Review article

DIABETIC FOOT ULCER, RISK FACTORS AND MANAGEMENT: A LITERATURE REVIEW.

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ABSTRACT

Diabetes mellitus is a rapidly rising disease worldwide. It has many complications affecting the overall health status of diabetic individuals as well as their life quality. Peripheral vascular and neuropathy are among the devastating complications of diabetes. They result in diabetic foot ulcer development. This should be prevented initially by preventative strategies which include annual screening of diabetic foot and patient's education of self-care. When ulcers happen, different approaches could be taken to manage patients. This review article spots light on different management methods to treat diabetic foot ulcers.

Key words: Diabetes mellitus, Wound management, Diabetic foot ulcer, wound dressing, offloading, wound debridement, growth factor

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INTRODUCTION

Diabetes mellitus (DM) is a chronic condition affecting many people around the world. It is a growing public health problem in many countries with increasing numbers of diagnosed patients. In 2014, the prevalence of type two DM was 422 million in the world compared to only 108 million in 1990 [1]. Those are alarming numbers of the danger of this non-communicable disease (NCD).

Diabetic complications are various including micro- and macro-angiopathy, retinopathy and nephropathy. Furthermore, DM has a considerable effect on nerves as patients became insensate over time. This consequently leads to the development of diabetic foot ulcers. This specific complication is a major concern that results in hospitalization of many diabetic patients. It is estimated that 2-3% of patients with DM will have foot ulcer during disease course. In addition, the lifetime risk of developing foot ulcers might be as high as 25% [2-3].

Management of diabetic foot ulcers (DFU) has an increasing socioeconomic burden. It is estimated that this costed the health care about 580 million pounds in the UK in 2011[4-5]. The management of DFU should begin as soon as possible in order to prevent later stages of complications that are associated with threatening morbidities and reduction of lifespan. Moreover, this doesn't only affects patient's health, but also the quality of life which decreases markedly with associated amputations [6-7]. There are approximately 5-7 patients of every 10 patients will undergo amputation due to DFU [8]. Unfortunately, there is at least one leg amputation every thirty second around the world [9].

This literature review aims to summarize risk factors contributing to the occurrence of DFU and to highlight up-to-date management of DFU. The article also considers recent evidence on recent approaches to prevent the development of DFU.

PATHOGENESIS OF DIABITIC FOOT ULCERS

DM is associated with many complications due to micro- and macro-vascular changes that appears with wide range of symptoms. Foot ulcers among diabetic patients are a devastating consequence of those vascular changes. Many risk factors have been highlighted to attribute to this such as male gender, duration of DM of more than 10 years, high body mass index, poor glycemic control (HbA1C > 6.5), infections and unhealthy care of foot [10-12]. In was concluded in [13] that 85% of DFU are due to peripheral neuropathy.

Many changes lead to DFU to develop. These changes are persistent hyperglycemic state that results in production of cytokines which increase

oxidative stress on nerves. This, in turn, causes motor, autonomic and sensory neuropathy, hence the name of neuropathic foot ulcer [14.] Skin insensitivity due to autonomic changes impairs the function of sweat glands which leads to formation of callus. Thus, decrease sensation, weight bearing and inadequate vascular supply all together are responsible for DFU [15-16]. Figure 1 explains how DFU develops.

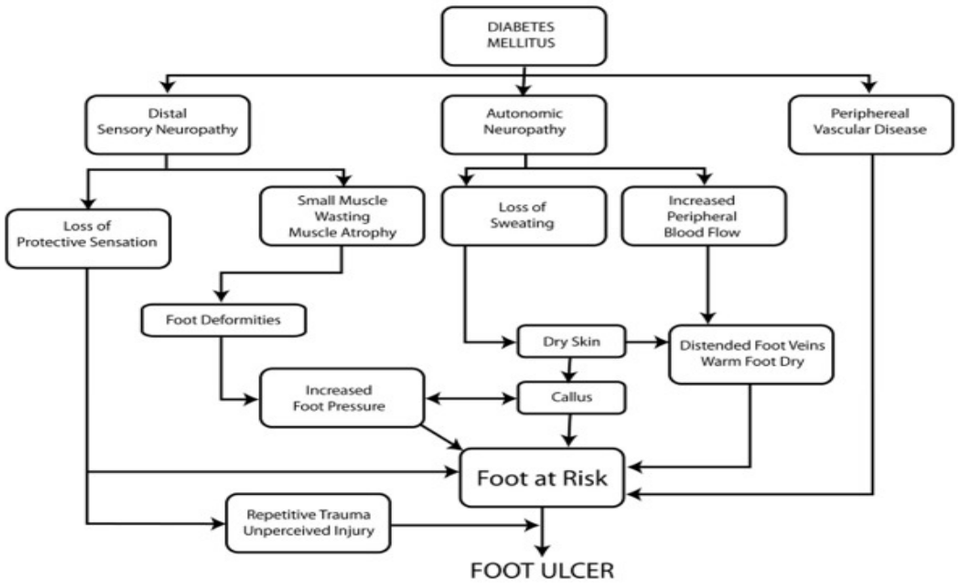

Figure 1: etiology of DFU[13]

MANAGEMENT OF DIABITIC FOOT ULCERS

Awareness and education are the most important steps in patients' management. Patients are often in denial of their disease and fail to manage themselves in early stages and don't take steps to prevent complications of DFU. Many studies emphasize that good management delays consequences of infection, gangrene, amputation and even death [17-19].

It is known that DM is a systemic disease which leads to many comorbidities affecting wound healing. Thus, the main aim of DFU management is to get wound closure as possible as we can [20-21]. This also mandates the fact that DFU among diabetic patients must be approached by multidisciplinary team for desirable outcomes [22].

Many researchers investigated the multidisciplinary approach and concluded that this approach can eliminate amputation rates, lower costs and lead to better life quality among diabetic patients [23-24]. American Diabetes Association defined a preventive care team as a multidisciplinary team can reduce risk associated with DFU and amputation by 50-85% [25]. Thus, we can conclude that applying this approach strategy for management of DFU lower the severity of complications, and improve quality of life. In the following sections, we will spot light on different measures to manage DFU.

MULTIDISCIPLINARY TEAM (MDT)

Diabetic foot ulcers affect many aspect of patients, so different specialists are required to manage the patient. Evidence showed that amputation rate is higher among diabetic patients who are cared by single specialist compared to patients managed by MDT[26]. Specialist team is composed of a diabetologist, podiatrist, ophthalmologist, general surgeon, vascular surgeon, microbiologist, specialized nurse and an orthopedic. This is important because glycemic and blood pressure control, renal function and retinopathy have all been highlighted as aspects need to be followed up thoroughly as all affect the prognosis of the patient [26].

GLYCEMIC CONTROL

There has been many supporting evidence that glycemic control postpones the progression of diabetic complications and slows down development of DFU among diabetic patients [26-27]. Nevertheless, glycemic control must be accompanied with continuous monitoring of glycemic state in order to prevent hypoglycemia. A meta-analysis conducted to assess the effect of intensive glycemic control demonstrated a significant reduction of neuropathy development among diabetic patients [28].

In other research evidence, it was suggested that tight glycemic control is the most important tool in prevention and delay of neuropathy development among diabetic patients. This is a useful tool also to measure distal sensorimotor neuropathy objectively [29].

PHARMACOLOGICAL TREATMENT

Raising awareness and education among patients improve diabetes knowledge and self-management among patients. This also make patients adhere more strictly to their medication and tips of their doctors. This was concluded from a case-controlled trial [30.] Neuropathic pain is a challenge for both patients and treating

physicians. It results from chronic sensorimotor distal symmetrical polyneuropathy that is the cause of DFU. The National Institute of Clinical Excellence recommends use of first-line agent duloxetine and pregabalin for pain control [31]. Other risk factors such as atherosclerotic risk factors should be addressed. The best strategy to reduce this is smoking cessation and use of statins irrespective of cholesterol levels. Antiplatelet medications are also recommended.
Superinfections over DFU must be treated also. A good targeted antibiotic treatment based on wound culture results is effective. Treatment duration ranges from two weeks to two months depending on the severity of underlying infection [32].

DEBRIDEMENT Elevated pressure on DFU leads to callus formation. Necrotic and hyperkeratotic tissue must be removed either by debridement of superficial ulcers or by selective sharp debridement. This enhances tissue ability of wound healing. On the other hand, deep ulcerations including bone and soft tissue requires aggressive debridement and may be requires surgery. Appropriate debridement timing results is decline in amputation rates among diabetic patients. This was concluded by 10-year review by [33].

OFFLOADING

Offloading techniques, also called pressure modulation, are the most important part of neuropathic ulcers managements [34-35]. Evidence from recent literature indicated that proper offloading promotes DFU healing [36-37].
There are many offloading techniques provided to this time, however, this issue was the focus of a few studies in which authors described frequency and rate of wound healing using some methods. Choice among those methods depends on patients' physical characteristics and the ability to adhere to treatment. In addition, ulcer site and severity play an important role in determining offloading techniques [35]. Table 2 presents some common offloading techniques.

WOUND DRESSING

Debridement provides an internal cleaning of the wound. On the other hand, dressing is significant to maintain external protection and barrier to forces and contaminations. Furthermore, it allows good absorption of exudate around the ulcer location. Dressing types vary along with advanced methods of promoting wound healing. Nevertheless, there is little evidence that moist dressings are more effective than dry ones or vice versa[38], yet there are advancements in wound dressings. Randomized controlled trials could answer the question of which is better dry or moist dressings[39]. Table 2 demonstrates different types of wound dressings [40].

Table 1: common offloading techniques

Technique	**Casting techniques**	**Footwear related techniques**	**Surgical offloading techniques**	**Other techniques**
Examples	TCC	Shoes or half shoes	ATL	Bed rest
	iTCC	Sandals	Liquid silicone injections/tissue augmentation	Crutches/Canes/Wheelchairs
	RCW	Insoles	Callus debridement	Bracing (patella tendon bearing, ankle-foot orthoses)
	Scotch-cast boots	In-shoe orthoses	Metatarsal head resection osteotomy/arthroplasty/osectomy/ exostectomy	Walkers
	Windowed casts	Socks	External fixation	Offloading dressings
	Custom splints			Felted foam/padding
				Plugs

Data adapted from Armstrong et al [35]. TCC: Total contact cast; iTCC: Instant TCC; RCW: Removable cast walkers; ATL: Achilles tendon lengthening.

Table 2: Dressing types used in managing diabetic foot ulcers [40].

Dressing type	**Description**	**Suggestions for use**
Alginates	Highly absorbent with bacteriostatic and hemostats properties.	Useful in cavitating lesions.
Foam dressing	Moderately absorbent with thermal insulation properties.	Used in light and heavy exudative wounds.
Hydrocolloids	Absorbent and aids rehydration and autolysis. Promotes granulation.	Useful for dry, sloughy, necrotic wounds. Avoid use on infected wounds.
Hydrogels	Absorbent, donates liquid and aids autolysis.	Useful for dry, sloughy, necrotic wounds. Avoid in concurrent/suspected infection.
Iodine preparations	Moderately absorbent with antiseptic properties.	Discolors wound. Avoid in case of iodine allergy, pregnancy or thyroid disease.
Low-adherence	Minimally absorbent with hypoallergenic properties.	Standard diabetic ulcer treatment. Often use in conjunction with anti-microbial.
Silver-impregnated	Absorbent with anti-septic properties.	Useful for infected diabetic foot ulcers. Avoid in known sensitivities to silver.

Table 3: different types of non-vascular diabetic foot surgery	
Type	**Explanation**
Elective	The main goal of this surgery is to relieve the pain associated with particular deformities such as hammertoes, bunions, and bone spurs in patients without peripheral sensory neuropathy and at low risk for ulceration
Prophylactic	These procedures are indicated to prevent ulceration from occurring or recurring in patients with neuropathy, including those with a past history of ulceration (but without active ulceration)
Curative	These procedures are performed to effect healing of a non-healing ulcer or a chronically recurring ulcer when offloading and standard wound care techniques are not effective. These include multiple surgical procedures aimed at removing areas of chronically increased peak pressure as well as procedures for resecting infected bone or joints as an alternative to partial foot amputation
Emergent	These procedures are performed to arrest or limit progression of acute infection

NEGATIVE WOUND PRESSURE

Negative wound pressure is a common method used in DFU management involving removal of tissue fluid through sealed vacuum. This improves tissue perfusion and formation of granulation tissue. It is a shorter treatment duration compared to traditional gauze dressing. An evidence-based study conducted in Canada revealed that there is no statistically significant difference between negative wound pressure and standard wound care regarding time needed for wound closure

SURGERY

Surgery among diabetic patients for managing DFU plays an important role for both ulcer prevention and management. It has increasingly been used in the past two decades [42-43]. Surgery procedures have significant risks since those patients are diabetic. Thus, selective of procedure for foot ulcers must be responsible to improve outcomes [44]. Surgeries include no-vascular and vascular foot surgeries and in some cases amputation. Table 3 shows different types of non-vascular diabetic foot surgeries [45].

GROWTH FACTORS

Patients with DFU have shown good benefit from growth factors such as platelet derived growth factor (PDGF), fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor and many others. However, there is one type that showed increased healing rates when compared to controls in RCTs [46-49]. This growth factor is recombinant human PDGF (rhPDGF). It is important to mention that this growth factor is FDA approved [50]. "In another randomized placebo-controlled trial, Sibbald et al demonstrated that patients with infection-free chronic foot ulcers treated with the best clinical care and once-daily applications of 100 µg/g (rhPDGF) gel had a significantly greater chance of 100% ulcer closure by 20 weeks than those receiving the best clinical care plus placebo (vehicle gel) alone"[51]

CONCLUSION

Diabetic patients are prone to have DFUs which frequently leads to lower limb amputation. This is very preventable by many interventions. The most important is patients' awareness and education. The presence of MDT is essential in managing these conditions. Approaches mentioned in the review should be utilized whenever they are feasible and applicable. They reduce morbidity and mortality among diabetic patients.

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