



# The Burden of Diabetic Foot Disorders on the Patient and the Methods of Treatment

**Khadiga IA<sup>1\*</sup>, Abdou Kha<sup>1</sup> and Badwy AS<sup>2</sup>**

<sup>1</sup>Department of Toxicology and Forensic Medicine, Beni-Suef University, Egypt

<sup>2</sup>Department of Orthopedic Surgery, Tamin Hospital, Egypt

**Submission:** May 28, 2016; **Published:** June 20, 2016

**\*Corresponding author:** Khadiga Ibrahim Ahmed, Department of Toxicology and Forensic Medicine, Faculty of Veterinary Medicine, Beni-Suef University, Benisuef, Egypt, Tel: 00201001906577; Fax: +20822327982; Email: khadiga12345@yahoo.com

## Abstract

Foot infections are a common and serious problem in persons with diabetes. Diabetic foot infections (DFIs) typically begin in a wound, most often a neuropathic ulceration. Diabetes Mellitus is known to have many complications and one of the most distressing is diabetic foot ulcer which affects 15% of people with diabetes. It puts enormous financial burden on the patient and the health care services, even though it is preventable. Diabetic foot ulcer is characterized by a classical triad of neuropathy, ischemia, and infection. Most DFIs are polymicrobial, with aerobic gram-positive cocci (GPC), and especially staphylococci, the most common causative organisms. Empiric antibiotic therapy can be narrowly targeted at GPC in many acutely infected patients, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections usually require broader spectrum regimens. Imaging is helpful in most DFIs; plain radiographs may be sufficient, but magnetic resonance imaging is far more sensitive and specific. This review is conducted to provide a general idea about Pathophysiology, Etiology, Epidemiology, Prognosis, Risk factors, Foot Complications, Patient education, Prevention and methods of treatment and also the aim of this review is to discuss the current diagnostic and management options for diabetic foot.

**Keywords:** Diabetic foot; Complications; Prevention; Treatment

**Abbreviations:** DFIs: Diabetic Foot Infections; GPC: Gram-positive Cocci; DM: Diabetes Mellitus; DFU: Diabetic Foot Ulcer; CN: Charcot Neuroarthropathy; SSR: Sympathetic Skin Response; TCC: Total Contact Cast; ECM: Extracellular Matrix; HBO: Hyperbaric Oxygen

## Introduction

Diabetes mellitus (DM) is a serious and complex disease affecting almost all the vital organs in the body. About 347 million people in the world are diagnosed with DM [1] and majority of them are due to DM type 2. In recent years, studies have substantiated the relationship of sugar sweetened beverages and cardiovascular diseases, type 2 DM and long term weight gain [2]. The incidence of DM is on the rise and it has been predicted that it will increase by a double by the year 2030. DM is known to have many complications and one of the most distressing is Diabetic Foot Ulcer (DFU) which affects 15% of people with diabetes [3]. The incidence and importance of this complication is highlighted by the fact that papers on diabetic foot in Pub-Med have increased from 0.7% in the 1980-88 to 2.6% in 1998-2004 [4]. DFU is prone to infections, chronicity and recurrence which eventually affect the mental health of patients. A benign looking ulcer in a patient with diabetes often ends up in amputation. A study in the United States reported that 38% of all the amputations were associated with DM.

## Epidemiology of diabetic foot disorders

Diabetes is one of the foremost causes of death in many countries and a leading cause of blindness, renal failure, and no traumatic amputation. Global prevalence of diabetes in 2003 was estimated to be 194 million [5]. By 2030, this figures predicted to rise to 366 million due to longer life expectancy and changing dietary habits [6]. The estimated incidence of diabetes in the US exceeds 1.5million new cases annually, with an overall prevalence of 20.8 million people or 7% of the nation's population [7]. An estimated 14.6 million persons are currently diagnosed with the disease, while an additional 6.2 million people who have diabetes remain undiagnosed; this represents a six fold increase in the number of persons with diabetes over the past four decades [8]. A higher incidence of diabetes occurs among non-Hispanic blacks, Hispanic/Latino Americans, and Native Americans compared with non-Hispanic whites [9]. Diagnosed diabetes is most prevalent in middle-aged and elderly populations; with the highest rates occurring in persons aged 65 years and older [10]. As the sixth leading cause of death in the

US, diabetes contributes to more than 224,000 deaths per year [9].

**Aetiopathogenesis of diabetic foot:** The successful DFU management strategies involve intensive prevention, early assessment and aggressive treatment by a multi-disciplinary team of experts. Aetiopathogenesis DFU is characterized by a classical triad of neuropathy, ischemia, and infection. Due to the impaired metabolic mechanisms in DM, there is an increased risk of infection and poor wound healing due to a series of mechanisms which include decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis [11]. Thus, the feet are predisposed to peripheral vascular disease, damage of peripheral nerves, deformities, ulcerations and gangrene. Neuropathy Neuropathy causes more than 60% of the foot ulcers and affects patients with both type 1 and type 2 DM. Rise in blood glucose levels leads to increased enzyme production such as aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose into sorbitol and fructose. As these sugar products accumulate, the synthesis of nerve cell myoinositol is decreased, affecting nerve conduction [12]. Furthermore, hyperglycemia induced micro angiopathy leads to reversible metabolic, immunologic and ischemic injury of autonomic, motor and sensory nerves. This causes a decrease in peripheral sensation and damages the nerve innervations of small muscles of the foot and fine vasomotor control of the pedal circulation [13].

When the nerve gets injured, the patient is at a higher risk of getting a minor injury without noticing it until it becomes an ulcer. The risk of developing foot ulcers in patients with sensory loss is increased up to seven-fold, compared to non-neuropathic patients with diabetes [6]. DM also affects the autonomic nervous system, leading to dryness and fissuring of skin, making it prone to infection. Autonomic system also controls the microcirculation of skin. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss [14].

### Foot complications

**Vasculopathy:** Hyperglycemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial cells synthesize nitric oxide which causes vasodilation and protects the blood vessels from endogenous injury. Hence, in hyperglycemia, there is perturbation of the physiological properties of nitric oxide which usually regulates the endothelial homeostasis, anticoagulation, leukocyte adhesion, smooth muscle cell proliferation and antioxidant capacity. Endothelium-derived vasodilators and nitric oxide are decreased hence leading to constriction of the blood vessels [15]. And propensity for atherosclerosis eventually leading to ischemia. Ischemia can also occur even in the presence of palpable pedal pulses [16].

**Immunopathy:** The patient with diabetes is much weaker. Thus, foot infection in a patient with diabetes is a limb threatening and debilitating condition. The hyperglycemic state causes an elevation of pro-inflammatory cytokines and impairment of polymorphonuclear cell functions like chemotaxis, adherence, phagocytosis and intracellular killing [17].

**Mechanical stress:** The movements of the foot like flexion and extension are affected due to the damage to innervations of the foot muscles. Gradually, it leads to an alteration of the anatomical framework of the foot and formation of deformities. The deformities in turn create abnormal bony prominences and pressure points eventually predisposing to ulcers [18].

**Neuroarthropathy:** Charcot neuroarthropathy (CN) is a chronic painless progressive degenerative arthropathy resulting from the disturbance in sensory innervations of the affected joint. The impairment of the autonomic nervous system due to DM causes an increase in local blood supply and the resting blood flow is much higher than in the normal patient. The sudden increase in blood flow causes calcium to dissolve, leading to osteoclastic activity of the bone and thus damaging the bone. Another theory is that the repetitive minor trauma to the insensate joints leads to fracture and disintegration [19,20].

## Diagnosis and Management

### History and physical examination

A good history should include the duration of DM, neuropathic and peripheral vascular disease symptoms, previous ulcers or amputations and any other complication of DM like retinopathy or nephropathy [21]. A complete history will aid in assessing the severity and risk of foot ulceration. Foot examinations are reported to be effective in reducing the risk of amputations [22]. The foot should be carefully inspected for abnormalities like dry skin, fissures, deformities, and callosities. Ulcerations, prominent veins, and nail lesions should be looked out for. Changes in the foot temperature must be noted. An increase in temperature might suggest inflammation [23].

**Examination of ulcer:** A sterile stainless steel probe is used for assessing the ulcer to determine the depth and if there is sinus tracts present. The location, size, shape, depth, base and margins of the ulcer should be examined clinically. Presence of granulation tissue or slough should be looked for in the floor of the ulcer to determine subsequent management (Figure 1). Diagnosing a soft tissue infection in patient with diabetes is sometimes difficult, as the signs of inflammation of the overlying ulcer may be absent. The infection is mainly diagnosed based on presence of clinical signs and symptoms such as redness, warmth, tenderness, purulent secretions and fever. Palpation of the bone at the base of the ulcer with a sterile, blunt stainless steel probe has been suggested as positive predictor of underlying osteomyelitis [24].



Figure 1: Diagnosis of foot.

**Neurological testing:** Sensory neuropathy can be tested by using monofilaments and biothesiometer. Semmes-Weinstein monofilaments are reported to be easy to use and help in predicting the risk of ulceration and amputation [25]. Specialized tests for sudomotor dysfunction include thermo regulatory sweat testing, quantitative sudomotor axon reflex testing, silicone impressions, the Sympathetic Skin Response (SSR), and the quantitative direct and indirect axon reflex testing. These tests can be used in various combinations to localize the lesion of autonomic dysfunction (pre-ganglionic or post-ganglionic) [26].

**Laboratory investigations:** The standard procedure involves measuring blood glucose level and urine for glucose and ketones. Other investigations like full blood count, blood urea, electrolytes, and creatinine levels should be monitored regularly. Glycosylated hemoglobin (HbA1C) is important to gauge the patient's overall glycemic control as HbA1c shows the mean blood sugar concentration best over previous weeks to months. Hepatic and renal function tests are necessary for monitoring the patient's metabolic status. ESR can be done to assess the presence and response to treatment of infections like osteomyelitis [27]. In case of diabetic foot, it is hard to assess the depth of the ulcer especially when there is pus and slough covering it. Also, it is hard to determine the extent of deep infection as the rub or of inflammatory response is minimal in sub facial sepsis [28]. X rays are helpful to determine the depth of foot ulceration and to assess presence of bone infection or neuroarthropathy. In CN, radiographs may reveal bony erosions, fractures, subluxation/dislocation of multiple joints, osteosclerotic features or united fractures. Magnetic Resonance Imaging has emerged as a popular investigation for many of the foot problems. In Diabetic foot it is especially useful to detect infection and CN. It is used to evaluate the extent of foot infection by revealing the depth of ulceration, edema and localized fluid collections in the soft tissues, joints and tendon sheaths. Positron emission tomography demonstrates a high specificity for osteomyelitis [29,30].

## Management

Standard care for DFU is ideally provided by a multidisciplinary team by ensuring glycemic control, adequate perfusion, local wound care and regular debridement, off-loading of the foot, control of infection by appropriate antibiotics and management of comorbidities. Educating patients helps in preventing ulcers and their recurrence.

**Debridement:** Ulcers heal faster when the wound is clean as the devitalized necrotic tissues hinder cell migration and predispose it to infection and prohibit ealing. Debridement of the wound may hasten healing by removing the dead necrotic tissue, particulate matter, or foreign materials, and reducing bacterial load. The limiting factors of sharp debridement include inadvertent bleeding, poor pain tolerance by the patient and lack of any objective markers to differentiate impaired and healthy tissue to ascertain the extent of debridement [30]. Occasionally sharp debridement is combined with other forms of debridement to achieve ulcer healing.

**Dressings:** Dressing materials used include saline-moistened gauze dressings (wet-to-dry); moisture retaining dressings (hydrogels, hydrocolloids, hydrofibres, transparent films and alginates) that provide physical and autolytic debridement respectively; and antiseptic dressings (silver dressings, cadexomer). New advanced dressings are being researched, for example Vulnamin® gel made of amino acids and hyaluronic acid are used along with elastocompression has shown favourable results [31]. Medicated honey has anti-inflammatory, antiseptic and osmotic properties and has been used as such or in combination with sterile dressings [32].

**Offloading:** Total contact cast (TCC), removable cast walkers, custom shoes, half-shoes, soft heel shoes, padded socks, and shoe inserts, wheel chairs, crutches etc. have been used for offloading the foot to prevent and treat the DFUs. The aim is to reduce the plantar pressure by redistributing it to a larger area, to avoid shear and friction, and to accommodate the

deformities. A randomized control trial compared the efficacy of a TCC, removable cast walker and half-shoe in patients with DFUs found TCC to be the most effective modality [23].

### Medical treatment and prognosis

Strict glycemic control should be maintained with the use of diabetic diet, oral hypoglycaemic agents and insulin. Infections of the soft tissue and bone are the leading cause of hospital admissions in patients with DFUs. As stated earlier, the diagnosis of infection in DFUs is primarily clinical. Culture from the deeper tissues aids in selecting appropriate antibiotics. While awaiting the results of wound culture, patients can be given empirical broad spectrum antibiotic regimen. Antibiotics are preferably given intravenously for limb threatening infections. Gabapentin and pregabalin have been used for symptomatic relief for painful neuropathy in DM. A recent study in Greece found pregabalin to be more cost effective as compared to gabapentin. A double blinded randomised trial study of tramadol has been proven to be successful in alleviating pain symptoms in diabetic neuropathy. Aldose reductase inhibitors are being studied and have shown to be effective in inhibiting progression of peripheral neuropathy [33-35].

**Adjuvant therapy:** Management strategies that target the defective extracellular matrix (ECM) in DFUs include the skin substitutes that are derived from growing skin cells of autologous or allogenic source onto collagen or polylactic acid. They contain matrix which can be cellular for example DermagraftW (Shire Regenerative Medicine, Inc. La Jolla, California, United States) and Apligraf® (Novartis Pharma AG, Basel, Switzerland) or acellular like OasisW (Healthpoint, Ltd Fort Worth, Texas, United States) and Matriderm® (MedSkin Solutions Dr Suwelack AG, Germany) [36,37]. They promote wound healing by “promoting revascularization, cellular migration, and repopulation of wound fields through provision of an appropriate scaffold material to facilitate these processes. The high cost, limited availability, risk of transmissible diseases and immunological rejection limit their widespread use. Hyperbaric Oxygen (HBO) has been found to be a useful adjunctive therapy for DFUs and is associated with decrease in amputation rates. The beneficial role of topical oxygen therapy in treating chronic wounds has also been documented [38-40].

**Surgical management:** Wound closure is attempted once the ulcer is clean with healthy granulation tissue. Primary closure is possible for small wounds; tissue loss can be covered with the help of skin graft, flap or commercially available skin substitutes. Split-thickness skin grafts are preferred over full thickness grafts. Topical phenytoin application before auto grafting promoted granulation tissue formation and was found to enhance graft uptake in large DFUs [41].

**Revascularization surgery:** Patients with peripheral ischemia who have significant functional disability should

undergo surgical revascularization if medical management fails. This may decrease the amputation risk in patients with ischaemic DFUs. The traditional method of treatment for ischemic limbs is surgical bypass. Autologous vein (preferably) or synthetic grafts may be used. Peroneal and dorsalis pedis bypass have been used and have acceptable limb salvage rates [42].

**Amputation:** Amputations are generally used as a treatment of last resort when other measures fail. However, they may be also performed earlier to allow for earlier return to work or better functional status. For example, amputation is preferred over prolonged antibiotic therapy in case of toe infections (except for the great toe). The commonly performed amputations for ischaemic DFUs include toe, Ray, transmetatarsal, tarsometatarsal (Lisfranc), midtarsal (Chopart), hindfoot and ankle (Pirogoff, Boyd, Syme's) and trans-tibial. A two-stage technique of Syme's amputation has been described to decrease the risk of infection and wound healing reported with it in patients with diabetes. Avoiding hematoma formation by meticulous homeostasis is desired. Post-amputation, simple moistened gauze dressings are preferred. Depression and anxiety are the common psychiatric illness in amputees [43,44].

### Prevention

Patient education and self-care practices like maintaining foot hygiene and nail care should be promoted. Skin is kept moisturized with the application of topical moisturizers after washing the feet gently with soap and water. Harsher measures like hot soaks, heating pads and topical agents such as hydrogen peroxide, iodine and astringents are better avoided. There is direct correlation between glycemic control and ulcer formation. Neuropathic feet are warmer and temperature differences of 2-7°C have been noted between neuropathic and non neuropathic feet. Hence self-monitoring may reduce the risk of ulceration [45]. Smoking and alcohol consumption should be minimized, though the direct link between them and DFUs is weak. Offloading and appropriate footwear to relieve focal high pressure areas is recommended for foot at-risk. Other comorbidities like hypertension and hyperlipidaemia which predispose to vascular occlusion should be treated. Prevention of ulcer recurrence may also require corrective surgical interventions [46,47].

### Conclusion

Diabetic foot is a chronic complication of DM which is not accorded the “glamour” status of its more illustrious sisters like coronary heart disease, cerebrovascular disease, nephropathy or retinopathy. Nonetheless it is responsible for a significant proportion of morbidity in DM, causing severe patient distress and frequently permanent disability. It is therefore necessary to pay special attention to this complication when reviewing, or counseling, patients with DM. This is all the more so as it is a complication that is preventable by simple measures that

can largely be taken by the patient himself. Frequent clinical examination of the feet and related systems forms the mainstay of detecting diabetic foot; investigations are only an adjunct to clinical examination. The treatment is usually conservative and a limb sparing approach is used, along with proper diabetic control. Management of aetiological factors like Vasculopathy, neuropathy and infection is essential to get good outcomes. Amputation is usually used as a last resort in non-salvageable limbs. Above all, this is one condition which proves the maxim that "prevention is better than cure". Our vision A benign looking ulcer in a patient with diabetes often ends up in amputation. A study in the United States reported that 38% of all the amputations were associated with DM. The risk of developing foot ulcers in patients with sensory loss is increased up to seven-fold, compared to non-neuropathic patients with diabetes [6]. Ischemia can also occur even in the presence of palpable pedal pulses [16]. Diabetic Foot Ulcer (DFU) which affects 15% of people with diabetes [3]. This conclusion what is mean , it mean we fail to face complication of diabetic foot all over the world in spite of all effort done till now. the Couse may be wrong vision to management of the disease, or wrong application the vision. Our diagnosed to wrong application of present vision can concluded in; 1 -multi displaying team not working in harmony [ not directed by navigator who see all views of pictures]; 2-Most of researches towards haw treat the ulcer in DF in spite of [triad of disease is Neuropathy, Vasculopathy, ulcer]; 3- Lag of application and research of [Off-loading system] 4- High cost of new modality the patient can't use it. Our new vision to decrease complication of D F is 1- building D F hospitals. 2- Good strategy for screen all at risk people of DF.3- Universal protocol of management of DF all over the world.4- Link the research institute by clinical management centers. 5-Research methods must be used local environment tools in their research.6- Developing the off lauding system by linking the our demand by modern engineering technology.

### References

1. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 378(9785): 31-40.
2. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010) Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation* 121(11): 1356-1364.
3. Pendsey SP (2010) Understanding diabetic foot. *Int J Diabetes Dev Ctries* 30(2): 75-79.
4. Boulton AJ (2004) The diabetic foot: from art to science. *The 18th Camillo Golgi Diabetologia* 47(8): 1343-1353.
5. Brussels (2005) International Diabetes Federation and International Working Group on the Diabetic Foot, Diabetes and Foot Care: Time to Act, International Diabetes Federation.
6. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27(5): 1047-1053.
7. Centers for Disease Control and Prevention (2005) National diabetes fact sheet: general information and national estimates on diabetes in the United States, Centers for Disease Control and Prevention, Atlanta.
8. Centers for Disease Control and Prevention (2000) Diabetes: a serious health problem. At-a-Glance, Center for Disease Control and Prevention.
9. Centers for Disease Control and Prevention (2005) Diabetes: Disabling, Deadly, and on the Rise: At-a-Glance, Centers for Disease Control and Prevention, Atlanta.
10. American Diabetes Association (1996) Diabetes 1996 Vital Statistics, American Diabetes Association, Alexandria, VA.
11. Brem H, Tomic-Canic M (2007) Cellular and molecular basis of wound healing in diabetes. *J Clin Invest* 117(5): 1219-1222.
12. Clayton W, Elcasy TA (2009) A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients. *Clinical Diabetes* 27(2): 52-58.
13. Jeffcoate WJ, Harding KG (2003) Diabetic foot ulcers. *Lancet* 361(9368): 1545-1551.
14. Vinik AI, Maser RE, Mitchell BD, Freeman R (2003) Diabetic autonomic neuropathy. *Diabetes Care* 26(5): 1553-1579.
15. Creager MA, Lüscher TF, Cosentino F, Beckman JA (2003) Diabetes and vascular disease, Pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation* 108(12): 1527-1532.
16. Dokken BB (2008) The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids. *Diabetes Spectrum* 21(3): 160-165.
17. Gupta S, Koirala J, Khardori R, Khardori N (2007) Infections in Diabetes Mellitus and Hyperglycemia. *Infect Dis Clin North Am* 21(3): 617-638.
18. Wagner FW (1981) The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle* 2(2): 64-122.
19. Rogers LC, Frykberg RG, Armstrong DG, Boulton AJ, Edmonds M, et al. (2011) The Charcot Foot in Diabetes. *Diabetes Care* 34(9): 2123-2129.
20. Madan SS, Pai DR (2013) Charcot neuroarthropathy of the foot and ankle. *Orthop Surg* 5(2): 86-93.
21. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG (1998) Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med* 158(2): 157-162.
22. Mayfield JA, Reiber GE, Nelson RG, Greene T (2000) Do foot examinations reduce the risk of diabetic amputation? *J Fam Pract* 49(6): 499-504.
23. Armstrong DG, Nguyen HC, Lavery LA, Van Schie CH, Boulton AJ, et al. (2001) Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 24(6): 1019-1022.
24. Boulton AJ, Kirsner RS, Vileikyte L (2004) Clinical practice. Neuropathic diabetic foot ulcers. *N Engl J Med* 35(1): 48-55.
25. Mayfield JA, Sugarman JR (2000) The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. *J Fam Pract* 49(11): S17-29.
26. Illigens BM, Gibbons CH (2009) Sweat testing to evaluate autonomic function. *Clin Auton Res* 19(2): 79-87.
27. Rabjohn L, Roberts K, Troiano M, Schoenhaus H (2007) Diagnostic and prognostic value of erythrocyte sedimentation rate in contiguous osteomyelitis of the foot and ankle. *J Foot Ankle Surg* 46(4): 230-237.
28. Naraynsingh V, Maharaj R, Dan D, Hariharan S (2011) Puncture wounds in the diabetic foot: importance of X-ray in diagnosis. *Int J Low Extrem Wounds* 10(2): 98-100.

29. Rajbhandari SM, Jenkins RC, Davies C, Tesfaye S (2002) Charcotneuroarthropathy in diabetes mellitus. *Diabetologia* 45(8): 1085-1096.
30. Pai DR, Madan SS (2013) Techniques in Chronic Wound Management: Review of the Literature and Recent Concepts. *J Nov Physiother* 3: 134.
31. Abbruzzese L, Rizzo L, Fanelli G, Tedeschi A, Scatena A (2009) Effectiveness and safety of a novel gel dressing in the management of neuropathic leg ulcers in diabetic patients: a prospective double-blind randomized trial. *Int J Low Extrem Wounds* 8(3): 134-140.
32. Shukrimi A, Sulaiman AR, Halim AY, Azril A (2008) A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. *Med J Malaysia* 63(1): 44-46.
33. Athanasakis K, Petrakis I, Karampli E, Vitsou E, Lyras L (2013) Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: a cost-effectiveness analysis for the Greek healthcare setting. *BMC Neurol* 13: 56.
34. Hotta N, Kawamori R, Fukuda M, Shigeta Y, Aldose Reductase Inhibitor-Diabetes Complications Trial Study Group (2012) Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on progression of diabetic neuropathy and other microvascular complications: multivariate epidemiological analysis based on patient background factors and severity of diabetic neuropathy. *Diabet Med* 29(12): 1529-1533.
35. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y (2006) Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy: the 3-year, multicenter, comparative Aldose Reductase Inhibitor-Diabetes Complications Trial. *Diabetes Care* 29(7): 1538-1544.
36. Rizzi SC, Upton Z, Bott K, Dargaville TR (2010). Recent advances in dermal wound healing: biomedical device approaches. *Expert Rev Med Devices* 7(1): 143-154.
37. Lev-Tov H, Li CS, Dahle S, Isseroff RR (2013) Cellular versus acellular matrix devices in treatment of diabetic foot ulcers: study protocol for a comparative efficacy randomized controlled trial. *Trials* 14: 8.
38. Greaves NS, Iqbal SA, Baguneid M, Bayat A (2013) The role of skin substitutes in the management of chronic cutaneous wounds. *Wound Repair Regen* 21(2): 194-210.
39. Kalliainen LK, Gordillo GM, Schlanger R, Sen CK (2003) Topical oxygen as an adjunct to wound healing: a clinical case series. *Pathophysiology* 9(2): 81-87.
40. Sen CK, Khanna S, Gordillo G, Bagchi D, Bagchi M (2002) Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. *Ann N Y Acad Sci* 957: 239-249.
41. Younes N, Albsoul A, Badran D, Obedi S (2006) Wound bed preparation with 10-percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. *Dermatol Online J* 12(6): 5.
42. Simerjit S, Dinker RP, Chew Y (2013) Diabetic Foot Ulcer – Diagnosis and Management. *Clinical Research on Foot & Ankle* 1: 120.
43. Atherton R, Robertson N (2006) Psychological adjustment to lower limb amputation amongst prosthesis users. *Disabil Rehabil* 28(19): 1201-1209.
44. Singh R, Ripley D, Pentland B, Todd I, Hunter J (2009) Depression and anxiety symptoms after lower limb amputation: the rise and fall. *Clin Rehabil* 23(3): 281-286.
45. Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR (2007) Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* 120(12): 1042-1046.
46. Moss SE, Klein R, Klein BE (1992) The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 152(3): 610-616.
47. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM (1998) Preventive foot care in people with diabetes. *Diabetes care* 21(12): 2161-2177.