



An Update on Management of Diabetic Neuropathy with Diabetic Foot Syndrome-Optimization of Therapy Cost Effectively with Avoidance of Gangrene and Amputation-A Systematic Review

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Abstract

Earlier we have reviewed obesity and diabetes etiology (both type 1 and type 2 diabetes mellitus (T2DM)) and suggested best methods of classification of T2DM from effective management point of view utilizing weight neutral anti-diabetics, besides importance of empagliflozin a SGLT2 inhibitor in T2DM both with the idea of starting combination therapy for T2DM as well as for cardiovascular outcome trials point of view and emphasized on role of natural plant based therapies for better treatment of diabetes. Here we present a systematic review regarding better management of neuropathic pain accompanying T2DM along with best optimization, methods for treating diabetic foot ulcer (DFU). In view of complex etiology of DFU due to, multifactorial nature with importance of polyneuropathy we further highlight the role of neutrophil extracellular traps (NET) and how utilization of deoxyribonuclease might escalate wound healing besides roles of ozone and different kinds of dressings, role of recombinant human epidermal growth factor gel, and sucrose octa sulfate and other dressings besides importance of micronutrient deficiencies role of vitamin D, and importance of therapeutic footwear individualization and multidisciplinary team management in prevention of amputations and management of DFU cost effectively.

Keywords: T2DM; Neuropathic Pain; Diabetic Foot Ulcers (DFU); NET; Deoxyribonuclease; Recombinant Human Epidermal Growth Factor Gel; Sucrose Octa Sulfate Dressing; Therapeutic Footwear; Vitamin D; Ozone

Abbreviations: DFU: Diabetic Foot Ulcer; NET: Neutrophil Extracellular Traps; DF: Diabetic Foot; CPG: Clinical Practice Guidelines; DFS: Diabetic Foot Syndrome; ECM: Extracellular Matrix; NSS: Neuropathy Symptom Score; NDS: Neuropathy Dysfunction Score; NGF: Nerve Growth Factor; hEGF: Human Epidermal Growth Factor; T2DM: Type 2 Diabetes Mellitus; PAD4: Protein Arginine Deaminase; DUSS: Diabetic Ulcer Severity Score; Wifl: Wound, Ischaemia, and Foot Infection; citH3: Citrullinated Histone; OS: Oxidative Stress;

ADM: Acellular Dermal Matrix; ORC: Oxidized Regenerated Cellulose; BMI: Body Mass Index; FBG: Fasting Blood Glucose; CV: Cardiovascular; DNOAP: Diabetic Neuro-Osteo Arthropathy; TCC: Total Contact Cast; QOL: Quality Of Level.

Introduction

Diabetes is a disorder which afflicts millions all over the world, with global prevalence rapidly enhancing in the last

30 years [1], with the trend anticipated to enhance in the future from 5.1% at present to 7.7% in 2030 [2].

Diabetic Neuropathy

Diabetic neuropathy represents heterogeneous types of complicated etiopathological problems, affecting somatic as well as autonomic parts of the nervous system [1]. Diabetic foot (DF), that is one of the clinical parts of Diabetic neuropathy, by definition is the changes in structure or functions of the foot, like ulceration, infection and or gangrene related to Diabetic neuropathy as well as various degrees of peripheral vascular disease due to interconnection among several factor as stimulated by hyperglycaemia that has been maintained and earlier traumatic reasons though the foot does not come with any injuries [3]. Description of the DF is a reduction in pain secondary to as well as temperature sensations earlier and later by a reduction in vibratory sensitivity as well as superficial touch [3]. In view of this DF subjects might be unable to realize painful, mechanical, chemical as well as thermal stimuli under normal circumstances [3,4]. Such pathological conditions result in the formation of complications, like DF ulcer, Charcot osteoarthropathy and ultimate ulceration and amputation as the resultant evolutions [5]. Prevalence of DF side effects is right till 25% and represents the main cause for hospitalization as well as amputation in people with diabetes [6]. From 20-40% of the DM pathology available methodology get used for foot problems [6].

Clinical practice guidelines (CPG) means recommendations made on the basis of validation collected from systematic reviews and the risks along with advantages of the various examinations of various other methods for getting the best health care [7]. The basic idea of this review was to conduct a systematic review regarding levels of analysis and therapeutic methods which should be included in CPG concentrations on DF. Thus we decided to conduct a systematic review on the most efficient way of managing diabetic foot syndrome (DFS) along with DF Ulcers preventing gangrene amputations and getting a better QOL in DM pts with preventing morbidity and mortality for future life [8-15].

Methods

We utilized a pubmed search engine utilizing the MESH term Diabetic neuropathy, DFU; DFS; best dressings for DFU; Prognostic markers for healing of DFU; Charcots arthropathy; best medication for treating hyperglycaemia in those developing DFU; Deficiencies of micronutrients related to DFU.

Result and Discussion

We found a total of 25,454 articles out of which we selected 87 articles for this systematic review. No meta-analysis was done.

Diabetic Neuropathy-Types

Diabetic foot Neuropathy involving the distal lower extremities can be further sub grouped into

- Sensory
- Motor
- Autonomic peripheral neuropathy [16].

Presence of sensory neuropathy is reflected by a decrease in /absence of vibration sense (pally hypaesthesia) and superficial sensitiveness to pressure touch along with subjective paraesthesia. Most distressing is what is labeled as "burning feet syndrome". Its occurrence mostly starts at night accompanied by a feeling of pain [17]. This feeling of pain gets markedly reduced secondary to chronic sensory neuropathy. As a result chance of getting injured is markedly greater [18-21]. In view of the lack of pain symptoms, serious ulcerations might be under anticipated both by patient secondary to chronic sensory neuropathy as well as doctor [22,23]. Hence injuries go unnoticed for over wks. Mostly sensory neuropathy is associated with decreased feeling of temperature. Loss of sensation is mostly in a peripheral, sock like, and is symmetrical in the initiation phase. Sensation loss usually occurs symmetrically. Achilles reflex is mostly decreased secondary to chronic sensory neuropathy patellar reflex. Underlying sensory neuropathy causes muscular function impairment, mostly atrophy of the anterior muscle group of lower leg causes strain at the time of rollover process with enhancement on foot pressure. 3 side effects result secondary to absence of sensitivity

- Continuous pressure for multiple hrs. causing local ischemic necrosis like when pain is absent and wearing tight footwear
- High pressure in a short duration of time causing injuries immediately .Things that have a small surface like needles, nails, sharp stones etc. effect direct mechanical injury
- Repeated moderate pressure leads to inflammatory autolysis of tissue. Continuing pressure on tissue that is inflamed or already affected further facilitated formation of ulcers. Moreover gangrenes form from burns with hot items like hot water bottles as well as heating blankets, enhanced sunbathing, acid burn (corn plaster) along with imperfect use of disinfection products.

Motoric neuropathy can be visualized in an atrophy of small foot muscles causing malposition of toes (claw toe).

Further motor paresis and a loss of muscle self-reflex are seen. Moreover absence of Achilles tendon reflex is a very early sign that one observes during Motoric neuropathy [11,24]. Once both sensory and motor neuropathy present together it causes unequal foot load that gets together with gait that is not secure. As time passes, hyperkeratosis forms secondary to neuropathy and escalated plantar pressure load. From sub epidermal hygroma development and haematoma malum perforans form, with sites having >chances of development is metatarsal I as well as heel area.

Peripheral autonomic neuropathy resulting in vasomotor paralysis that causes arteriovenous shunts of subcutaneous vascular network. Further sweat secretion also gets impaired by sudomotor paresis resulting secondary to autonomic neuropathy with increased blood supply to the deeper skin layers overheating of the skin results. In addition impaired sweat secretion results in absence of humidification as well as cooling by evaporation. Hence foot skin dryness causing decreased protection of skin with > likelihood of damage. Furthermore autonomic neuropathy causes medial arterial sclerosis, Charcot's foot (diabetic osteoarthropathy), neuropathic oedemas along with chances of ulceration and 3 times > chances of amputation. Secondary to autonomic neuropathy, nonenzymatic glycosylation as well as cross link development of Extracellular matrix (ECM) interfere with viscoelastic foot working which then causes stiff wrists as well as foot joints in approximately 40% of patients [25-27].

Examination-Neurological

In standard measurement vibration assessment with use of a 128iHz graduated tuning fork (Rydel-Seiffer) and /or pressure as well as touch sensitivity through a 10g microfilament (Siemmes-Weinstein Filament) is needed. Marked factors causing apprehension are reduced warm/cold sensation (tip-therm testing), decreased sensation of pain, dysfunctional 2point discrimination and muscle self-reflex status. Sensitive marker is the Achilles tendon reflex. Moreover questionnaires like Neuropathy Symptom Score (NSS) and Neuropathy Dysfunction Score (NDS) complete the clinical diagnosis. Differential Diagnosis should include minimum the following laboratory tests namely haemogram, creatinine, ESR, TSH, Vitamin B12, Folic acid alanine aminotransferase, Gamma GT, Immunoelectrophoresis (paraproteinemia and (hs)cr P.Neurological basis assessment by novel and promising methods like checking vibration perception with the use of Vibra tip and/or the Ipswich Touch Test for simple outdoor bedside screening of peripheral sensory neuropathy.

Clinical-DF Ulcers Presentation

The ulcers are present at typical predisposed parts (like

areas of greater pressure bearing-metatarsal 1), are of round shape that has hyperkeratotic borders surrounding them which have formed due to excessive pressure load. Although it usually has a simple external ulcerated look, lot of extension of depth on probing or a subclinical co existent infection of the surrounding area is usually observed (Figure 1).



Figure 1: Courtesy reference number 87-Typical diabetic ulceration at stage 2 (Wagner/Amstrong classification) seen at typical predisposed location of metatarsal 1. The shape is typically circular and surrounded by a hyperkeratotic border. Modest erythema of the surrounding tissue suggests coinfection (if verified, stage 2b criteria are fulfilled).

Diagnosis

Clinically inspecting the status, gait, foot (skin integrity), muscular as well as bone structure, feet anomalies like claw foot, halux valgus, hollow foot, skew foot and flat foot) in addition to what kind of footwear the patient is wearing. Dry as well as fissured skin along with hyperkeratosis as a sign of polyneuropathy. Other visual diagnosis made is of Charcot's foot (diabetic-neuronal osteoarthropathy). Charcot's foot has the property of reactive erythema with marked swelling and break down of osseous area that ultimately=> sintering of the metatarsus area.

Neuropathy Dependent Cellular Impairment of Wound Healing

Complicated Impairment of Cellular Wound repair occurs in the DF lesions. Additionally general factors that interfere with healing of wound like age, fluid as well as nutritional status along with hyperglycaemia, the systemic nature of diabetic diseases results in changes in cellular level. These are altered microcirculation, decreased inflammatory reaction, and decreased fibroblast

proliferation, with a changed cytokine-protease profile. Due to this, Wound Healing is impaired continuously [28-33]. By itself neuropathy has a negative influence on Wound Healing. Skin that is enervated displays altered wound healing, with T2DM patients and poly neuropathy revealing a decreased density of nerves in the skin [34]. Shortage of nerve growth factor (NGF) as observed in DM ulcers interferes with Wound Healing. On supplementation of NGF, wound contraction enhances as well as leukocyte chemotaxis with a keratocyte escalation turnover. DM poly neuropathy basically influences NGF based structures like sensorial as well as sympathetic neurons. Marked structural resemblance of NGF with insulin exists [30,35-39].

Management of DF Syndrome

Most important thing for healing is relief of pressure for healing of trophic diabetic dysfunctional tissues [40,41]. Further metabolic control along with recognizing clinically important infection in time along with antibiotic initiation is essential. Ensuring of good blood supply inside the wound bed is the basic law for all conservative as well as operative methods. This means cleaning of wound with debridement, an effective infection fighting along with revascularisation when required (PTA, bypass hyperbaric oxygenation).

In the acute phase, initially and subsequently radical necrosis clearing is a must. This infected tissue that is non-vital now has to be cleared off for stimulating granulation. In the granulation phase wound pads and therapeutics which stimulate and maintain Wound Healing need to be utilized. More than that it is the primary measures that are most essential. Generally a nonocclusive as well as moist wound treatment is what needs to be planned for the treatment of DF ulcers (DFUs) [24-26].

Role of Recombinant Human Epidermal Growth Factor (hEGH)

For proving the effectiveness of recombinant human epidermal growth factor (hEGH) in healing DFUs at biochemical and molecular level Viswanathan, et al. enrolled 50 noninfected DFUs patients for the study, dividing them into 2 groups on the basis of treatment given to the individuals. Group1- DFUs treated with hEGH gel-based product known as Regen D 150(n=27) and Group2-DFUs patients receiving placebo as control group (n=23). After watching the patients for 30days as well as punch biopsy on day 0 and 14. Histology was performed to examine the matrix alignment, cellular infiltration as well as differentiation of epithelial layers. Biochemical analysis was performed for quantitative testing the collagen content as well as proteoglycan regenerated in the wound area. Total healing of ulcers was seen in 78% patients (27) of group 1, while only

52% patients (12) belonging to group 2 showed complete healing of ulcer following study completion period of 30days. Collagen and fibroblasts were formed markedly in group 1 on observing in follow up samples. Healing time of wound in group 1 patients was much < as compared to group2 patients (45±12 vs 72±18 days, p<0.001) and also displayed a better glucose level. Early and regular application of hEGH on DFUs will avoid leg amputations and work as a main therapeutic strategy for healing chronic wounds [27].

Role of Neutrophil Extracellular Traps (NETs)

Inflammation is a special characteristic of Wound Healing process, with neutrophils getting recruited early to the wound bed [28]. The importance of neutrophils in DFUs has taken a new twist with the neutrophil extracellular traps (NETs) getting involved. Hyperglycaemia can stimulate NETs release, showing a connection between neutrophils, Inflammation and tissue damage in type 2 diabetes, mellitus (T2DM) [29]. Additionally, infection is usually present in DFUs patients with NETs might be representing a natural response against infection. Activated neutrophils liberate NETs that are made up of granular proteins / enzymes and nuclear material. Then NETs entrap and eliminate bacteria by utilizing a sticky extracellular network that is enriched with bactericidal proteins [30]. NETosis comprises of a combination of citrullination of histone 3 which is modulated by protein arginine deaminase (PAD4), marked chromatin decompensation, and the nuclear localization of granular enzymes like elastase [31]. That NET induction might result in tissue damage has been observed, with inhibiting NETosis by PAD4 knockout and interfering with NETs with deoxyribonuclease might increase Wound Healing rate in DFUs patients [32]. Thus Yang, et al. tried to analyze the correlation with interference with NET specific markers as well as Wound Healing in DFUs patients that were treated in a multidisciplinary setting. They recorded clinical data of diabetic patients with active foot ulcers, presenting from Jan 1 2016 to June 30. The Diabetic ulcer severity score (DUSS) as well as wound, ischaemia, and foot infection (WIFI) score were calculated. NET specific markers in plasma and wound tissues were examined. The ability of plasma and platelets to prime neutrophils, to liberate NETs was evaluated. Prognostic value of NET specific markers for Wound Healing was examined. NET specific markers were markedly > in DFUs patients in contrast to subjects without DFUs or healthy controls and were observed to associate positively with DUSS as well as WIFI score. Elastase values in ulcer tissue markedly enhanced in wounds with infections as well as delayed healing. Greater amounts of NET liberation were seen following the stimulated plasma or platelets from ulcer related vessels as compared to non-ulcer related vessels of the DFUs patients. Citrullinated histone 3 (citH3) was found to be a risk factor for dysfunctional wound healing rates

as well as >amputation rates than those with the lower 3 quartiles. Thus concluding that NET specific markers were negatively associated with Wound Healing in DFUs patients [33].

Role of Ozone (O₃)

Besides foot problems of diabetics being a major factor on considering morbidity, a cost burden with lot of expenditure related to therapy of DF is there [34]. Use of ozone (O₃) within the medical community started in 19th century. Medicinal application of O₃ is met with lot of discourse because it is unstable due to inherent quality. But it is assumed that O₃ can be started in pharmaceutical science with lot of treatment advantages in particular biological systems and might not just work as an obscure method [35]. O₃ has been observed in use in many medical applications like from dentistry to good sterilizing of medical instruments [36]. Also good effects seen in orthopaedics, mucosal as well as cutaneous infections [37]. In future it might be used in heart failure therapy [38]. Moreover there is enhancing proof that it may be used for treating DFUs. A study revealed that O₃ given through rectal insufflations might improve glycaemic index as well as prevent oxidative stress (OS) in Diabetic rats [39]. Efficiency gets measured by how properly the wound has closed in DFUs following O₃ therapy [40]. Thus Kushmanov, et al. tried to review the proof for probable use of O₃ therapy in DFUs. Good results were seen in various studies. Mostly a mixture of both O₂ and O₃ is observed in pressurized machines like the ones given to foot ulcer. DFUs need to be examined, cleaned and treated as rapidly as feasible. With rapidly increasing clinical trials in O₃ therapy and fast giving of O₃ therapy, O₃ therapy might be rising in the therapy of DFUs. Lot of proof in clinical trials is there but >work is needed to fully get insight in the role of O₃ therapy in DFUs [41].

Role of Dressings

Nano-Hydrogel Embedded with Quercetin and Oleic Acid: Wound Healing, particularly DM related, needs surgery often. For getting over any invasive process, various methods like drugs/natural compounds get utilized. In an experimental study Gallelli, et al. detailed an enhancement of keratinocyte proliferation following their exposure to quercetin with oleic acid recently. Now they examined both clinical effectiveness as well as safety of nano-hydrogel embedded with quercetin and oleic acid for treating lower limb skin wound in DM patients. 56 type 2 diabetes mellitus (T2DM) patients (n=28 male, n=28 female having mean age 61.7±9.2yrs) unsuccessfully treated with mechanical compression were recruited as well as randomized for getting an add on therapy with hyaluronic acid (0.2%) or nanohydrogel embedded with quercetin with oleic acid. Significant prediction in

wound healing time (p<0.01) occurred with nanohydrogel embedded with quercetin with oleic acid as compared to hyaluronic acid without development of any side effects, pointing that this formulation might be utilized in the Wound Healing, management with more clinical trials to further prove their findings [42].

Cellular Dermal Matrix (ADM): Lee, et al. tried to study the effectiveness of applying a paste formulation of acellular dermal matrix (ADM) to DFUs. Patients having Wagner grade 2 or 3 DFUs (n=49) got either (ADM paste (treatment group n=23) or conventionally used foam dressing (control group n=26). All chronic wounds got debrided and irrigated for controlling infection. Following paste application, mild compaction was done to fill ulcer cavities, and foam dressings were utilized for covering the surface for absorbing any discharge. All DFUs were evaluated regarding area of ulcer, its depth, propagation, rate of healing and time taken for total healing. At 60 day primary outcome mark, 56.52% (13/23) of the DFUs in the treatment group were healed, as compared to 23.08% (6/26) of control group. Mean rates of wound area healing in the treatment and control group were 74.17%±30.84% and 51.87%±32.81% respectively (p<0.05) with mean times to heal (within 60days) of 13.54±9.18 days and 21.5±11.98 days respectively (p<0.05%). No serious side effects occurred in both groups and no complications regarding ADM paste application. Thus this paste escalated tissue regeneration, shortened ulcer duration and avoided any complications related, and removing the requirement for additional ulcer treatment processes. This paste of ADM supplies a matrix for tissue in growth, facilitating the healing of DFUs [43].

Oxidized Regenerated Cellulose (ORC)/ Collagen/Silver-ORC Dressing: Griffin, et al. carried out a comparative effectiveness study that evaluated the value proposition of 2 collagen-containing wound dressings-Oxidized Regenerated Cellulose (ORC)/ Collagen/Silver-ORC Dressing Versus Ovine Collagen Extracellular Matrix in matched cohorts of patients undergoing therapy for DFUs. Data was extracted from the US Wound Registry found DFUs that got treated with either dressing and had wounds with total data records (n=3230). 37 variables were checked in propensity score matching for forming a case matched cohort of 844 DFUs (n=422 DFUs/group). The ORC/ Collagen/Silver-ORC Dressing group gave a significantly >percentage of DFUs which healed or improved (82% vs 74.6%; p=0.0096). The ovine collagen ECM dressing group gave a significantly >percentage of DFUs which deteriorated (15.2% vs 23.9%; p=0.013). The ORC/ Silver-ORC Dressing group showed a > percentage of DFUs which obtained 75% to 100% granulation at 0 depth at 4,8,12 and 16wks. Median time to 75% to 100% granulation was 42 days for the ORC)/ Collagen/ Silver -ORC Dressing group vs. 60days for the ovine collagen ECM dressing group (p=0.109).

Hence as per comparative effectiveness study utilizing real world data, (ORC)/ Collagen/Silver-ORC Dressing seems to give enhanced healing with decreased time to granulation compared to ovine collagen ECM dressing [44].

Sucrose Octasulfate Wound Dressing: No satisfactory treatment for neuroischaemic ulcers is present right now. Hence Edmonds M conducted a double blind, randomized controlled trial (Explorer) in 43 hospitals having specialized DF clinics in France, Spain, Italy, Germany and the UK. Participants eligible were in Patients or out Patients ≥ 18 yrs with Diabetes and a noninfected neuroischaemic DFUs $> 1\text{cm}^2$ of grade C or IIC (as defined by University of Texas Diabetic Wound Classification System-see ref 41 for detailed Classification Systems). Patients were randomized (1:1) by a computer generated randomization method (concealed block size 2); further stratified by study centre as well as wound area ($1\text{-}5\text{cm}^2$ and $5\text{-}30\text{cm}^2$) to treatment with either a Sucrose octasulfate wound dressing or control dressing (the same dressing without Sucrose octasulfate) for 20wks. Both groups otherwise got similar standard of care for a 2week screening period before randomization and all through the 20wks trial. Dressings were applied by nursing staff (or by relatives that had received instructions for certain out Patients). How frequently dressing was to be changed was decided by the investigator depending on the clinical condition of the wound. Patients were evaluated 2wks following randomization, then monthly till wk. 20 or occurrence of wound closure. The primary outcome, evaluated by intention to treat, was %age of Patients with wound closure at wk 20. From mar 21 2013 to 31 mar 16 they randomly assigned 240 subjects to treatment; 126 to Sucrose octasulfate dressing and 114 to control dressing. Following wk20 wound closure took place in 60 Patients (48%) in the Sucrose octasulfate dressing group and 34 Patients (30%) in the control dressing group (18 percentage points difference, 95% CI 5-30; Adjusted OR 2.60, 95%CI 1.43-4.73; $P=0.002$). In both groups, the commonest side effect were infections of the target wound; 33 infections in 25(20%) Patients of 126 in the Sucrose octasulfate dressing group and 36 in 32(28%) Patients of 114 in the control dressing group. Minor amputations not affecting the wound site were also documented in 1(1%) Patient in the Sucrose octasulfate dressing group and 2(2%) in the control dressing grp. 3 (2%) Patients from the Sucrose octasulfate dressing group and 4(4%) from the control dressing grp died although none of the deaths had any correlation with treatment, procedure, wound propagation, or following amputation. Thus a Sucrose octasulfate dressing significantly improved wound closure of neuroischaemic DFUs without safety issues 20wks post treatment in addition to standard of care. These findings validated the use of Sucrose octasulfate dressing as a local treatment for neuroischaemic DFUs [45].

TLC-NOSF dressing-Cost: Further Lobmann R analysed the clinical Outcome of 2 treatment options for patients having DFUs; a TLC-NOSF dressing versus a neutral dressing assessed through the Explorer trial was related to direct costs (costs for dressings, nursing time, hospitalization etc.) of both dressings from the point of view of the statutory health insurance in Germany). In view of long mean healing time of a DFU, the observation time was prolonged from 20 to 100 wks in a Markov model. Following 20wks and with total closure as the primary outcome, the model showed direct treatment costs for DFUs of €2,864.21 when treated with TLC-NOSF dressing as compared to €2958.69 with the neutral dressing (cost effectiveness €6017.25 versus €9,928.49). In the Markov model (100wks) the costs of TLC-NOSF dressing was €5,882.87 as compared to €8440.39 with neutral dressing (cost effectiveness; €6,277.58 versus €10,375.56). The markedly good results were affected by different sensitivity analysis for different presumptions. The frequency of weekly dressing changes made the biggest impact with regard to uncertainty of the parameter. Thus in total the treatment of DFUs with a TLC-NOSF dressing gets supported even from the point of view of health economic point of view since both treatment cost as well as cost effectiveness were better than neutral dressing [46].

Micronutrients Deficiencies

For evaluating the prevalence of micronutrient deficiencies in patients having DFUs and associate this with foot disease severity Pena, et al. conducted a prospective cohort study of DFU's in multidisciplinary foot clinics across Adelaide or admitted to Royal Adelaide Hospital from Feb 17 to Sep 18. Total 131 patients got enrolled in this study. Plasma serum values of vitamins A,C,D and E, copper, zinc and ferritin were measured. Demographic as well as a clinical values including Body Mass Index (BMI), smoking status DM duration, deficiency and Wifi Score were obtained. The most common nutritional deficiency found was of Vitamins D affecting 55.7% of patients. Suboptimal vitamins C amounts were seen in 73% patients comprising marginal levels in 22% and deficient in amounts in 50.8%. Zinc deficiency, Vitamins A deficiency and low ferritin values were 26.9%, 10.9% and 5.9% of patients respectively. No association among body mass index (BMI), grip strength, DM duration, Hb A1c or smoking status with micronutrient deficiency was seen. Increased severity of DF Disease correlated with micronutrient deficiencies particularly Vitamin D, vitamin C, zinc and vitamins A is common in DM patients with DFU'S. Thus given the role of vitamins C and zinc in wound area healing prevalence of these deficiencies is highlighted in DFU'S patients. Though future research needed one should always consider micronutrient deficiencies in patients having DFUs [47].

Vitamins D Deficiency: Neuropathic pain, a common complication of T1DM as well as T2DM. Cause attributed for this occurring in 50% of diabetics [48] is due to toxic effects of chronic hyperglycemia [49]. These include development of advanced glycation end products and reactive oxygen radicals that can cause damage in the microvasculature which vascularizes peripheral nerves [50,51]. Hence patients might report different Neuropathic symptoms comprising of peripheral sensations, numbness, tingling, burning as well as pain [52]. Sad thing is that it may worsen and cause serious conditions like foot ulcers as well as infections [53]. Increasing proof that points that vitamins D deficiency comprises a risk factor for DM Neuropathy [54-56]. Though vitamins D is understood to participate in calcium homeostasis and bone remodeling, it possesses other systemic functions which might be manipulated by its actions on vitamins D receptors (VDR) that are expressed on different cell kinds [57]. Hence vitamins D deficiency is not only implicated in pathogenesis of bone diseases but also might participate in the formation of other diseases like DM as well as CVD [58,59]. Various workers have demonstrated that vitamins D deficiency might predispose patients to hyperglycaemia and thus enough vitamins D might improve their glycaemic control [60]. Further side effects might get decreased or delayed by sustaining normal serum vitamins D levels [61]. Lot of proof points that vitamins D administration, might improve DM Neuropathy. Like Lee, et al. [54] pointed that vitamins D might be utilized as an analgesic for pain that occurs secondary to DM Neuropathy. Similarly Nadi, et al. pointed that vitamins D administration in combination with training might improve symptoms of sensorimotor Neuropathy in T2DM women. Multiple other studies have further shown an improvement of symptoms of painful Diabetic peripheral neuropathy on vitamins D administration [62,63]. A recent meta-analysis has proved that vitamins D deficiency could be correlated with the formation of Diabetic peripheral neuropathy in Caucasian patients with T2DM [54]. Similarly lot of studies done in separate populations demonstrated association among serum vitamins D and Diabetic peripheral neuropathy [55,64].

But contrary to that Alkhatatbeh and Abdul Razzak conducted a cross sectional involving 239 subjects having T2DM. Neuropathic pain was assessed using Pain DETECT questionnaire. Serum 25hydroxy vitamins D was measured utilizing electroilluminescence immunoassay, fasting blood glucose (FBG) was measured by the hexokinase method and Hb A1c by the turbidimetric inhibition immunoassay. The prevalence of Neuropathic pain among T2DM patients was 26.8%. Vitamins D deficiency was documented in 67.8% of T2DM patients. The Neuropathic score for females was significantly >than that for males ($p < 0.01$). No significant variation in serum vitamins D among patients with T2DM as per their gender and according to their neuropathy status

($p > 0.05$). Original logistic regression analysis displayed that female gender was the only significant predictor of Neuropathic pain of all T2DM enrolled ($p < 0.01$) with an OR of 2.45 (1.29-4.67). Thus concluding Neuropathic pain was not correlated with serum vitamins D but correlated with female gender in T2DM patients. Since their results were not consistent with other studies which utilized other Neuropathic assessment tools, they suggested future research for validating these tools in finding the subjects with neuropathy [65].

Role of Liraglutide

Since the long-term, data that finds out the efficiency of individual glucose lowering agents on DFUs are not there Dhatriya, et al. using whatever data is present from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, carried out a posthoc analyses to find the effect of Liraglutide versus placebo with type 2 diabetes and at high risk of Cardiovascular (CV) events on the incidence of DFUs and their side effects. The LEADER trial (NCT01179048) was a randomized, double blind multicenter CV Outcomes trial that evaluated Liraglutide (1.8mg/day) versus placebo in addition to standard of care for up to 5yrs. Information regarding DFUs was systemically gathered at the time of trial with DFUs complications evaluated posthoc by review of case narratives. In a median 3,8yr follow up, similar proportion of patients documented a minimum of 1 episode of DFUs in the Liraglutide and placebo groups [3.8%[176/4668] versus 4.1%[191/4672], respectively [HR0.92 [95% CI0.75, 1.13;P=0.41]. Analysis of DFUs associated complications showed a significant decrease in amputations with Liraglutide versus placebo [HR0.65 [95%CI 0.45, 0.95; P=0.03]. But no differences were found for foot infections, involvement of underlying structures, or peripheral revascularization in the main analysis. Thus concluding that Liraglutide in type 2 diabetes at high risk of CV events in the LEADER trial did not increase the risk of DFUs events and correlated with a significantly < chances of DFUs-associated amputations compared with placebo. This association might be probably due to chance, and hence needs more exploration [66].

Charcot's Foot (Diabetic Neuro-Osteo Arthropathy)

Diabetic Neuro-Osteo arthropathy (DNOAP) or Charcot's foot represents sterile damage of bones and joints. Secondary to neuropathy, this process continues painlessly. Visually typical reactive hyperaemia in line with swelling as well as osseous structures and grounding of the metatarsus. Its differential diagnosis is phlegmons or erysipelas commonly. The foot that is involved displays increased perfusion locally in view of the neurovascular (as per Charcot) part resulting

in washing out as well as demineralization of osseous structures. Thus, bone resistance reduces fractures and thus deformity results. As per Volkmann repeated injuries in view of continued improper stress secondary to sensorimotor

neuropathy. Subsequently chronic soft tissue damage of soft tissues as well as osseous areas. Current theories posit more part of nuclear transcription factor NF κ B along with RANKL/OPG cytokine (Figure 2).

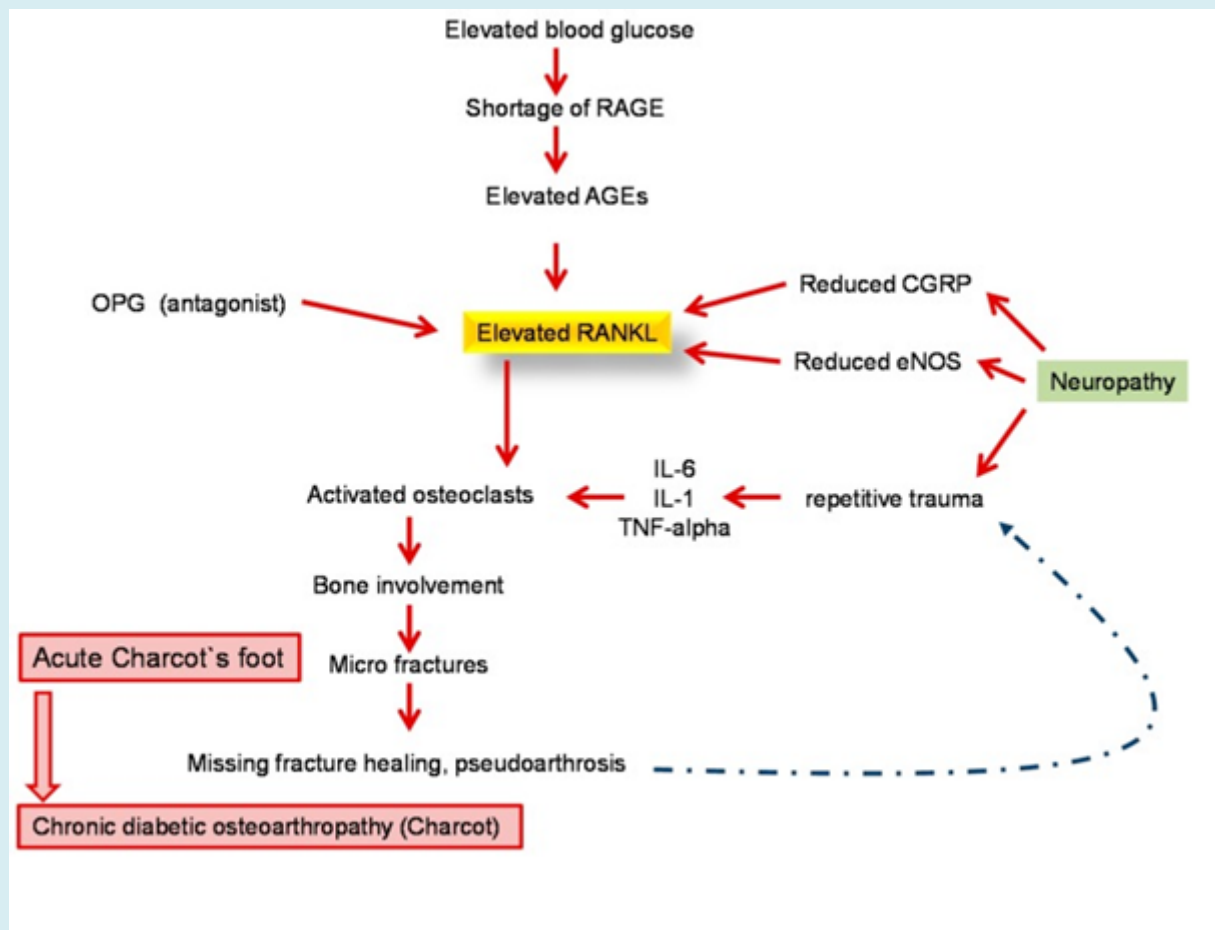


Figure 2: Courtesy ref no.87- Pathophysiology of diabetic osteoarthropathy underlying the central role of the RANKL-OPG system in the development of destructive bone alterations. RANKL= receptor activator of nuclear factor-kappa B ligand; AGE = advanced glycation end product; CGRP= calcitonin gene-related peptide; eNOS= endothelial nitric oxide synthase; IL= interleukin; OPG= osteoprotegerin; RAGE= receptor for advanced glycation end products; TNF= tumor necrosis factor.

Clinically to think of DNOAP are swelling as well as redness along with excess heating of foot mostly in the absence of pain in patients already having neuropathy. To diagnose DNOAP, a routine X-ray image for checking the 5D's of the X-ray alterations

- Distended joints
- Dislocation of joints as well as bones
- Debris of bones
- Disorganization of joints as well as bones
- Density rise of bones

Further it is always essential to do an MRI for properly

depicting cortical injury, periosteum reaction, and questration as well as gas development. Therapy can be

- Conservative
- Surgical

Conservative

Basic idea is to prevent propagation and avoid future deformity of feet occurring from ulcers. For estimating the degree of disease activation, amount of swelling along with redness, particularly skin temperature is estimated. There should be a minimum of 2°C in contrast to the unaffected

limb. Basic principle of treatment is rapid and continued pressure relief by affecting immobilisation for limited period by wearing a cast that gives protection either Total contact cast (TCC) or orthosis (like VACO ped Diabetic till the acute phase is over. Both the doctor and patient need to have enough patience since healing might take months to occur. The only proven therapy considered gold standard is the TCC. Recent pharmacological therapies used in DNOAP have not shown any effectiveness and are not recommended for clinical therapy. New therapeutic approaches are required to prevent bone destruction of Charcot's foot in an acute phase [67].

Surgical

It becomes essential to operate when plantigrade foot placement as well as resilience of foot can't be achieved utilizing Conservative Methodologies. On completion of ulcers healing, resection of local exostoses needs to be carried out. An elliptical circumcission of the ulcers given to remove these exostoses might be a 2nd way to deal with plantar ulcers as well as exostes. If the Charcot's feet deformities as well as instabilities are marked, one needs to utilize arthrodesis methods. Ultimately biggest aim of treating is to get resilience of foot, plantigrade foot posture and proper shoe or giving orthosis.

Prevention as well as Rehabilitation

It is highly essential for seeing to it that there is good care following treatment regularly and utilizes preventive methods to make it most likely that ulcers don't recur avoiding chances of amputation. If aftercare is inadequate 70% experience a minimum of one ulcer occurring again, with 12% requiring amputation within 5yrs of the original foot lesion. Once amputation has been done previously, total accumulated chances of repeated amputation in the subsequent year is roughly 27% and 61% following 5yrs [68-71]. Concentration has to be done on individualistic orthopaedic shoe being supplied with treatment of insole for adapting the pressure distribution in an equal manner for every foot. By this occurrence of new fresh lesions will get avoided [22,23].

Moreover what is being looked into in the surgical method for avoiding ulcers and amputation is nerve decompression operations. Removing peripheral nerves that are under pressure chronically had a significant correlation with better sensibility and reduction in both ulcer as well as amputation rates [72].

Role of Therapeutic Foot Wear

Most guides agree on Therapeutic Foot Wear recommendation with a level of evidence B, although the

moderate grade of. As per Ashbury, et al. [73] and Daza, et al. [74] therapeutic shoes are recommended only in pts with foot deformities, but Kennon, et al. [75] recommended the use for all T2DM to prevent recurrence of foot pathologies and ulcerations. From the literature it is pointed that all people having T2DM utilize therapeutic shoes for protection as well as accommodation of the foot to decrease the incidence of pathologies and DFU's. This is believed to prevent shearing and friction of the footwear but needs to be carried out under health professional supervisions [76-80].

Use of Multidisciplinary Methods

Diabetic Foot Syndrome (DFS) therapy is complicated. Hence Multidisciplinary as well as multiprofessional team work is required [81-83]. Further one needs medical help from cross sectional and among various disciplines, besides integration of nonmedical health care professionals (DM advisor, diet provider, podiatrist, and orthopaedic master shoemaker) is of utmost importance.

To get a team format that gets success one requires formal as well as content-associated specifications. Both national as well as international guidelines in addition to guidelines of one's own centre are needed. For making a plan that utilizes shared plan, critical for getting outcome is good communication amongst every professional group as well as seeing to it that constantly plan is brought into action. Further for good patient care there is need of making interfaces in the good collaboration among all professional groups. Like in case of Germany there is working group "Diabetic Foot" of the German Diabetes Society (DDG) gives certification to hospitals, practices that are ambulatory and OPD Clinics for both in patient treatment of DFUs. What approach they utilize for patient care at its core Multidisciplinary (www.ag-fuss-ddg.de) along with its structure as well as process quality have been validated by retrospective evaluation of their data of >18,000 patients. Their data revealed a cure rate >55% within 6mths as well as very less amputation rate of 3.1%. Of the biggest importance is requirement of major amputation i.e. 3.1% is significantly < than national average (10-15%) that is especially necessary since amputation is the biggest factor determining quality of level (QOL) as well as mortality [84].

Summarizing, all predefined as well as certified structures that have been advised by the working group "Diabetic Foot" are good for seeing to it that the amputation rate remains constantly low in a time frame of 8yrs [85]. Basically objective of all professionals should be to get maximum healing rate that is feasible. Best utilization of financial sources is necessary and should not be associated with non-crucial primary amputation that needs to be prevented. Further the rest of foot needs to have enough

functionality to ensure that relapse rate is as less as feasible by utilizing the right secondary preventive ways like shoe inlays and or shoe provision.

Conclusion

Thus in a systematic Review based on PRISMA and Appraisal of Guidelines for Research and Evaluation (AGREE II) utilizing 12 articles for Clinical practice guidelines (CPGs) concluded that the heterogeneity of levels and recommendations of CPG included regarding the management, approach of treatment of DF make it difficult to interpret and assume them in clinical practice in order to select the most correct procedures despite this and as per the full study of the Guidelines. Perez-Penero, et al. concluded that the highly recommendable interventions in DF Management are debridement (very high level of evidence and strongly recommended), foot evaluation (moderate level of evidence and fairly recommended) and therapeutic Foot Wear (moderate level of evidence and fairly recommended) [86].

After having reviewed on etiopathogenesis of type 1 diabetes mellitus and type2 DM, we have reviewed how to classify type2 DM, use of combination therapy in type2 DM and advantages of SGLT2 Inhibitors especially empigliflozin in both CVOT for type2 DM in those at risk of CVD and as an initial combination therapy of type2 DM with metformin and advantages of using monoterpenes and PTP1B Inhibitors from natural plant sources [87-94], here we have emphasized on role of use of Liraglutide, the only antihyperglycaemic tested for DFUs, advances in dressings that give best results like sucrose octasulphate dressing, Oxidized Regenerated Cellulose (ORC)/ Collagen/Silver-ORC dressing, nanohydrogel embedded with quercetin and oleic acid, a cellular dermal matrix paste and use of ozone. Role of various micronutrients especially Vitamin D,C zinc for better healing although controversy arisen regarding Vitamin D, Importance of NETosis in predicting severity of DFU's and chances of amputation as biomarkers. No benefit of GMCSF has been found in this chronic problem in diabetes mellitus than can spoil the full life of a young diabetic if not properly dealt with. Importance of multidisciplinary care is again emphasized with local specialized DFU treating groups with importance of staff nurses, dieticians with regards to nutrition, proper footwear specialist. Use of deoxyribonuclease might help in wound healing as per NET trap hypothesis. Further role of recombinant human epidermal growth factor (hEGF) is discussed.

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