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Causal Pathway for Foot Ulceration in a Patient with Diabetes

Dr. Mohamed Elgabsi[1], Dr. Yousuf Sulayman Asteetah[2]

[1]Consultant Surgeon, Alwahda Hospital Derna
Email: *m.saleh[at]uod.edu.ly*

[2]Consultant Surgeon, Alwahda Hospital Derna
Corresponding Author Email: *yussifestata[at]mail.com*

Abstract: ***Diabetic foot has a distortion of its anatomy and structural function which influenced by chronic peripheral neuropathy with or without peripheral vascular disease associated with infection, ulceration and destruction of deeper tissues (1, 2, 3, 4,) The annual incidence of foot ulcer world over is 9.1 to 26 per million (5) Diabetic patient carries a lifetime risk of developing a foot ulcer from 15 to 25 % (6) Male gender, hyperglycemia, increase in glycosylated hemoglobin , peripheral neuropathy, previous ulceration and traumas are some of the common risk factors for the development of the diabetic foot ulcers (7) Foot deformity, loss of protective sensation and peripherals vascular disease are important factors (8) The gold standard for diabetic foot ulcer care includes debridement of the wound, management of any infection, revascularization when indicated and offloading of the ulcer (9) Hyperglycemia produces oxidative stress on nerve cell and leads to neuropathy (10) Non enzymatic glycosylation of nerve protein lead to further ischemia. Damaged motor neurons of the foot musculature result in an imbalance of flexor and extensor groups of muscle and result in deformities and skin ulceration. Autonomic nerve impairment causes dryness of skin causing cracks and skin breakdown. blood supply required to heal a diabetic foot ulcer is greater than that needed to maintain skin intact, chronic ulceration can develop (11) Thickening of the basement membrane, the decrease in the size of the capillary lumens and the degeneration of periocysts around venules causes derangement of microcirculation of diabetic foot ulcer (29) The present study is aimed at looking into the pathogenesis of diabetic foot ulceration and its evaluation, classification, and management.***

Keywords: Diabetes mellitus, Diabetic foot, ulceration, Diabetic foot ulceration

1. Introduction

Diabetes has been mentioned in Ebers Papyrus of 1500 B. C, Diabetes mellitus affects **8.3%** of the general population that increases with age to about 11% in those above 65yrs those who are not diagnosed constitutes an equal number this has lead to a six fold increase in the number of patients over the past 40 yrs. (12) A delayed diagnosis carries potential risk for the limb or the patient (13) The annual incidence of foot ulcers world over is 9.1 to 26 per million (5), Diabetic patient carries a lifetime risk of developing a foot ulcer from 15to 25 % (6)

Male gender, hyperglycemia, increase in glycosylated hemoglobin, peripheral neuropathy, previous ulceration and trauma are some of the common risk factors for the development of the diabetic foot ulceration (7) foot deformity, loss of protective sensation and peripheral arterial disease are important factors (8) There is abundant evidence to show that perforating ulcers are caused by peripheral nerve degeneration secondary to diabetes (14) these ulcers occur in the region of the foot which encounters repetitive trauma and pressure sensations (15) nearly 60 - 80 % of the foot ulcers will heal while 10 - 15 % remain active, 5 - 24 % of them will end up in limb amputation within 6 - 18 months following diagnosis, Neuropathic ulcers heal over period of 20 weeks, neuro - ischemic take a long time and may often lead to limb amputation (16), 40 - 70 % of all non - traumatic amputations of the lower limb occur in a patients with diabetes (17) Incidence of limb amputation and ulceration increase with age and duration of diabetes (18 - 19) It is seen from previous studies that 40% of the ulcers which had healed recurred within a year, 60% of healed ulcers recur in three years and about 65% of the healed ulcers recur in a period of 5 years and end up in amputations (20) The present study is aimed at looking into the pathogenesis of diabetic foot ulceration, its evaluation, classification and management.

Pathogenesis

Peripheral neuropathy, foot trauma, minor trauma, and peripheral arterial disease are some of the risk factors for the development of foot ulcer in diabetics (20 - 21) Lower extremity neuropathy is found in 2/3rd of diabetics (22) In some of the other studies diabetic neuropathy was found in 90% of the diabetic foot ulcers (23 - 24), Hyperglycemia of long standing is a causative factor for the neuropathy (22, 25). Motor neuropathy causes muscle weakness, atrophy, and paresis, sensory neuropathy leads to loss of protective sensation of pain, pressure, and heat, autonomic dysfunction causes vasodilatation and decreased sweating (26), Sensorimotor neuropathy is the most prevalent neuropathy in diabetics, (25) The foot is susceptible to mechanical pressure or thermal injury because of the loss of the protective sensations caused by peripheral neuropathy (20) Repetitive shear stress on an area is the common cause of diabetics foot ulcers (5) Altered sense of proprioception has negative effects on gait, loss of protective changes in biomechanical loading results in sustained stress and tissue damage (27), Autonomic neuropathy causes decreased sweat secretion and increased blood flow from the thermoregulatory shunt resulting in a hot dry foot (27)

With neuropathy there is atrophy of the intrinsic muscle of the foot, Imbalance of the flexor and extensor muscles results in deformities increasing the biomechanical loading

of the metatarsal head during standing and walking (27) The process of healing of the foot ulcers is impaired by impaired diabetic foot microcirculation (28) Thickening of the basement membrane, the decrease in the size of the capillary lumen and the degeneration of the periocytes around venules causes derangement of microcirculation in diabetic foot ulcers, Endothelial cell dysfunction leads to decrease in vasodilatation, also plasma thromboxane A2 levels become elevated (30) This results in vasoconstriction, causes hypercoagulation in peripheral arteries leading to ischemia and an increased risk of ulcerations. Immunological change which is met with diabetic foot ulceration is an increase in T lymphocytes apoptosis which inhibits healing (31).

Hyperglycemia causes an oxidative stress on nerve cell inducing neuropathy (10), Glycosylation of the nerve cell protein leads to further ischemia, Hyperglycemia induced changes in the peripheral arteries of the foot begin at the cellular level (10), Inadequate transfer of oxygen and nutrients to the wound area due to peripheral arterial disease causes chronicity of the ulcer and infection (20, 21m22, 32) The process of normal wound healing occurs in overlapping phases which are controlled by cellular components, extracellular matrix ECM, cytokines, growth factors, (33, 34, 35) Neuropeptides play an important role in inflammation, angiogenesis, cytokine expression and in the release of growth factors, derangement of neuropeptides is linked to peripheral neuropathies, hypoxia is related to peripheral arterial diseases, response to hypoxia is altered by hyperglycemia (22, 36, 37, 38)

Assessment and Diagnosis

Based on risk factors patient should be assessed for arterial insufficiency and neuropathic diseases (11) Temperature, respiratory rate, heart rate and blood pressure in both THE extremities are recorded (11), Patient with an infected ulcer may have fever, tachycardia or tachypnea. All the peripheral pulses are palpated and the temperature of the extremities assessed,. Arterial insufficiency is associated with intermittent claudication or limb ischemia, dry skin which is shiny and hairless on the affected side, brittle nail and skin which is cool to touch, Assess arterial flow by elevating the limb above the level of the heart, letting pooled blood drain. A normal limb will remain pink, one with arterial insufficiency becomes pale, symptoms of neuropathic disease include numbness, paresthesia and burning sensation, loss of protective sensation can be tested with any of the following tests (39).

- The 10g monofilament test best determines patient sense of touch, regions tested include plantar surface of the distal hallux, head of the 1st, 3rd and 5th metatarsal
- A 128 –H2 turning fork is used for testing vibratory sensation
- A pin prick test is conducted proximal to toe nail of the hallux
- Ankle jerk is tested with a percussion hammer
- Vibration perception threshold is tested with abiothesiometer

Ulcer are to be inspected, palpated and probed on initial presentation and in follow up to evaluate and track the extent of soft tissue damage and to assess for bone involvement (40) The above tests have predicative value of 87% for the risk of incident neuropathy (41)

Diabetic foot ulcer is classified as neuropathic in the presence of peripheral neuropathy, ulcer is called ischemic if it is associated with peripheral arterial disease without neuropathy. If the ulcer is associated with both is peripheral neuropathy and peripheral arterial diseases it is classified as a neuroischemiculcer. Many efforts have been made to categorize foot ulcers according to extent, size and depth, location, presence of infection or ischemia. The Meggitt - Wagner classification is one of the most popular validated classification for the foot ulcers, other classification systems for diabetic foot ulcer have been proposed and validated

Risk factors for foot ulceration on diabetics

- Pervious lower extremity amputation
- History of a foot ulcer
- Anatomic foot deformity
- Peripheral vascular disease
- Diabetic neuropathy in those on dialysis
- Poor glycemic control
- Smoking

Wagner ulcer classification system

Grade	Lesion
0	No open lesion
1	Superficial diabetic ulcers
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis or joint sepsis
4	Gangrene localized to a portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

University of texas classification system to assess the severity of diabetic foot lesions

Stage	Grade 0	Grade 1	Grade 2	Grade 3
A	Healed pre or post ulcerative lesion completely epithelialized	Superficial wound not involving bone, tendon or capsule	Wound penetrating tendon and capsule	Wound penetrating to bone or joint
B	With Wound infection	With Wound infection	With Wound infection	With Wound infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

Classification system for DAFs

Proper classification helps in predicting the need for hospitalization, in planning strategies for treatment of diabetic foot lesions or lower extremity amputation (22, 21) Various classification system have been proposed for the assessment of the severity of diabetic foot lesions including PEDIS, In PEDIS system perfusion in the affected foot extent of the ulcer, depth or tissue loss of the ulcer, symptoms and sign of infection and sensation on the affected foot are graded, the higher grade shows the more severity of the ulcer, this classification is used to predict the need for hospitalization or lower extremity amputations (21)

Wound ischemia and foot infection WIFI system of classification

The society of vascular surgery proposed a new system of classification which combines the classification system based on PAD perfusion patterns with a foot infection, A separate grade is given to the wound (the presence and depth of the ulcer), Ischemia is based on ABI, toe pressure or transcutaneous oxygen pressure (TcPo2) and infection (local or systemic) the three grades are combined to give a risk of amputation and estimated benefit for revascularization (43)

Management of diabetic foot ulcer

Wound closure is the chief aim of diabetic foot ulcer management (44) Aim of the wound management would be to prevent ulceration from developing elsewhere on the foot or on the contralateral limb and to achieve limb preservation (45) Appropriate information is provided to the patient and is allowed to participate in the decision making (46) Treatment of severe critical ischemia is essential for wound healing (44)

Components of management are

- Treating underlying disease process
- Adequate blood supply is to be ensured
- Controlling infection and local wound care
- Pressure offloading

Treating the underlying causes

Regardless of other interventions, sever ischemia which is critical to wound healing has to be treated (44), Critical limb ischemia with rest pain, ulceration and loss of tissue, revascularization has to be an option (47) A tight glycemic control has to be achieved, other risk factors such as high blood pressure, hyperlipidemia and smoking are to be managed (48).

Peripheral neuropathy, foot deformity, peripheral arterial disease, frequent minor trauma and infection need to be well managed, Local debridement, wound offloading, wound moisture balance with appropriate dressings, control of edema and control of infection are considered to be a part of the standard wound care (49, 32) a multidisciplinary approach results in a substantial decrease in amputation rate (20, 33)

Glycemic control

Glycosylated Haemoglobin measurement is a must for diabetic foot ulcer patient, It is inversely related to healing rate of the ulcer especially in the case of a patient with peripheral neuropathy and peripheral arterial disease (50) Achieving optimal diabetic control should involve tight glycemic control and managing risk factors such as high blood pressure and smoking (48, 33)

Ensuring adequate blood supply

A cute limb ischemia is a clinical emergency and may be at great risk if not managed in a timely and effective way, Decreased perfusion or impaired circulation may be an indication for revascularization in order to achieve and maintain healing and to avoid or delay a future amputation (20)

Local wound care

According to the European wound care association (EWCA) wound care for the diabetic foot ulcer should be radical and repeated debridement, bacterial control and moisture balance to prevent maceration (52) steps in wound bed preparation include the following

- Tissue debridement
- Inflammation and infection control
- Moisture balance
- Epithelial edge advancement

Tissue debridement various methods available for achieving debridment include surgical, larval, autolytic or hydrosurgery and ultrasonic (53, 54), Removal of necrotic tissue from an ulcer by debridment is the first critical step in wound care especially in the control of deep infection (20, 55), Debridement can decrease bacterial counts, facilitate wound drainage and reduce pressure on the ulcer, adequate debridement decrease the possibility of limb amputation (56) Surgical debridement should be done after the blood supply to the wound / extremity is optimized to ensure that viable tissue is not removed (20), new necrotic tissue needs further debridement (56), The gold standard technique for tissue management in diabetic foot ulcers is regular sharp debridement using a scalpel, scissors and forceps (57, 33, 58), The benefits of debridement are that it (59) removes the necrotic tissue, reduces pressure, drains secretions or pus and stimulate healing. it is important to debrid the wound margins to allow spread of granulation to the edge. (5, 60) Debridment should remove all devitalized tissue, callus and foreign body down to the level of viable bleeding tissue (61, 62)

Other methods of debridement:

- Hyrdrosurgical debridement: here a high energy cutting beam is created by forcing water or saline into a nozzle, the enables precise visualization and removal of devitalized tissue in the wound bed (53)
- Autolytic debridement: this ia a natural process that uses a moist wound dressing to soften and remove devitalized tissue , care is taken not to increase moisture which macerates tissues, this type of debridment is not recommended in presence of ischemia and or dry gangrene (61,) 63)
- Larval therapy: green bottle fly larvae rapidly remove slough from the wound and also ingest pathogenic organisms (54) larval therapy has been shown to be safe and effective in the treatment of diabetic foot ulcers (64), As callus cannot be removed by larvae this method of debridmenet cannot be applied to as a single treatment of diabetic foot ulcers (63), Recent evidence suggests that larval therapy may improve outcomes when compared to autolytic debridement with a hydrogel (59)

Inflammation and infection control:

Early and aggressive treatment of infections in diabetic foot ulcers is needed to prevent mortality and morbidity (61) In one study nearly 50% of the patient admitted with diabetic foot infection underwent amputation (65), Clinically uninfected wound should not be treated with systemic antibiotic therapy, however all infected wounds require antibiotic therapy (66)

Role of topical antimicrobials
Topical antimicrobiala can be used to reduce wound bioburden (67), Topical antimicrobial agents provide local concentrations but do not penetrate intact skin or into deeper soft tissue (68) Topical antimicrobials may be beneficial in patient with poor vascular supply and those with increase bacterial bioburden (67), In these situations topical antimicrobials have the potential to reduce bacterial load and may protect the wound from further contaminations (67), A recent consensus recommends an appropriate use of silver dressings (69

Deep tissue infection
For treating cellulitis, lymphangitis, septic artheritis and fascitis which are treated with broad sepectrum antibiotics to begin with and later change according to culture and sensitivity studies (70)

Biofilms and chronic persistent infection
Biofilms are complex polymicrobial communities that develop on the surface of chronic wound, which may lack the overt clinical signs of infection (70) They are not visible to the naked eye and can not be detected on routine cultures (71), treatment should be aimed at disrupting the biofilm burden through regular repeated debridement (71)

Dressing of the wound
After debridement, wound have to be closed with wound cleansing addressing solution or saline, cleansing removes devitalized tissue, rebalances the bioburden and reduce exudate to help in preparing the wound bed for healing

Osteomyelitis
Underlying osteomyelitis is frequently present in a patient with moderate to severe infections and requires aggressive bony resection of the infected bone and joint followed by four to six weeks of more culture directed antibiotic (73, 74), Probing the ulcer with sterile metal probe in abed side test that can help with the diagnosis of the underlying osteomyelitis , if the probe hits the bone it is a positive test (75) Positive probe to bone test results are helpful especially when conducted on patients with diabetes mellitus (76)

Offloading
Offfloading or pressure modulation is the cornerstone management for neuropathic foot ulcers and ulcer with increased biomechanical stress (77, 57), There are many offloading modalities which can be divided into nonsurgical and surgical. It is important to offload at risk area of the foot in order to redistribute pressures evenly (78) A threshold of a peak pressure $<$200 kpa has to be achieved by offloading system to allow the ulcer to heal (20), The nonsurgical offloading modalities include soft and shock absorbing materials, custom moulding forefoot or heel offloading shoes, rocker bottom shoe casts, walkers, crutches and wheel chair. Achilles tendon lengthening (ALT) is performed to reduce planter pressure because of the foot deformities (20, 77) Common procedures include hammer toe repair, metatarsal osteotomies and plantar exostomies (79, 80), The most effective method of the offloading which is condidered to be the gold standard is the non - removable total contact cast (TCC) It is made up of plaster or fast setting fiberglass cast material relatvely low cost, and allows restricted activity (81), TCCs are contraindicated in patient with ischemia because of the risk of inducing further diabetic foot ulcers (82) They are not suitable for patients with infected ulcers or with osteomyelitis as they do not allow inspection (60), A removable cast walker is suggested as an alternative for patient who need frequent dressing changes (51)

Adjunctive therapies
Adjunctive therapies are considered for diabetic foot ulcers which fail to show more than 50% wound reduction after 4 weeks of standard wound therapy (51) Hyperbaric oxygen delivered by hyperbaric chamber has been reported to be helpful in healing diabetic foot ulcers (83) Hyperbaric oxygen delivered by hyperbaric boot is totally ineffective
growth factors

PDGF - beta is used in form of a once daily gel applied with debridment on a weekly basis (84), Initial studies have indicated a significant positive effect of becrplermin (85, 86)

Bioengineered skin (apligraft) and human dermis (Dermagraft)

The are new types of biologically active implants for ulcers that are derived from fibroblasts of neonatal foreskins (87) These bioengineered products enhance healing by acting as delivery system for growth factors and extracellular matrix components through the activity of live human fibroblast contained in their dermal elements.

Prevention
Prevention of an initial or subsequent foot ulcer is crucial to avoiding amputation (86, 60), therapeutic shoes with pressure relieving insoles are an essential element of ulcer prevention and have been associated with significant reduction in ulcer development

2. Conclusion

Diabetic foot ulcers are chronic wounds that result from repetitive trauma in an insensate foot, the incidence of diabetic foot ulcers will increase in the future and require a high cost of care, diabetic foot ulcer healing also takes a longtime and can lead to amputation in the lower extremities thus increasing the morbidity and mortality, the basis of the diabetic foot ulcer therapy are debridement, offloading, infection control with appropriate antibiotics and dressings

References

[1] Boulton A, late sequelae of diabetic neuropathy. in; Boulton AJM editor. Diabetic neuropathy. Lancaster, unite kingdom. marinspress: 1997, p63 - 76
[2] Mayfield AJ, reiber GE, saundersLz, Janisse D, Pogach LM, American Diabeties association , preventive foot care in people with diabetes, diabetes care 1998; 21: 2161 - 77
[3] Veves, murray HJ, young Mj Boulton Aj. the risk of foot ulceration in patients with high foot pressures; a prospective study. diabetology 1992: 35: 660
[4] Gontijo PVC, Pascoal LM, Santos LH, Santos FAAS, Rolim ILTP, Santos Neto M, et al. Assessment of

tissue integrity in patients with diabetic foot. Rev Bras Enferm.2020

[5] David G. ***Armstrong***, D. P. M., M. D., Ph. D.,; Andrew J. M. Boulton, M. D.,; and Sicco A. ***Bus***, Ph. D. June 15, 2017. N Engl J Med 2017; 376: 2367 - 2375

[6] MutuogluM, Uzun G. Turhan V. gornek L, Ay H, Lipsky BA, How reliable are cultures of specimens from superficial swab compared with those of deep tissue in patient with diabetic foot ulcer ? J diabetes complication 2012 may Jun.: 26 (3): 225 - 9 (pub med: 22520404)

[7] Diabetic foot and peripheral arterial disease - clinical key

[8] IWGDF – guidelines 2019 –spanish

[9] Doups J. Veves A, classification, diagnosis and treatment of diabetic foot ulcers, wounds 2008; 20: 117 - 26

[10] Clayton W Jr, Elasy TA, A review of the pathiphsiology, classification, treatment of the foot ulcers in diabetic patient , clinical diabetes, 2009; 27 (2): 52 - 58

[11] SumpioBE, contemporary evaluation snd management od diabetic foot, scientifics, 2012; 435487

[12] Asociación Española de Enfermería vascular Y heridasguia de practicaclinical, cinsenso sober ulcerasvasculares Y pie DIABETES DE LA Asociacion Espanola de Emfermeria vascular heridas (AEEVH) 3rd, 2017

[13] Asociación Española de Enfermería vascular Y heridasguia de practica clinical (AEEVH) 2nd, sevilla 2014

[14] Pryce TD: A case of perforating ulcers of the feet associated eith diabetes and ataxic symptoms lancet 18887; 11: 11 - 2.

[15] Singer Aj, tassiopoulos, kirsner RS. Evaluation and management of lower extremity ulcers N engel J Med.2018 Jan; 378 (3): 303 (pub Med; 29342384)

[16] KatsilambrosN, Dounis E, MAKRILAKIS k TENTOLOOURIS n, TSAPOGAS r, Atlas of the diabetic foot.2ndOsford; wiley –black well; 2010

[17] MoxeyPW, Gogalniceanu P, Hinchliffe RJ, et al. lower extremity amputations - areview of global variability in incidence. DiabetMed, 2011; 28: 1144 - 53.

[18] LarveryLA, Armstrong DG, vela SA, Q uebedeaux TL, Fleischli TG, practical criteria for screening patients at high risk for disbetic foot ulceration . Arch intern. Med.1998; 158: 157 - 62

[19] MalgrangeD, Richard TL, Leymarie F, French working group on the diabetic foot. screening patients at high risk for diabetic foot ulceration . A multi - center hospital - based study in France. Diabetes Metab, 2003; 29: 261 - 8

[20] Apelgvist J. Diagnosis and treatment of the diabetic foot. Endocrine 2012; 41 (3); 384 - 97

[21] Lipsky BA, Aragon – sanchez J. Diggle M, Kono S, Lavery L, et al IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab. Res Rev.2016; 32 (sup; , 1): 45 - 74

[22] Noor S, Zubair M, Ahmad J, diabetic foot ulcer – A review on pathophysiology classification and microbial etiology, Diabetes MetabSyndr 2015; 9 (3): 192 - 9

[23] Kumar S, Ashe HA, Parnell LN , et al. the prevelance of foot ulceration and correlates in type two diabetic patients; a population based study, Diabet Med, 1999; 480 - 4

[24] TesfayS, Stevens LK, Stephenson Jm, etla, the prevalence of diabetic peripheral neuropathy and it is relation to glycemic control and patient risk factors; THE EURO DIAB IDDM complications study Diabetology, 1996; 3977 - 84

[25] TesfayA, Boulton Aj, Dyck Pj, Freeman R, Horowitz M, Kempler P, etla, Diabetic neuropathies; up date on definitiona, diagnostic criteria estmation of the severity and treatments diabetes care 2010; 33 (10); 2285 - 93

[26] BremH, Sheehan, boultonAj, protocol for treatment of diabetic foot ulcer, AM J surgery, 2004; 187; 15 - 105

[27] Dewi H, Hinchiffe RJ, foot complication in patient with diabetes surgery (oxford) febrero de 2020; 38 (2); 1108 - 13

[28] SharmasS, achaper N, Rayman G, micro angiopathy; is it relevant to wound healing in diabetic foot diseae, Diabetes / Metabolism research and reviews 2020; 36 (s1); 3244

[29] Dinh T, veves A, microcirculation of diabetic foot, CPD et 1 de Julio de 2005; 11 (18) 2301 - 9

[30] ParakevasKI , Baker DM , pompella A, MikhailidisDp. Does diabtes mellitus play a role in restenosis and patency rates following lower extremity peripheral arterial vascularization; A critical over view, Ann vasc surgery, 2008 (33); 481 - 491

[31] Arya Ak, Gargs, Kumar S, etla, Estimation of lymphocyte apoptosis in patient with chronic non healing diabetic foot ulcer, JNT J medi sci pub health; 2013; 766 - 768

[32] IsidonAM, Venneri MA, Fior D, Angiopoietin 1 and angiopoietin 2 in metabolic disorders; therapeutic strategies to restore the highs and the low of angiogenesis in diabetes, J endocrine invest 2016; 39 (11); 1235 - 46

[33] Bakker K, Apelgvist J, lipsky BA, Van netten JJ. the 2015 IWGDF Guidance documents on prevention and management of foot peoblems in diabetes; development of an evidence based global consensus, diabetes Mwttab res Rev 2016; 32 (suppl1): 2 - 6

[34] Sen CK, Roy s < wound healing in Neligan PC plastic surgery 3rd Elsevier inc.2013; 240 - 99, e5

[35] Mirastchijski U JokusziesA, Vogt PM, skin wound healing; repair biology, wound and scar treatment In; Neligan PC, ed , plastic surgey 3rd Elsevier inc.2013 267 /96 e8

[36] Zhao R, Liang H, Clark E, Xue M, imflammation in chronic wounds Int J Mol ci 2016; 17 (12); 2085

[37] Catrina SB, Okamoto K, perira T, Brismar K, poellinger L, hyperglycemia regulates hypoxiaindued factor 1X protein stability and function Diabetes 2004; 53 (12); 3226 - 32

[38] Pradhan L, Nabzdyk C, Andersen ND, logerfo FW, Veves A,. inflammation and neuropeptides the connection in diabetic wound healing, Expert Rev Moc Med 2009; 11: e2

[39] debridement

[40] Covanaghpr, Bus AS, offloading the diabetic foot for ulceration prevention and healing Jvasc surg 2010; 52; 375 - 435
[41] FrykbergRG, Armstrong DG, Giurini J, Edwards A, Kravette M , Kravitz S, et al Dabetic foot disorder Aclinical practice guidline American collage of foot and ankle surgeons. J foot ankle surg.2000; 39 (suoo1): 51 - 60
[42] CatanzaritiAR, Blitch KL, Karlock LG, LG , Elective footAND ANKLE SURGERY IN THE DIABETIC PATIENT, j FOOT ANKLE SURG 1995; 34: 23 - 41
[43] Burns J, Begg L, optimizing the offloading properities of the total contact cast for plantar foot ulceration. Diabet MED.20111; 28; 179 - 85
[44] National institute for health and clinical Execellence type2 diabetes prevention and management of foot problems clinical guidline ID, London; NICE, 2004
[45] CianiP, Hunt TK, Adjunctive hyperbaric oxygen therapy in treatment of diabetic foot wound, In Levin ME, O Niel LW, Bowker JH , eds the diabetic foot 5th ed ST, Louis Mosby year book 1993, 305 - 19
[46] PapanosIN, M allezos E. Benefit risk assessment of becaplermin in the treatment of diabetic foot ulcers, Drug saf, 2010; 33; 455 - 61
[47] Steed DL, Clinical evaluation of recombinant human platelet derived growth factor for the treatment of the lower extremity diabetic ulcers, diabetic ulcer study group, J Vasc. Surg.1995; 71 - 8
[48] WiemanTJ, Smiell JM, Su Y, Efficacy and safety of a topical gel formulation of recombinant human platelet derived growth factor BB in patient with chronic neuropathic diabetic ulcers, A phase III randomizes placebo controlled double blind study. diabetes care 1998; 21; 822 - 7
[49] HoggeJ, krasner D, Ngugen H, Harkless LB, Armstrong AD, the potential benefits of advanced therapeutic modalities in the treatment of diabetic foot wounds J Am podiatarMes Assoc.2000; 90; 57 - 65
[50] Fry berg RG, diabetic foot ulcers; current concept J Foot Ankle surg.1998; 37; 440 - 6