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Review Article

**DIABETIC FOOT ULCER; MANAGEMENT AND NOVEL
TREATMENT APPROACHES****Vikash Sharma, Raj Kumar Tiwari, Shiv Shankar Shukla, Ravindra Pandey*.**Department of Pharmacology, Columbia Institute of Pharmacy
Raipur, Chhattisgarh, India.**Abstract:**

Objective: The present study is aimed to reveal the patho-physiology, epidemiology of serious complication associated with diabetes mellitus viz: Diabetic foot ulcer (DFU). In this study various conventional, herbal as well as novel treatment approaches are also focused. Another objective of the study is to provide beneficiary information to the diabetic patients who are at the risk of DFU.

Review: DFU is one of the most serious complications associated with the diabetes mellitus. Characteristics of DFU are infection, leads to ulceration, and if preventive steps not taken then converted to gangrene and results in Amputation. Major contributors to the development of diabetic foot are neuropathy, poor circulation, Ischemia and susceptibility to infection. Diabetic foot ulcers occur in approximately 15% of patients with diabetes and of these, 14% to 24% of ulcers will end in amputation. Several therapies like Herbal therapy, Hyperbaric Oxygen Therapy, Low-level laser therapy, Operative Debridement are used to treat the DFU now days. Some novel approaches like larval therapy and maggot's therapy for treatment of DFU are also included in the study.

Conclusion: On the basis of present review we have come to know DFU is a serious complication if serious concern is not taken. But if a care is taken, it is curable due to various treatment approaches according to the condition of wounds. But the primary approach is control of blood glucose.

Keywords: Diabetic foot ulcer, Amputation, Novel approaches, Diabetes Mellitus.

Corresponding author:**Dr. Ravindra Pandey,**

Associate Professor

Department of Pharmacognosy

Columbia Institute of Pharmacy

Vill- Tekari, Near Vidhansabha

Raipur (C.G), India

Email- ravindraiop@gmail.com

Mob. No.- +91 9826229321

QR code



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INTRODUCTION:

Diabetes Mellitus (DM) is chronic metabolic disorder characterized by the high blood glucose level. DM is again classified in two categories i.e. Type-1 And Type-2. DM is seems to have many major complications associated with it. Among these Diabetic Neuropathic foot ulcer (DNFU) is supposed to be a major concern. About 15% of total diabetic patients are affected with DNFU(1). DNFU is mainly characterized by ulceration that is associated with neuropathy and peripheral arterial disease (PAD) in a patient with diabetes. Diabetic foot is one of the most significant and severe complications of diabetes. This problem is mostly found in old patients. India comes under top ten most affected countries with approx 42 million cases. According to WHO, by 2030 type 2 diabetes will affect 360 million people worldwide(2).

It is assumed that approximately 5% diabetic patients are having history of foot ulceration(3,4). A 22-year period of the(between 1979-2001) retrospective study in Tehran university of medical sciences, revealed that over the 281 patients (61% men and 39% women) were hospitalized for diabetic foot ulcers and overall lower limb amputation rate was 30% (5).

It is a challenging task for the medical personals to prevent and cure the complications of diabetic foot. Diabetic foot initially begins as a wound and sometimes results as neuropathic ulceration. The other complications of DFU are myocardial infarction, stroke, deformity of organs and ischemia etc(6). the management of DNFU involves better prevention, care and earlier treatment. The present review article is aimed to explain the etiology, various treatment approaches for DNFU.

Epidemiology of DFU:

Diabetic foot ulcer (DFU) are most common complication of Diabetes and it is estimated to affect 10-15% of all diabetic individuals. The major causes for the DFU includes acute and chronic cutaneous destruction of skin, insufficient arterial supply, peripheral sensory neuropathy. include barefoot walking, lack of awareness, low socioeconomic status, late presentation by patients, ignorance and belief in alternative system of medicine (7).

Pathophysiology of DFU:

Neuropathy and Ischemia are the major cause for the DFU. Infection due to the delayed care of the wound in diabetic patients might also be the result of DFU.

- **Neuropathy:** Approx 60% of DFU are associated with the neuropathy. (warren Clinton) There is a

little difference between the neuropathy caused by type 1 and type 2 diabetes. The exact mechanism of pathogenesis of neuropathy is not clear but may be due to accumulation of sorbitol and fructose as a result of hyperglycemia, leading to deficiency of the myoinositol, which is required for the normal neuron conduction; which is associated with the loss of sensation experience by the patients which make them vulnerable to the physical, chemical and thermal trauma (8).

- **Ischemia:** oxygen is required by tissues to energy and performs various metabolic functions. Deficiency of same results in failure to carry out these functions. This is also a major cause for cell injury. Blood supply is reduced to cells due to ischemia. Tissues are also become ischemic due to vascular ailments like atherosclerosis(9).
- **Infection:** Infection is not only the cause for the foot deformities but actually it is the consequence which occurs after injury takes place(10).
- **Peripheral arterial disease (PAD):** In diabetic patients increased blood glucose causes change in the functioning of endothelial cell and results in abnormalities in peripheral arteries. The endothelial cells are responsible for the synthesis of nitric oxide. Hence in case of hyperglycemia there is perturbation of nitric oxide which maintain the homeostasis anticoagulation, leukocyte adhesion, smooth muscle cell proliferation and antioxidant capacity (1).
Management of DFU: The intense care for the DFU should be provided by multidisciplinary foot care team. Each hospital should have a skilled team for the management, which includes health professionals like diabetologist and surgeon and other supported skilled personals to provide inpatient care for patients with diabetic foot problems(11).
They should go through the visual examination of the patient for the identification of the cause for DFU. Diagnosis procedures for the assessment and care of DFU should be carried out. These procedures includes laboratory tests as Blood glucose, Hemoglobin (HbA1c), Blood count, Erythrocyte sedimentation rate (ESR), wound and blood culture and urinalysis
The major cause for foot ulceration in peripheral neuropathy is unperceived trauma and in such case ulceration should be examined to get its level(12).

Wagner ulcer classification system (13):

| Grade | Description |
|-------|---|
| 0 | Skin intact |
| 1 | Superficial ulcer |
| 2 | Deeper, full-thickness extension of ulcer |
| 3 | Deep abscess or osteomyelitis associated with ulcer |
| 4 | Partial forefoot gangrene with ulcer |
| 5 | Extensive foot gangrene with ulcer |

Brodsky Depth/Ischemia Classification(14) :

| Grade | Description |
|-------|---------------------------|
| A | No ischemia |
| B | Ischemia, no gangrene |
| C | Partial forefoot gangrene |
| D | Total foot gangrene |

Treatment approaches:

Synthetic agents effective in Diabetic neuropathy: Not all diabetic foots are preventable, but we can reduce their occurrences by taking the appropriate preventive measures. Awareness about foot problems in diabetic patients, clinical examination, clinical assessment, and regular foot examination, patient education about diabetic foot, hygienic practices and prompt treatment of minor injuries can reduce occurrence of ulcer by 50 % (15). First line of treatment includes the control of glucose level by using hypoglycemic agents, insulin and controlled diabetic diet. If the wound culture consists of some bacterial infection then broad spectrum antibiotic should be given to the patients.

Gabapentin and pregabalin have been recommended as first line agent for the treatment of diabetic neuropathy. Aldose reductase inhibitors like 'Epalrestat' were also studied and found to be much effective in diabetic neuropathy (16).

Herbal treatment- Natural products and herbal formulations are preferred in developing countries because they have less side-effect and are cheaper than conventional medicines. In Saudi Arabia, some herbs, natural preparations and Complementary and Alternative Medicine (CAM) products are occasionally combined with honey, or used separately by people with diabetes. Similar to other patients in developed countries. Now a day's herbal formulation and natural remedies are more preferred in developing countries (17).

Patient used honey alone or along with other herbal preparation. In a study performed on Saudi's diabetic wound patients has been revealed that the use of

honey alone or along with other herb myrrh (Commiphora Molmol) produces effective healing in diabetic wounds (18).

In another study 'Agnipars' is found to be very much effective in diabetic neuropathy, as it acts by increasing the velocity of nerve conduction and hence improve the wounds caused due to diabetic neuropathy (19).

A Polyherbal preparation containing Glycyrrhiza glabra, Musa paradisiaca, Curcuma longa, Pandanus odoratissimus, Aloe vera, Cocos nucifera oil, was evaluated for its efficacy in diabetic wound healing and found very much effective as results showed that there was a 50% decrease in the size of wound (20).

Hyperbaric Oxygen Therapy- Hyperbaric oxygen therapy (HBOT) is also found to be a good approach in treatment and healing of DFU. Besides neuropathy, ischemia is also a major cause of DFU. So this approach works by availing adequate oxygen supply to the tissues of wound, and oxygen is known to be an important factor of wound healing. In this therapy oxygen above the atmospheric pressure is used (21).

Low-level laser therapy - low-level lasers therapy (LLLT) have been widely used in medical fields from last three decades. In this therapy low intensity laser radiation are used which act by photobiostimulatory effect and thereby stimulation and improvement of the circulation in the damaged tissues and hence improved healing of wounds. LLLT has been reported as better option for open tissue injuries (22).

Operative Debridement of Diabetic Foot Ulcers – Debridement means the removal of dead or infected

tissue by means of surgery, radiation, chemically. Debridement has been suggested as a good approach as it causes the early healing of tissues and thereby inhibition of microbes (23).

Off-loading - Off-loading of the ulcer area means reduction in the pressure of wound, which is important for the healing. Several studies have shown that elevated plantar pressures leads to the development of plantar ulcers in diabetic patients (24–26). If there is an already foot deformity, that may increase the possibility of ulceration, as in case of diabetic peripheral neuropathy and inadequate off-loading. Diabetic foot ulcers (DFU) are frequently located on weight bearing areas of the foot which are supposed to be at high pressure. Hence, offloading on the ulcerated area is mandatory step in the treatment of DFU to prevent further injury (27).

Negative-Pressure Wound Therapy- Negative-pressure wound therapy (NPWT) has found as a novel treatment approach for diabetic foot ulcers. In this therapy continuous sub atmospheric pressure is generated over the wounds with the help of a pump. Doing so results in collection of wound discharge, exudates. This therapy affects blood flow, decrease in fluid accumulation and removal of microorganisms and proinflammatory cytokines. Now a days, NPWT is restricted for patients with an active bleeding ulcer. Several studies showed that NPWT is effective approach in the healing rate and time of DFU (28,29).

Novel Approaches:

Larval Therapy and Maggots therapy:

Frank et al in a study found that larval therapy is supposed to be a novel approach in the treatment of the diabetic foot ulcer. In this therapy larvae are used over the infected area which can help to remove the infected tissues from the wound. This therapy was found to be successful in removing the necrotic tissue from ulcer and facilitate the healing process of wound. Therapy was assessed to the patients with methicillin resistant *Staphylococcus aureus* (MRSA) colonization in diabetic foot wounds(30).

In a case study a novel approach was taken into action. They used maggots for the healing of amputation area in diabetic ulcer patients. They applied it over the amputation area and after some time observed that there was rapid development of tissues. In the study it was suggested that it can be a first line therapy over the conventional approaches (31).

It has been reported by Gupta et al that topical fentanyl stimulates healing of ischemic wounds in diabetic rats. Opioids promote angiogenesis and

healing of ischemic wounds in rats. Researchers found that healing of diabetic foot followed mechanisms like stimulating growth-promoting signaling, angiogenesis, lymphangiogenesis and nerve regeneration. NO and PDGFR- β signaling were associated with fentanyl-induced tissue remodeling and wound healing.(32).

CONCLUSION:

Diabetic foot ulcer is a serious complication of Diabetes Mellitus and if a serious care is not taken it will be result in permanent disability. In the study we have revealed the complications, and the possible treatment approaches for the serious complication 'Diabetic foot ulcer'. In our study we found that the severity and condition of amputation can be minimize if a prior care and treatment is taken. We also found that at early stage the foot ulcer is curable.

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