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CURRENT TREATMENT OF DIABETIC FOOT ULCER WITH INDEGENOUS PLANT; A REVIEW

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ABSTRACT

The prevalence of diabetic Foot ulcer is increasing day by day among global population. The most frequent underlying etiologies are neuropathy, trauma, deformity, high plantar pressures, and peripheral arterial disease. The disease etiology suggest that Gram-positive bacteria, such as Staphylococcus aureus and beta-hemolytic streptococci, are the most common pathogens in previously untreated mild and moderate infection. Diabetic foot ulcer (DFU) is one of the important complications, since the major deaths in diabetes are due to DFU, which arises as a consequence of complicated and multi-factorial pathologies. This review is based on plant related drugs, as available antibiotics resistance is global concern. For the treatment of disease with single strategy might unlikely less effective and also the overall costs of these therapies are high. The use of many commonly used herbs and spices are claimed to have wound healing effects with various mechanisms since long time. The treatment with herbal drugs can improve the quality of life of Diabetic foot ulcer patients with less adverse effects.

KEYWORDS: Diabetic Foot ulcer, Foot Infection, wound healing, herbal medicine of foot ulcer.

INTRODUCTION

Foot Ulcer

Complications of foot ulcers are the major source of hospitalization and amputation in diabetic patients and lead to significant health care costs as confirmation by the fact that 20–40% of health care resources are diabetic foot infection. Diabetic foot infection is called,

according to the World health Organization, as "ulceration of the foot associated with the neuropathy and different grades of ischemia and infection".[4]

The Foot disorders are such as ulceration, infection, sickness leading to causes of hospitalization in patients with both diabetes mellitus. Approximately 15 to 20 percent of the estimated 16 million peoples in the United States with diabetes mellitus will be hospitalized with a foot syndrome at some time during this disease. Unfortunately, many of these patients will require amputation within the foot ankle as a consequence of severe infection or peripheral ischemia. Neuropathy is a predisposing factor for ulceration and amputation. The diabetic foot and its significance account for billions of dollars in direct medical expenditures, as well as long time period hospital stays and periods of disability. The most characteristic lesion of the diabetic foot is a ulceration peripheral neuropathy, trauma, and deformity. Any other factors are such as ischemia, callus formation, and edema.[3]

The herbs also enhance the rate of tissue healing by providing different vital substances (vitamins, proteins and minerals) required at different stages of wound regeneration and proliferation. Herbals are also found to be safe and cost effective than allopathic drugs. This review discusses the possible use of herbs in treating DFUs with their mechanisms.[17]

Risk factors

Risk factors for foot ulcers in patients with diabetes include:

- Amputation
- History of a foot ulcer
- Foot deformity
- Peripheral vascular disease
- diabetic nephropathy in dialysis
- Poor glycemic control
- Smoking

Sign & Symptoms

- Swelling, discoloration, and warmth on every side of the wound
- Pain and firmness
- Callused or thickened skin around the ulcer
- Fever and chills in stages of foot ulcers

Causes

- Poor circulation of blood
- High blood sugar level
- Nerve damage
- Irritated or wounded feet.[21]

EPIDEMIOLOGY OF DIABETIC FOOT SYNDROME

Approximately 82000 lower extremity amputations directly related to diabetes are performed in the USA annually of these amputations, the majority (80%) have been preceded by foot ulceration. Foot ulceration is the most common single precursor to lower extremity amputation among diabetics. In the exist of foot ulceration is considered an important risk for morbidity, mortality, and disability as supported by the fact that about 80% of non traumatic amputations are caused by the presence of diabetes and 85% of these amputations are preceded by a foot ulceration. An estimated 15% of patients with diabetes will develop a lower extremity ulcer during the course of their disease.[4]

Although prevalence of diabetes morbidity is high, specific data on complications related to skin disorders are limited. Several epidemiological studies evaluating occurrence of skin disorders on type 1 and type 2 DM were performed worldwide, with pattern of skin disorders varying according to DM type and region where the study was conducted. Overall the frequency of skin disorder in both type 1 and 2 DM varied from 51.1 to 97 % in different regions worldwide. The highily prevalence of dermal disorder among DM patients described in literature endorses the clinical importance and high impact of this complication.[11]

It is estimated that the incidence rate of SSTIs is 24.6 cases per 1,000 persons per year, but because most of these infections are self-limiting in a range of 7-10 days this estimation may not be very precise. About 2% of visits to Emergency Departments (EDs) concern SSTIs, with a hospitalization rate of 0.1% among the adult population. The prevalence is higher in males and among adults 45-65 years old. Approximately, 70-75% of SSTIs are managed in an out-patient setting and lower extremities are the most frequent location.[15]

DIABETES MELLITUS

Diabetes mellitus (DM) is the major issue in the world wide and it is the chronic disorder which occurs due to the inadequate amount of insulin uptake (or) release. The main factors for the increasing DM are inactive lifestyle, obesity, ageing and in few cases it was genetical.

The negligence of DM condition will result in a number of consequences which include neuropathy, retinopathy, endothelial dysfunction, atherosclerosis, myocardial infractions, diabetic foot. The circumstances of diabetes became a heavy load into the patient as well as physician.[17] Diabetes mellitus is a complex disorder resulting from dysregulated glucose sensing or insulin secretion, autoimmune-mediated β-cell destruction in type 1 diabetes or insufficient compensation for peripheral insulin resistance in type 2 diabetes. Hyperglycemia and dyslipidemia are two devastating concomitants of diabetes known to play a major role in creating secondary disorders such as macro- and micro-vascular complications.[18] Type 1 and Type 2 diabetes are both common chronic diseases, affecting millions of people worldwide, leading to poor health outcomes and increased health care costs. In addition, both diseases (T1D and T2D) are associated with reduced quality of life.[26]

Diabetes is a metabolic disorder that affects more than 340 million people individuals and about 20% of them develop diabetic wounds infection worldwide. Leg or foot ulcers are most common wounds in diabetic patients in world wide. This can result in stalled chronic wounds. The incidence of delayed healing process in diabetic patient is increasing globally due to lack of preventive and control measures. About 2.5%–15% of yearly world-wide health budgets are consumed on diabetes mellitus and diabetic wounds stake a major part.[1]

FACTORS AFFECTING WOUND HEALING

Wound involves a disturbance in the cellular, anatomical, and functional epithelial integrity of the skin consequent to physical, chemical, thermal microbial, or immunological insult; followed by disruption of the structure and function of underlying normal tissue. The basic response in wound healing involves a process of connective tissue restoration and is characterized by four overlapping phases such as hemostasis, inflammation, proliferation, and remodeling in which the repair process requires the coordination of different cells, growth factors, and cytokines.[18],

In the wound healing is look as an interaction between a complex cascade of cellular and bio-chemical activities in the restoration of structural, functional integrity, and enhance the strength in injured tissues. The phases of wound healing usually go on in a fashionable and time-dependent manner. Any distubance in the process of wound healing may potentially lead to chronic wound or pathological scarring. Factors that affect wound healing are dis-cussed below-

Wound site

The site of the wound is an important factor in wound healing as wound infection is a common reason for impaired wound healing. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are few of the organisms responsible for wound infection, and reports have found that *S. aureus* is the main pathogen associated with diabetic foot infection.

Immune state

Various components of the immune system are affected in patients with diabetes. It has been reported that polymorphonuclear leukocyte function is reduced particularly in the presence of acidosis while leukocyte adherence, chemotaxis, and phagocytosis may also be negatively affected in diabetic state, consequently causing delayed wound healing. Antioxidant systems that participate in bactericidal activity may be impaired in diabetic state, making the wounds in diabetic patients to be susceptible to infection.

Age

There seems to be a relationship between the ages of an individual and wound healing process. Wound healing seems to be delayed in older age. This is possibly due to the fact that fibroblast growth and activity decrease in older people while collagen synthesis and wound contraction are also reduced in injured older people.

Disease state

S. aureus and beta-hemolytic streptococci are treated as pathogens in early diabetic foot infections. These studies have reported a higher incidence of bacterial infection in diabetic women than in non-diabetic women. It seems that diabetic patients are more susceptible to wound infection. This review reported a higher incidence (11%) in wound infection in diabetic patients than in the general patient population.

Reactive oxygen species (ROS)

The high concentration of ROS could induce serious tissue damage which could lead to neoplastic transformation, further leading to the impaired healing process by inducing cellular, DNA, proteins, and lipids damages.

PATHOPHYSIOLOGY

The skin, especially subcutaneous tissue, is the largest organ in the body. The epidermis layer has no blood vessels and it is protected against infection by the stratum corneum. These

Infections are correlate with skin and underlying soft tissues, which occur when the microbial attack into various layers overwhelm host defences and these are clinical existence with variable presentations, causes, and levels of clinical severity.[5]

In this physiology the diabetic foot ulcers has neuropathic, vascular, and immune system components. This is show a basic relationship with the hyperglycemic state of diabetes. The hyperglycemia is produces oxidative stress on nerve cells and conduct to neuropathy. The Additional nerves are dysfunction from glycosylation of nerve cell proteins, leading to further ischemia. These cellular changes manifest in motor, autonomic, and sensory components of foot ulcers. That are damage to motor neurons of the foot and an imbalance of flexors and extensors, anatomic deformities, and eventual skin ulcerations. Autonomic nerves are damage of sweat gland function, and the foot may develop inhance the ability to moisture in skin, then the epidermal cracks and skin breakdown. In the Last stage, the patients have not notice foot wounds because of reduced the peripheral sensation because the blood supply required to heal a diabetic foot ulcer and the ulcer can be reached in chronic stage.[2]

In diabetes the Patients are lose the protective sensations for temperature and pain. Motor neuropathy can produce the result in foot deformities like, claw toe that is contribute to local pressure from footwear, then making skin ulceration even more likely. Once the skin is broken (typically on the plantar surface), then underlying tissues are open for colonization by pathogenic organisms. After that the result the wound infection may begin superficially, but with delay in this treatment and impaired body, the mechanisms caused by neutrophil dysfunction and vascular insufficiency, it can also extent to the contiguous subcutaneous tissues and to even deeper structures.[12]

“The majority of foot ulcer look to the result from minor trauma in the presence of sensory neuropathy.” All of the three risk factors are present in 65% of diabetic foot ulcers. The calluses, edema, and peripheral vascular disease have been identified as etiological factors in the growth of diabetic foot ulcers.[14]

For the appearance of a DFU, the convergence of several factors is necessary: usually, an initial injury (trauma) that is not detected by the patient because of an existing neuropathy, together with a peripheral vascular disease.

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is the presence of symptoms or signs of peripheral nerve dysfunction in people who have Diabeties Melitus after excluding other causes. DPN is the most common chronic complication in the lower limbs with a prevalence of over 60% in people with DM. The effect on sensory, motor, and autonomic nerves can modify the ability of the patient to perceive certain stimuli such as pain, temperature, pressure, and touch. Motor neuropathy can affect the small muscles of the foot causing atrophy; weakness; toe deformities; prominent metatarsals; and, in turn, limited joint mobility.

Peripheral Arterial Disease

Hyperglycemia together with oxidative stress produces the final products of advanced glycation, which are involved in the development of microvascular and macrovascular complications in people with DM. Peripheral arterial disease(PAD)is a vascular condition characterized by atherosclerotic occlusive disease of the lower extremities that has been found in approximately 30% of patients with a DFU. Their development is a gradual process, in which the artery becomes blocked, narrowed, or weakened, and, in addition to prolonged inflammation with in the microcirculation, leads to thickening of the capillary, thus limiting the elasticity of capillaries leading to ischemia.

Infection

When a DFU appears, it is susceptible to the onset of infections, mainly owing to prolonged environmental exposure of the wound; pathogen-related factors such as density, virulence, and interactions; and immune defects linked to the host. Several immunological defects have been reported in patients with DM, such as altered phagocytosis and bactericidal activity of polymorphonuclear cells; impaired chemotaxis and phagocytosis functions of monocyte/macrophage; disturbances of cellular innate immunity, including a low serum level of complement factor 4 (C4) and abnormal production of cytokines by monocytes.[16]

CLINICAL EVALUATION OF DFU

The Diabetic foot ulcer must be identify clinically rather than bacteriological causes of all skin ulcers microorganisms. The clinical diagnosis of foot infection is based on the presence of ulcer and the ulcer's classic signs of inflammation. The local inflammatory findings may be less important and absent in some diabetic foot infections. For example, the pain and softness may be reduced or absent in patients who have neuropathy, whereas the erythema

can be absent in those with vascular disease. Most of the patients with diabetic foot ulcer do not have systemic features such as fever or chills.

Various clinical trials were on going to uncover a novel treatment approach for this worldwide health ailment performed a clinical trial using photodynamic therapy and result shown that rate of amputation in the photodynamic therapy group was 0.029 times the rate in the control group. Performed a phase III multicenter, double-blind, randomized, placebo controlled trial to evaluate the efficacy and safety of anovelspray-applied growth factor therapy containing recombinant human epidermal growth factor (rhEGF) for the treatment of diabetic wounds. This group concluded that patients in the rhEGF treated group notably completed healing as compared to placebo group.[1]

Twelve clinical signs of localized wound infection have been reported. Erythema, edema, heat, and pain are signs of inflammation. Signs of inflammation plus purulent exudate are known as "classic" signs of infection, traditionally associated with wound infection. Serous exudate, delayed healing, friable granulation tissue, discolored granulation tissue, foul odor, pocketing of the wound base, and wound breakdown are thought of as "signs specific to secondary wounds".

In a heterogeneous sample of chronic wounds, none of the classic signs or signs specific to secondary wounds was found to be a useful diagnostic test for infection. The specific target of that study were to identify:

1. Sensitivity, specificity, and concordance probability of each sign as compared to microbial load (reference standard),

2. Sensitivity, specificity, and concordance probability of the IDSA combination of signs as compared to microbial load, and

3. Discriminatory accuracy of a composite predictor computed from the classic and signs specific to secondary wounds as compared to microbial load.[8]

CURRENT TREATMENT OF DIABETIC FOOT ULCER

The first aim in the treatment of diabetic foot ulcers is to obtain wound cease. The foot ulcer management is largely determined by its severity, vascularity, and the presence of infection. A systematic treatment should be taken for all diabetic foot lesions.[3]

The successful treatment for diabetic foot syndrome is consists of three basic issues: Debridement, Offloading, and Infection control.[14]

The diabetic foot ulcers may be cause complications that include cellulitis, osteomyelitis (bone infections), or gangrene. In advanced treatment of foot ulcers often require **wound debridement**, this is a process that carefully removes dead tissue. The doctors are perform debridement in various ways, the one of which is probing the wound to determine the size of the ulcer. The various doctors may be also recommend at-home diabetic foot ulcer treatments that include:[21]

- Keeping the ulcer dry and covered with appropriate wound dressings.
- Maintaining proper blood glucose levels to facilitate healing.
- Cleaning the ulcer each day with appropriate topical ointments.
- Avoiding excessive walking on your ulcerated foot.
- Wearing loose-fitting shoes made of soft suede or leather with laces or Velcro fasteners.
- Wearing socks that contain extra padding for protection.

COMPLICATION IN TREATMENT OF DIABETIC FOOT ULCER

MRSA

The current available treatment with antibiotics like Vencomycin, Linzolid are having ressistance and the main culprit is methicillin resistant Staphylococcus aureus, vencomycin resistant enterococci.

The first defense against S. aureus infection is the neutrophil response. When S. aureus enters the injured skin, neutrophils and macrophages migrate to the site of infection. S. aureus evades this response using different methods (e.g., blocking sequestering host antibodies, chemotaxis of leukocytes, hiding from detection via capsule or biofilm formation and resisting destruction after ingestion by phagocytes.[10]

Treatment with herbal drug

S. No.	Scientific Name of the Plant / Common Name	Family Name	Major Constituents	Mechanism of Action	Ref.
1.	Curcuma longa / Turmeric	Zingiberaceae	Curcumin, desmethoxycurcumin and bis-	Curcumin is reduce the activity of NF-(κ)B, TNF-α and IL-1 cytokines. This is increase the fibroblast proliferation, fibroblast	[13]

			desmethoxy curcumin.	migration, granulation tissue formation and collagen deposition. These wound closure enhance the rate by reduced inflammatory induction and antioxidant activity	
2.	Persea Americana / Avocado	Lauraceae	Monosaturated fatty acid, leutin, Vitamin A and E, phospho and glycolipids.	The Persea Americana promotes wound healing by collagen formation at the proliferative stage of wound healing. These constituent like Vitamins A and E, proteins, beta-carotene, lecithin, fatty acids and potassium which acts as nutrient wound healing.	[27]
3.	Aloe barbadensis / Aloe vera	Xanthorrhoeaceae	Saponons, naftoquinones, anthroquinones, sterols and triterpenoids.	Aloe is reduce the inflammation and pain, and Increased the blood flow to the wound.	[22]
4.	Carica papaya / Papaya	Caricaceae	Papain, cystatin, chymopapain, tocopherol, flavonoids, cyanogenic glucosides and glucosinolates.	Debridiment agent convert proline to hydro proline and it act as antimicrobial on the wound infection.	[27]
5.	Leptospermum scoparium / Manuka honey	Myrtaceae	Methylglyoxal	The methylglyoxal is a major effective antimicrobial active against forms of MRSA.	[17]
6.	Actinidia deliciosa / Kiwi fruit	Actinidiaceae	Lutein, beta-carotene, fisetin, Vitamin C, E, K and ascorbic acid.	Actindia is having Protein-dissolving property (Debridement action) and antimicrobial.	[28]
7.	Vitis vinifera / Grape seed extract	Vitaceae	Oligomeric procyanidins	These chemical oligomeric procyanidins induced vascular endothelial growth factor and conduct the healing of injured skin.	[23]
8.	Rosmarinus officinalis / Rosemary	Lamiaceae	Carnosic acid and rosmarinic acid	Carnosic acid and rosmarinic acid reduce the inflammation of wound and facilitate wound contraction and re-epithelialization, regeneration of granulation tissue, angiogenesis and collagen deposition.	[24]
9.	Annonasquamosa L. / custard apple	Annonaceae	Annotemoyin	Annotemoyin increase epithelialization rate, and cellular proliferation and collagen synthesis.	[18]
10.	Catharanthus roseus / Vinca rosea	Apocynaceae	Limoene	In this drug The influence of ethanol extract of C. roseus on wound healing in diabeties, because this is reduce the blood glucose level.	[25]

CONCLUSION

The review suggested that diabetic patient is at risk for developing diabetic foot ulcer. Current available treatment proven its efficacy but increasing resistance with them is a new threat for the treatment. Recent approaches with herbal drugs can be a new way to treat those patients but standardization is to be needed with herbal drugs.

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