an endocrinologist (diabetologist), a microbiologist, a senior physiotherapist, and a podiatrist, collaborate to offer the best possible treatment for the patient in this paradigm. Daily contact among team members allows for quick decision-making based on new clinical findings. The network aids in the formulation of treatment plans by streamlining making critical decisions. Implementing a multidisciplinary team approach has also been shown to decrease the frequency of major amputations.

Pathogenesis

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

The precise incidence of P.N. cannot be determined. In most investigations, the prevalence of clinical neuropathy is estimated to be between 10 and 20 percent. 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 familiar in P.N. patients. According to a series of studies, painful symptoms are common in individuals with P.N. regardless of foot ulcers. The insensitivity of diabetic patients' feet does not mean they cannot have uncomfortable symptoms. 33 percent of those with foot ulcers reported experiencing pain. As a result, both painful and non-painful P.N. may exist simultaneously 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 severe infection.

Peripheral neuropathy significantly impacts the diabetic foot because it reduces feeling, making it 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].

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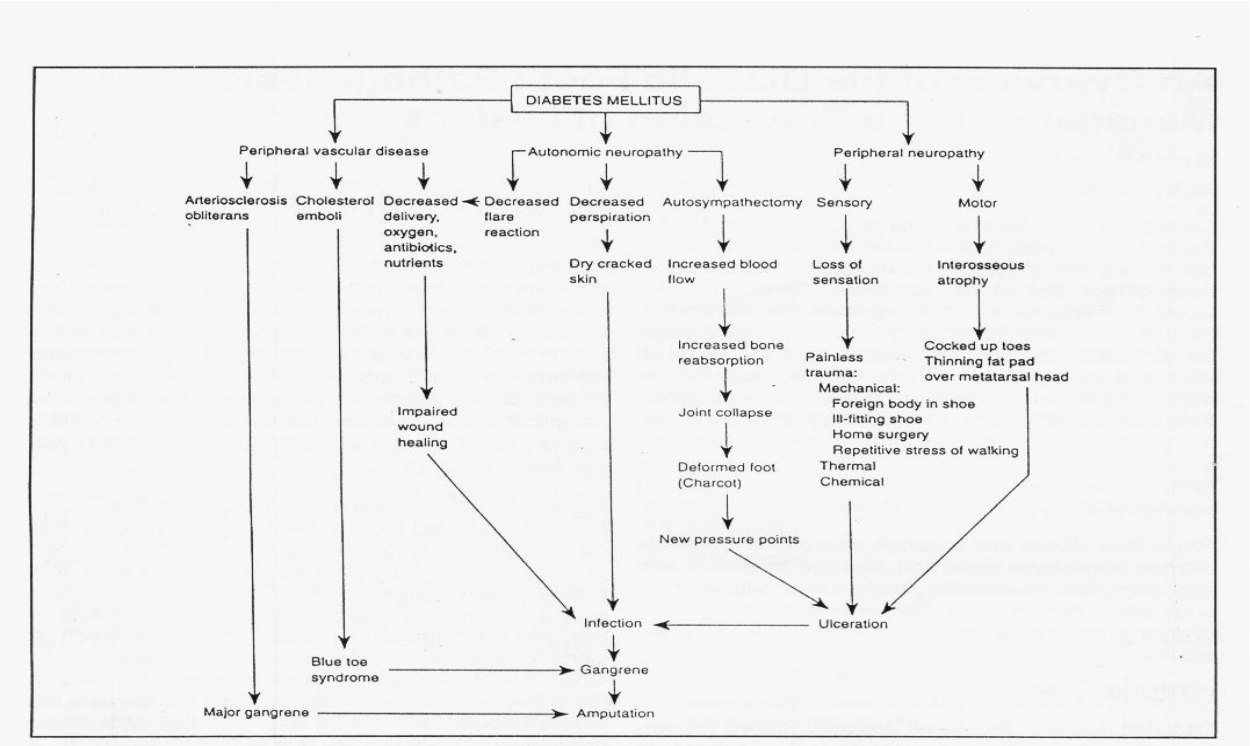

Fig 1: Pathogenesis of Diabetic Foot Ulcers

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 develop neuropathy when blood sugar levels are elevated. The intracellular glucose is transformed into sorbitol and fructose as a result. Myoinositol synthesis is reduced due to the sugar product buildup to maintain proper neuronal conduction. This chemical change also depletes the conversion of glucose into a molecule required to detoxify reactive oxygen species (ROS) and create a nitric oxide vasodilator [12]. Ischemia is caused by vasoconstriction and increased oxidative stress in nerve cells, increasing the chance of damage and death. Oxidative stress and hyperglycemia cause nerve cell proteins to be glycated in a weird way, resulting in further nerve damage and ischemia. Eighty percent of instances of diabetic polyneuropathy are distal symmetric length-dependent, even though people with diabetes 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 behavior 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 ischemia and a decrease in blood flow [14]. Increased serum glucose levels cause a buildup of advanced glycation end products (AGEs) in the intraneural space, inhibiting axoplasmic protein trafficking for repair and signal transduction. The capacity of a neuron to interact with its end organs, such as muscles or skin mechanoreceptors, will be impaired if these processes are mixed. 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 due to 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, the wound often goes untreated due to recurrent pressure and shear pressures from ambulation and weight-bearing [18].

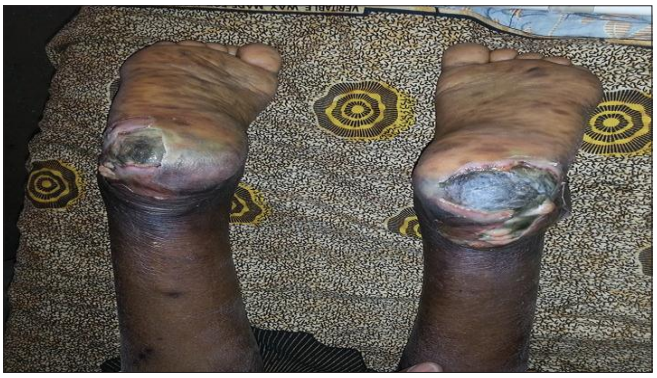

Fig 2: Feet affected neuropathy leading to ulceration

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 long-term hyperglycemia conditions. Constriction occurs as a result of a decrease in endothelium-derived vasodilators. There is an increased risk of plasma hypercoagulability due to increased thromboxane A2 generation caused by diabetes-induced hyperglycemia [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, people with diabetes are at greater risk of developing occlusive vascular disease, leading to ischemia in the lower extremities and ulcers [Fig 3].

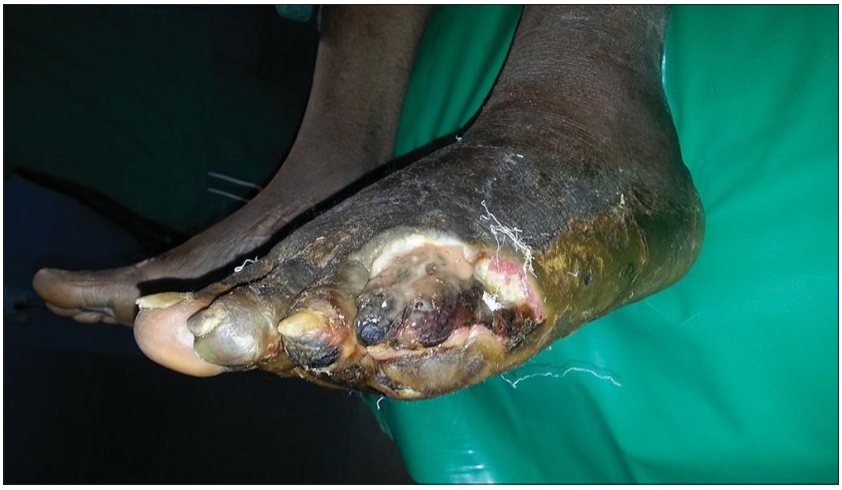

Fig 3: Foot affected by Peripheral arterial disease

Management Therapeutic Approaches of Diabetic foot ulcers

Patients with DFIs may have their feet or legs amputated and die in extreme cases. Ischemia in combination with an infected DFU is one of the most challenging 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 infection therapy 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, even though necrotic tissue prevents the formation of new tissue [22]. Isotonic saline solutions are widely used with antibiotic therapy (0.9 percent NaCl). By eliminating the hyperkeratotic edges of plantar neurotrophic ulcers, the bio-burden of these ulcers can be minimized. 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 utilizing manual treatments such as surgical debridement frequently results in bleeding in the wound. Hydro-surgical debridement can remove dead tissue. In outpatient settings, ultrasonic-assisted debridement is convenient using a forceful water jet. 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 and increase the area's dampness so that new tissue can grow and autolytic debridement can occur. Autolytic debridement accelerates the breakdown of necrotic tissue by endogenous proteolytic enzymes. Existing dressing types include films, hydrogels, acrylics, hydrocolloids, calcium alginates, hydrofibers, and foams. High secretions demand absorbent dressings compared 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. According to some research, hydrogel dressings may be more effective for repairing DFUs than other types of dressings [25].

Alginate Dressings

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

Acrylics

Water vapor permeability is an inherent characteristic of the dressing. In addition to the fact that it has a low absorption capacity, 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. These long-lasting, self-adhesive components aid autolytic debridement. The wound may be disturbed during the removal process, and allergic responses may ensue[28].

Foam Adhesive

This glue, composed of absorbent polyurethane with various pore sizes, can 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, the second layer of defense is required. '

Topical Antimicrobials

A topical antibiotic is not recommended for chronic wounds because of moisture equilibrium and autolytic debridement. Topical antimicrobials with low toxicity to the host tissue are essential when applying them topically. This section details some of the topical antiseptics and antimicrobials 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. On the other hand, it is possible to develop hypothyroidism and tissue toxicity from long-term use.

Chlorhexidine
This substance provides antibacterial and wound-healing properties. However, cartilage tissue may be damaged [31].

Systemic Antibiotic Therapy
Systemic antibiotic therapy is required when there is evidence of localized, progressive, or systemic infections. Antimicrobial treatment is regulated by various elements, including a patient's immunocompetence, clinical symptoms, body structures implicated, and microbiological culture. 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. If the first fails to control the infection, adding a second antibiotic 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. A single course of antibiotics is typically sufficient; for a more severe 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." However, these therapies are not alternatives for standard diabetic foot care and should not be used as substitutes. Below, we will 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 wound site was the method used in this study. A sustained medication release followed an initial quick-release of medication in the dressings, which were effective against 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 a 1:10 aqueous solution. The chlorite ion is an effective treatment when chronic inflammation is to blame for symptoms

such as proctitis or cystitis. The ability of WF10 to improve immunological response by promoting macrophage phagocytic activity via stimulating the myeloperoxidase–hydrogen peroxide–halide pathway[35]. In a study by Yingsakmongkol, WF10 was utilized in conjunction with standard treatment for severe DFUs. According to the results of this study, patients with neuropathic ulcers had an excellent or fair prognosis.

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 and reduce TNF-secretion and TNF-associated levels. The efficacy of topical PFD + M-DDO (an antimicrobial and antiseptic agent) versus ketanserin, a 5-HTR2 antagonist with no agonistic properties (approved for wound treatment by the Mexican Comisión Federal para la Protección contra Riesgos Sanitarios: COFEPRIS) was compared in an experimental study in Mexico. Patients were given either PFD + M-DDO or ketanserin [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

Humans, animals, and microbes are biological (vaccines, blood and blood components, and gene therapy). Biologics used in wound healing include cell-based and growth factor therapy. The FDA's Center for Biologics Evaluation and Research regulates biologics [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 fundamental problem with applying topical insulin is the molecule's volatility [39].

Neuropeptides

During routine wound healing, peripheral nerves and cutaneous neurobiology maintain a bidirectional relationship between the nervous and immune systems. A condition known as diabetic peripheral neuropathy (DPN) can lead to chronic wounds and ulcers. A lack of neuropeptide production by C-nociceptive fibers, damaged by neuropathy, has hindered

recovery.

Cell and Gene Therapy

Cell and gene therapy can be used to improve DFU therapies. Stem cells, keratinocytes, and fibroblasts have been examined to treat chronic wounds. Stem cell therapy can increase blood flow in ischemic limbs. 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 can self-renew and specialize into a wide range of cell types. Bone marrow (B.M.) 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 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 body's soft tissues, muscles, joints, or bones 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 (non-cross-linked collagen). A fluid version of the collagen scaffold, the wound fluid matrix is the most advanced form of the collagen scaffold. On the other hand, the wound tunnels are difficult to treat because of their distinctive design [44].

Honey

Since ancient times, honey has been used to cure various chronic skin diseases. Wounded and burned skin can benefit from honey's antibacterial, antioxidant, and anti-inflammatory properties. Treating DFUs with honey has gained much attention over the last several decades. Various research has analyzed 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 actual value [45].

Ozone Therapy

In response to the lack of oxygen in wounds caused by DFUs, ozone therapy was proposed, supplied in various formulations, such as ozonized oils (for example, sunflower or olive oil) and 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, overuse of this medicine can lead to undesirable outcomes [46-48]. Previous studies have shown that intracellular ozone injections can help treat severe gangrene and DFUs. The patient had to switch to a new treatment to avoid unpleasant side effects [49]. It was thus unable to evaluate if ozone therapy

for the treatment of DFUs was beneficial. More research and training are needed after a clinical case demonstrated that ozone therapy was being utilized inappropriately in patients with advanced DFUs [50].

2. CONCLUSION

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

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