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Review Article

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

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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, Diabetes mellitus, Treatment

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 non traumatic amputation. Global prevalence of diabetes in2003 was estimated to be 194 million [5]**.** By 2030, this figure is 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 1.5 million new cases annually, with an overall prevalence of20.8 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 than224,000 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 andfructose. As these sugar products accumulate, the synthesis of nerve cellmyoinositol is decreased, affecting nerve conduction [12]**.** Furthermore, hyperglycaemia induced microangiopathy 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

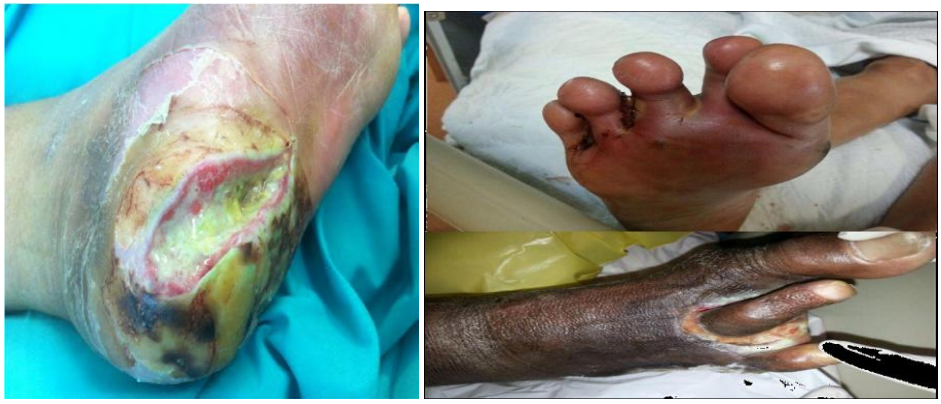
Hyperglycemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial cells synthesize nitric oxide which causes vasodilation and protects the blood vessels from endogenous injury. Hence, in hyperglycemia, there is perturbation of the physiological properties 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 hyperglycaemicstate causes an elevation of pro-inflammatory cytokines and impairment of polymorph nuclear cell functions like chemo taxis, 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]**.**



(Figure: 1 and 2)

Diagnosis and Manegement

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]**.**

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 are 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 (Figure1 and 2). 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]

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 thermoregulatory sweat testing, quantitative sudomotor axon reflex testing, silicone impressions, the Sympathetic Skin Response (SSR), andthe quantitative direct and indirect axon reflex testing. These tests can be used in various combinations to localise 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 monitoredregularly. 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 andrenal 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 rubor of in flammatoryresponse is minimal in subfascial 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 revealbony erosions, fractures, subluxation/dislocation of multiple joints, osteosclerotic features or united fractures. Magnetic ResonanceImaging 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 co morbidities. **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 healing. 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 (silverdressings, cadexomer). New advanced dressings are being researched, for example Vulnamin© gel made of amino acids and hyaluronic acidare used along with elastocompression has shown favourable results [31]**.** Medicated honey has antiinflammatory, 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, wheelchairs, 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 [33].

Medical treatment and prognosis

Strict glycaemic 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 canbe 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 foundpregabalin to be more cost effective as compared to gabapentin. A double blinded randomised trial study of tramadol has been provento be successful in alleviating pain symptoms in diabetic neuropathy. Aldose reductase inhibitors are being studied and have shownto be effective in inhibiting progression of peripheral neuropathy [34-36].

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 orpolylactic 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. SuwelackAG, Germany) [37-38]**.** 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 [39-41].

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 phenytoinapplication before auto grafting promoted granulation tissue formation and was found to enhance graft uptake in large DFUs [42].

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 surgicalbypass. Autologous vein (preferably) or synthetic grafts may be used. Peroneal and dorsalis pedis bypass have been used and have acceptable limb salvage rates [43].

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), hind foot and ankle (Pirogoff, Boyd, Syme's) and trans-tibial. A two-stagetechnique 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 haemostasis is desired. Post-amputation, simple moistened gauze dressings are preferred. Depression and anxiety are the common psychiatric illness in amputees [44-45].

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 andtopical agents such as hydrogen peroxide, iodine and astringents arebetter avoided. There is direct correlation between glycemic controland ulcer formation. Neuropathic feet are warmer and temperature differences of 2-7 °C have been noted between neuropathic and nonneuropathicfeet. Hence self-monitoring may reduce the risk of ulceration [23]**.** 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 co morbidities like hypertension and hyperlipidaemia which predispose to vascular occlusion shouldbe treated. Prevention of ulcer recurrence may also require correctivesurgical interventions [22, 46].

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 counselling, patients with DM. This is all the moreso as it is a complication that is preventable by simple measures that canlargely 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 treatmentis usually conservative and a limb sparing approach is used, along with proper diabetic control. Management of aetiological factors likevasculopathy, 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 "preventionis 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 worled.4- Link the research institute by clinical management centers. 5-Research methods must be used local environment tools in there research.6-Developing the off lauding system by linking our demand by modern engineering technology.

References

1. Danaei, G.;Finucane, M.M.; Lu, Y.; Singh, G.M. and Cowan, M.J. (2011). National, regional, and global trends in fasting plasma glucose and diabetes prevalencesince 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2•7 million participants. Lancet 378: 31-40.
2. Malik, V.S.;Popkin, B.M.; Bray, G.A.;Després, J.P and Hu, F.B. (2010). Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation 121: 1356-1364.
3. Pendsey, S.P. (2010). Understanding diabetic foot. Int J Diabetes DevCtries 30:75-79.
4. Boulton, A.J. (2004). The diabetic foot: from art to science. The 18th Camillo Golgi lecture. Diabetologia 47: 1343-1353.
5. International Diabetes Federation and International Working Group on the Diabetic Foot, (2005). Diabetes and Foot Care: Time to Act, International Diabetes Federation, Brussels, 2005.
6. Wild, S.; Roglic, G.; Green, A.; Sicree, R. and King, H. (2004).Global prevalenceof diabetes: estimates for the year 2000 and projections for 2030.Diabetes Care 27:1047-1053.

7. Centers for Disease Control and Prevention, (2005). Diabetes: Disabling, Deadly, and on the Rise: At-a-Glance, 2005, Centers for Disease Control and Prevention, Atlanta.
8. Centers for Disease Control and Prevention, (2000).Diabetes: a serioushealth problem. At-a-Glance 2000, Center for Disease Control and Prevention.
9. 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.
10. American Diabetes Association, (1996). Diabetes 1996 Vital Statistics, American Diabetes Association, Alexandria, VA.
11. Brem, H. and Tomic-Canic, M. (2007). Cellular and molecular basis of wound healingin diabetes. J Clin Invest 117: 1219-1222.
12. Clayton, W. and Elcasy, T.A. (2009). A Review of the Pathophysiology, Classification and Treatment of Foot Ulcers in Diabetic Patients. Clin Diabetes 27: 52-58.
13. Jeffcoate, W.J. and Harding, K.G. (2003). Diabetic foot ulcers. Lancet 361: 1545-1551.
14. Vinik, A.I.; Maser, R.E.; Mitchell, B.D. and Freeman, R. (2003). Diabetic autonomic neuropathy. Diabetes Care 26: 1553-1579.
15. Creager, M.A.;Lüscher, T.F.;Cosentino, F. and Beckman, J.A. (2003). Diabetes and vascular disease, pathophysiology, clinical consequences, and medical therapy: Part I. Circulation. 108: 1527-1532.
16. Dokken, B.B. (2008). The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids. Diabetes Spectr 21: 160-165.
17. Gupta, S.;Koirala, J.;Khardori, R. and Khardori, N. (2007). Infections in Diabetes Mellitus and Hyperglycemia. Infect Dis Clin North Am 21: 617-638.
18. Wagner, F.W. (1981). The dysvascular foot: a system for diagnosis andtreatment. Foot Ankle 2: 64-122.
19. Rogers, L.C.;Frykberg, R.G.; Armstrong, D.G.;Boulton, A.J.M. and Edmonds, M. (2011). The Charcot Foot in Diabetes. Diabetes 34: 2123-2129.
20. Madan, S.S. and Pai, D.R. (2013). Charcot neuroarthropathy of the foot and ankle. OrthopSurg 5: 86-93.
21. Lavery, L.A.; Armstrong, D.G.; Vela, S.A.;Quebedeaux, T.L. andFleischli, J.G. (1998). Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 158: 157-162.
22. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM (1998) Preventive foot care in people with diabetes. Diabetes care 21: 2161-2177.
23. Armstrong, D.G.; Holtz-Neiderer, K.;Wendel, C.;Mohler, M.J. and Kimbriel, H.R. (2007).Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. Am J Med 120: 1042-1046.
24. Boulton, A.J.;Kirsner, R.S. and Vileikyte, L. (2004).Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med 351: 48-55.
25. Mayfield, J.A. and Sugarman, J.R. (2000). The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. J FamPract 49: S17-29.
26. Illigens, B.M. and Gibbons, CH. (2009). Sweat testing to evaluate autonomic function. ClinAuton Res 19: 79-87.
27. Rabjohn, L.; Roberts, K.;Troiano, M. and Schoenhaus, H. (2007). Diagnostic and prognostic value of erythrocyte sedimentation rate in contiguous osteomyelitisof the foot and ankle. J Foot Ankle Surg 46: 230-237.
28. Naraynsingh, V.;Maharaj, R.; Dan, D. and Hariharan, S. (2011). Puncture wounds inthe diabetic foot: importance of X-ray in diagnosis. Int J Low Extrem Wounds10: 98-100.
29. Rajbhandari, S.M.; Jenkins, R.C.; Davies, C. and Tesfaye, S. (2002). Charcotneuroarthropathy in diabetes mellitus. Diabetologia 45: 1085-1096.
30. Pai, D.R. and Madan, S.S. (2013).Techniques in Chronic Wound Management:Review of the Literature and Recent Concepts. J Nov Physiother 3: 2.
31. Abbruzzese, L.; Rizzo, L.;Fanelli, G.;Tedeschi, A. and Scatena, A. (2009). Effectiveness and safety of a novel gel dressing in the management ofneuropathic leg ulcers in diabetic patients: a prospective double-blind randomized trial. Int J Low Extrem Wounds 8: 134-140.
32. Shukrimi, A.;Sulaiman, A.R.;Halim, A.Y. and 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: 44-46.
33. Armstrong, D.G.; Nguyen, H.C.; Lavery, L.A.; Van Schie, CH. And Boulton, A.J. et al. (2001). Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care24: 1019-1022.

34. Athanasakis, K.; Petrakis, I.;Karampli, E.;Vitsou, E. and 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.
35. Hotta, N.;Kawamori, R.; Fukuda, M.;Shigeta, Y. and Aldose Reductase Inhibitor-Diabetes Complications Trial Study Group (2012). Long-term clinical effects ofepalrestat, an aldose reductase inhibitor, on progression of diabetic neuropathyand other microvascular complications: multivariate epidemiological analysisbased on patient background factors and severity of diabetic neuropathy.Diabet Med 29: 1529-1533.
36. Hotta, N.; Akanuma, Y.;Kawamori, R.; Matsuoka, K. and Oka, Y. (2006). Longtermclinical effects of epalrestat, an aldose reductase inhibitor, on diabeticperipheral neuropathy: the 3-year, multicenter, comparative Aldose ReductaseInhibitor-Diabetes Complications Trial. Diabetes Care 29: 1538-1544.
37. Rizzi, S.C.; Upton, Z.;Bott, K. and Dargaville, T.R. (2010). Recent advances in dermal wound healing: biomedical device approaches. Expert Rev Med Devices 7:143-154.
38. Lev-Tov, H.; Li, C.S.;Dahle, S. and Isseroff, R.R. (2013). Cellular versus a cellular matrixdevices in treatment of diabetic foot ulcers: study protocol for a comparative Efficacy randomized controlled trial. Trials 14: 8.
39. Greaves, N.S.;Iqbal, S.A.;Baguneid, M. andBayat, A. (2013). The role of skin substitutesin the management of chronic cutaneous wounds. Wound Repair Regen 21:194-210.
40. Kalliainen, L.K.;Gordillo, G.M.;Schlanger, R. and Sen, C.K. (2003). Topical oxygen as an adjunct to wound healing: a clinical case series. Pathophysiology 9: 81-87.
41. Sen, C.K.;Khanna, S.;Gordillo, G.;Bagchi, D.;Bagchi, M. (2002). Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. Ann N Y AcadSci 957: 239-249.
42. Younes, N.;Albsoul, A.;Badran, D. and Obedi, S. (2006). Wound bed preparation with10-percent phenytoin ointment increases the take of split-thickness skin graft in large diabetic ulcers. Dermatol Online J 12: 5.
43. Simerjit, S.;Dinker, R.P. and Chew, Y. (2013).Diabetic Foot Ulcer – Diagnosis and Management. Clinical Research on Foot & Ankle, 1:3. http://dx.doi.org/10.4172/2329-910X.1000120.
44. Atherton, R. and Robertson, N. (2006). Psychological adjustment to lower limb amputation amongst prosthesis users. DisabilRehabil 28: 1201-1209.
45. Singh, R.; Ripley, D.;Pentland, B.; Todd, I. and Hunter, J. (2009). Depression and anxiety symptoms after lower limb amputation: the rise and fall. ClinRehabil 23: 281-286.
46. Moss, S.E.; Klein, R. and Klein, B.E. (1992). The prevalence and incidence of lower extremity amputation in a diabetic population. Arch Intern Med 152: 610-616.