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AN OVERVIEW ON ETIOPATHOGENESIS OF DIABETIC FOOT ULCER

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Abstract:

Diabetes mellitus (DM) is a complex disease affecting almost all the vital organs in the body. DM is known to have many complications and one of the most distressing is Diabetic Foot Ulcer (DFU). Infections, chronicity, and recurrence are the opportunistic problem of DFU. Approximately 15% of all people with diabetes will be affected by a foot ulcer during their lifetime. The diabetic foot may be defined as a group of syndromes in which neuropathy, ischemia and infection lead to tissue breakdown, resulting in morbidity and possible amputation (World Health Organization, 1995). Impaired metabolic mechanisms in DM increased the risk of infection and poor wound healing. It happens due to series of mechanisms which include decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis. So, the feet are influenced by damage to peripheral nerves, the peripheral vascular disease, ulcerations, deformities and gangrene. There are several components that cause the emergence of diabetic foot ulcers in diabetic patients, can be divided into two major factors, namely: Causative factor (Peripheral neuropathy, high foot plantar pressure, and trauma) and contributive factors (atherosclerosis, diabetes). The General Symptoms that help in the prediction of the appearance of late phase of the diabetic foot ulcer include- In Legs and arms: Deep pain, most commonly in the feet and legs; Loss of the sense of warm or cold; Muscle cramps; Numbness (if the nerves are severely damaged); Tingling or burning sensation in the extremities, particularly the feet; General Weakness. Thus Diabetic foot is a complication often due to a combination of sensory neuropathy (numbness or insensitivity) and vascular damage. It increases the risks of skin ulcers (diabetic foot ulcers) and infection and, in worse cases, it causes necrosis and gangrene. As a result of this, in this developed world it becomes the underlying cause of non-traumatic adult amputation, usually of toes and or feet.

Keywords: *Diabetes mellitus, Diabetic Foot Ulcer, Peripheral neuropathy, atherosclerosis.*

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INTRODUCTION:

Diabetes mellitus (DM) is a complex disease affecting almost all the vital organs in the body. About 415 million people in the world diagnosed with DM and majority of them are due to DM type 2. DM incidence predicted to increase 642 million people by the year 2040. [1] DM is known to have many complications and one of the most distressing is Diabetic Foot Ulcer (DFU). Infections, chronicity, and recurrence are the opportunistic problem of DFU. they can affect the mind of the patient. The amputation decision is often in a benign-looking ulcer in a patient with diabetes. A research in the United States presented that 38% of all the amputations associated with DM. It can induce to advance morbidity and mortality. DFU puts the huge financial load on the patient and the healthcare services, even though it is preventable. The successful DFUmanagement strategies involve intensive prevention, early assessment and aggressive treatment by a multi-disciplinary team of experts. [2,3] Diabetes is a serious chronic disease that requires special attention and is also described as "Global Epidemic". About 415 million people have diabetes globally which accounts to 1 in 11 people. India has world's second largest diabetic population with approximately 69 million people withdiabetes.Approximately 15% of all people with diabetes will be affected by a foot ulcer during their lifetime. There is increased incidence of Type2 Diabetes Mellitus (DM 2)in the past several decades owing to the advancing age of the population, substantially increased prevalence of obesity and decreased physical activity, all of which have been attributed to a western life style. Occurrence of diabetes at an early age and longer life of diabetic patients have increased the risk of development of the duration dependentcomplications.These complications are not only dependent on duration but also on the level of chronic glycaemia, which is best measured by glycosylated haemoglobin assay (HbA1cLevel). Foot problems remain very common in people with diabetes throughout the world, affecting up to 15%ofdiabetic patients during their lifetime. Frequency of lower limb amputations can be lowered by 49-87% by preventing the development of diabetic foot ulcer. [4]

DEFINITION:

The diabetic foot may be defined as a group of syndromes in which neuropathy, ischemia and infection lead to tissue breakdown, resulting in morbidity and possible amputation (World Health Organization, 1995). [5] Impaired metabolic mechanisms in DM increased the risk of infection and poor wound healing. It happens due to series of mechanisms which include decreased cell and growth factor response, diminished peripheral blood flow and decreased local angiogenesis. So, the feet are influenced by damage to peripheral nerves, the peripheral vascular disease, ulcerations, deformities and gangrene. [3]

EPIDEMIOLOGY:

According to epidemiological studies, the number of patients with DM increased from about 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and estimated if the situation continues, more than 360 million people by 2030 will have DM. [6-8] According to Wilman et al,diabetic foot ulceration is worldwide health problem approximately 15% of the 10 million diabetic patients in USA will develop foot ulcer at some time in their life time. [9] The foot ulcer in this population is extremely debilitating and dramatically increases the risk of lower extremity amputation. According to the Diabetes Atlas 2013 published by the International Diabetes Federation, the number of people with diabetes in India currently is 65.1 million, which is expected to rise to 142.7 million by 2035. [10] by 2015 prevalence data from the International Diabetes Federation, it estimated that, annually, foot ulcers develop in 9.1 million to 26.1 million people with diabetes worldwide. The proportion of persons with diabetes and a history of foot ulceration are understandably higher than the proportion with an active ulcer; 3.1 to 11.8% of persons with diabetes, or 12.9 million to 49.0 million persons worldwide and 1.0 million to 3.5 million in the United States alone, have a history of foot ulceration. The lifetime incidence of foot ulcers has previously been estimated to be 15 to 25% among persons with diabetes, but when additional data are considered, between 19% and 34% of persons with diabetes are likely to be affected. [1,11A] common complication for patients with diabetes, the lifetime risk for lower extremity ulceration, is as high as 25%, with over 7% of individuals with diabetic neuropathic foot ulcers progressing to amputation. [12]

ETIOLOGY:

There are several components that cause the emergence of diabetic foot ulcers in diabetic patients, can be divided into two major factors, namely:

Causative factor:

Peripheral neuropathy (sensory, motor, autonomic):
The main and most important causative factors. Sensory neuropathy is usually fairly deep (>50%) before experiencing a loss of protective sensation which resultin susceptibility to physical and thermal trauma, thus increasing the risk of foot ulcers. Not only the sensation of pain and pressure are lost, but also the

proprioceptionof the sensation of foot position also disappeared. Motor neuropathy affects all the muscles in the legs, resulting in protrusion of abnormal bones, normal architecture of the foot changed, distinctive deformity such as hammer toe and hallux rigidus. As for autonomic neuropathy orautosimpatectomy, characterized by dry skin, no sweating and increased secondary capillary refill due toarteriovenous shorts in the skin, triggering fissures, skin crust, all make the foot vulnerable to minimal trauma.

High foot plantar pressure:
The second most important causative factor. Thissituation is related to two things: limitations of joint mobility (ankle, subtler and first metatarsophalangeal joints) and foot deformities. In patients with peripheral neuropathy, 28% with high plantar pressure, within 2.5years there will be a foot ulcer compared with patients without high plantar pressure.

Trauma:
Especially recurring trauma, 21% trauma from friction from footwear, 11% due to foot injuries (mostly due to fall), 4% cellulitisdue to tinea pedis complications and 4% due to fingernail cut errors.

Contribute factor
Atherosclerosis:
Atherosclerosis due to peripheral vascular disease, especially regarding the blood vessels of femoropoplitea and small blood vessels below the knee, is the most important contributing factor. The risk of ulcers, twice as high in diabetic patients as compared to non-diabetic patients.

Diabetes:
Diabetes leads to intrinsic wound healing, includingcollagen cross-linkingdisorders, metricoproteinasematrix functional disorders and immunologic disorders, especially impaired PMN function. In addition, diabetics have higher rates of onychomycosis and tinea infections, so the skin is easy to peel and infections. In DM, characterized by sustained hyperglycaemias well as increased inflammatory mediators, triggering an inflammatory response, leading to chronic inflammation, but this is considered to be low-grade inflammation, since hyperglycaemia leads to impaired cellular defensemechanisms. Inflammation and neovascularisation are important in wound healing, but must be sequential, self-limited and closely controlled by the interaction of molecular cells. In DM, acute inflammatory responses are considered weak and angiogenesis is disruptresultingin wound healing disorders. Wound healing disorders in diabetes are shown in Figure 1. [13]

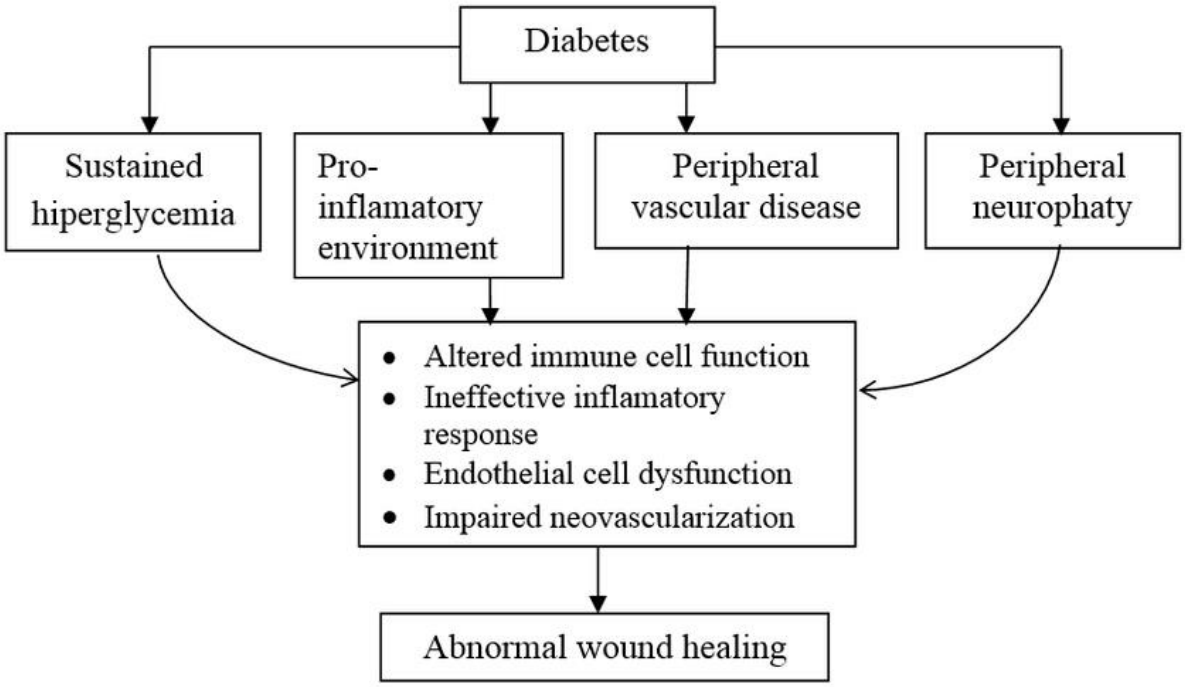

Figure 1: Wound healing disorders in diabetes [13]

CLINICAL MANIFESTATIONS:

The General Symptoms that help in the prediction of the appearance of late phase of the diabetic foot ulcer include- In Legs and arms: Deep pain, most commonly in the feet and legs; Loss of the sense of warm or cold; Muscle cramps; Numbness (if the nerves are severely damaged); Tingling or burning sensation in the extremities, particularly the feet; General Weakness. Other symptoms which are common for diabetics include: Dizziness; Drooping eyelid; Drooping face; Drooping mouth; Impotence; Light-headedness when standing up (orthostatic hypotension); Loss of bladder control; Rapid heart rate; Speech impairment; Vision changes. As discussed above specific symptoms cannot be predicted immediately .The symptoms vary depending on the nerves affected and usually develop gradually over years and may include symptoms other than those mentioned earlier. The condition where there is an abnormal and decreased sensation of pain or touch is often termed as diabetic neuropathy, usually it has a 'glove and stocking' distribution starting in the feet later on it affects the fingers and hands. The condition is much more worsened with damaged blood vessels and can lead to diabetic foot. Mon neuritis or autonomic neuropathy is the other forms of diabetic neuropathy. Diabetic amyotrophic on the other hand is muscle weakness due to neuropathy. Thus Diabetic foot is a complication often due to a combination of sensory neuropathy (numbness or insensitivity) and vascular damage. It increases the risks of skin ulcers (diabetic foot ulcers) and infection and, in worse cases, it causes necrosis and gangrene. As a result of this, in this developed world it becomes the underlying cause of non-traumatic adult amputation, usually of toes and or feet. [14]

PATHOPHYSIOLOGY OF DIABETIC FOOT ULCERS:

Neuropathy:

Peripheral neuropathy (loss of sensation) frequently occurs, 20% at the time of diagnosis and about 8-12 years after developing type 2 diabetes, and is the permissive factor in ulcer development. Diabetic peripheral neuropathy is an impairment of normal activities of the nerves throughout the body and can alter autonomic, motor, and sensory functions. The reported prevalence of diabetic peripheral neuropathy ranges from 16% to as high as 66%[1].More than 60% incidence of foot ulcers caused by Neuropathy and affects patients with both type 1 and type 2 DM. The hyperglycaemic conditions increased the production of some enzyme such as aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose into sorbitol and fructose. As these sugar products accumulate, the synthesis of nerve cell myoinositol is decreased, affecting nerve conduction. Further, hyperglycaemia-induced microangiopathy conducts the reversible metabolic, motor and sensory nerves, immunologic and ischemic injury of autonomic. It induces low peripheral sensation and compensation fine vasomotor control of the pedal circulation and the nerve innervations of small muscles of the foot. When the nerve gains hurt, the patient is at a high risk of a minor injury without spotting it until it makes an ulcer. The risk of expanding foot ulcers in patients. The sensory loss is increased up to seven-fold, oppose to non-neuropathic patients with diabetes. DM also influences leading to dryness and fissuring of skin, making it prone to infection, the autonomic nervous system. The microcirculation of skin is controlled by the autonomic system. These changes assist in the expansion of gangrene, ulcers, and limb loss. [2, 11, 15]

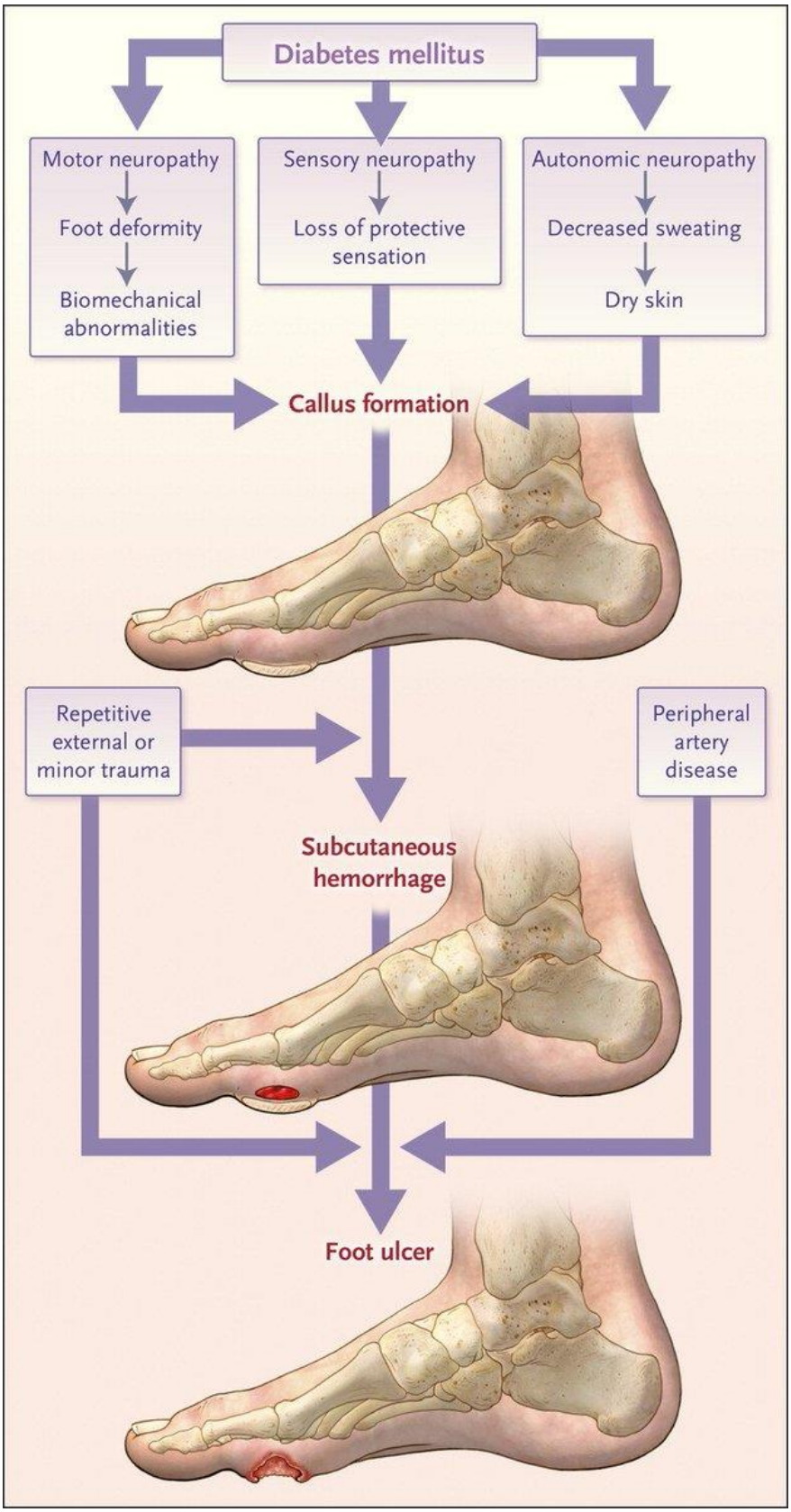

Figure 2. Common pathway of diabetic foot ulcer occurrence and recurrence[11]

Vasculopathy:
Hyperglycaemia causes endothelial cell dysfunction and smooth cell abnormalities in peripheral arteries. Endothelial dysfunction is the most serious impairment affecting microcirculation, owing to changes in the proliferation of endothelial cells, thickening of the basement membrane, decreased synthesis of nitric oxide, increased blood viscosity, alterations in micro vascular tone and decreased blood flow.[1]Nitric oxide is synthesized by endothelial cells which influence vasodilatation and secure the blood vessels from the endogenous wound. Accordingly, in hyperglycaemia, perturbation of the physiological properties of nitric oxide usually anticoagulation regulates the endothelial homeostasis, smooth muscle cell proliferation and antioxidant capacity, leukocyte adhesion. Endothelium-derived vasodilators and nitric oxide decreased. It leads to the propensity for atherosclerosis, constriction of the blood vessels and eventually leading to ischemia. Ischemia also happens, in fact, the attendance of palpable pedal pulses. The microcirculation is also disturbed due to arteriolar-venular shunting, reducing the blood circulation to the area of need. Hyperglycaemia in DM also associated with an increase in thromboxane A2 leading to plasma hypercoagulability. Clinically the patient may have signs of vascular insufficiency such as claudication, night pain or rest pain, absent peripheral pulses, thinning of the skin, loss of limb hair, etc. [2]

Immunopathy:
The immune system of a patient with diabetes is much weaker than the healthy people. Thus, foot infection in a patient with diabetes is a limb-threatening and debilitating condition. The hyperglycaemic state causes an elevation of pro-inflammatory cytokines and impairment of polymorphonuclear cell functions like chemotaxis, adherence, phagocytosis and intracellular killing. The immune system is compromised by lowered leukocyte activity, inappropriate inflammatory response and the disruption of cellular immunity (inhibition of fibroblast proliferation and impairment of the basal layer of keratinocytes, reducing epidermal cell migration). [1] Leukocyte phagocytosis was significantly reduced in patients with poorly controlled diabetes, and improvement of microbiocidal rates was directly correlated with correction of hyperglycaemia. Decreased chemotaxis of growth factors and cytokines, coupled with an excess of metalloproteinases, impede normal wound healing by creating a prolonged inflammatory state. Fasting hyperglycaemia and the presence of an open wound create a catabolic state. Negative nitrogen balance ensues secondary to insulin deprivation, caused by gluconeogenesis from protein breakdown. This metabolic dysfunction impairs the synthesis of proteins, fibroblasts, and collagen, and further systemic deficiencies are propagated which lead to nutritional compromise. Research indicates impairment of the immune system with serum glucose levels ≥150 ml/dl. Patients with diabetes tolerate infection poorly and infection adversely affects diabetic control. This repetitive cycle leads to uncontrolled hyperglycaemia, further affecting the host's response to infection.[16]High blood glucose is a good medium for the growth of bacteria, mainly aerobic gram-positive cocci like S. Aureus and β-hemolytic streptococci but in one research conducted in India, gram-negative aerobes were the common microorganisms in the diabetic foot. Muscles sheaths, tendons, the soft tissues of foot like plantar aponeurosis, and fascia cannot resist infections.Further, some part of the foot are interconnected and could not restrict the dissemination of infection from one to another. The soft tissue infection dissemination to the bones, making osteitis. So an ulcer on the foot can outcome in complications such as gangrene without appropriate and care osteitis/osteomyelitis. [2]

Mechanical stress:
Insensate limbs are inclined to wound which is often neglect. The movements of the foot similar flexion and extension are influenced because of the harm to innervations of the foot muscles. It guides to a transformation of the anatomical structure of the foot and formation of deformities. The deformities create abnormal bone elevated and pressure points impress ulcers. Metatarsal fat pads are stranded reducing the cushioning result of the metatarsal heads and increase the pressure points which guide to callus formations that induce skin damage and ulceration. [2] In people with neuropathy, minor trauma (e.g. from ill-fitting shoes, walking barefoot or an acute injury) can precipitate ulceration of the foot. Loss of sensation, foot deformities, and limited joint mobility can result in abnormal biomechanical loading of the foot. This produces a high pressure in some areas, to which the body responds with thickened skin (callus).[17]Usually, ulcers happen in the plantar of great toe and heel and unfitting shoes (which are the source of trauma) can cause ulcers on the dorsal aspect. Hence neuropathic foot ulcer formation in patients with diabetes has a complex multifactorial aetiopathogenesis wherein areas of high pressure complimented by peripheral neuropathy and associated skin changes lead to ulcer formation. [2]

Neuroarthropathy:

A chronic painless progressive degenerative arthropathy is popular as Charcot neuroarthropathy (CN) resulting from the disruption in sensory innervations of the affected joint. Charcot foot is an insidious, destructive, and progressive pathological condition that affects the foot bones and leads to a deformitythat may cause ulcer formation and subsequent disability. The development of Charcot's foot is characterized by subluxation and joint dislocation, osteolysis and bone fragmentation, and soft tissue edema.[18]The demolition of the autonomic nervous system because of DM causes an upgrade in local blood provide and the resting blood flow is higher than in the normal patient. The incidental elevated in blood flow due to calcium to dissolve, leading the osteoclastic activity of the bone and damaging the bone. Another theory is that the repeated small trauma to the insensate joints conducts to fracture and disintegration. The pro-inflammatory cytokines production conducts to uncontrolled osteolysis in CN. The cytokines like tumor necrosis factor-α and interleukin-1β increase the expression of receptor activator of nuclear factor-κb (RANKL), which in turn makes maturation of osteoclasts by causing the production of nuclear factor-κb. The hallmark deformity associated with this condition is a midfoot decay, also known as "rocker-bottom" foot. There might be hallux valgus deformity and lose bodies in the joint cavity. The deformities connected with CN also predispose torecurrent ulcerations. [2]

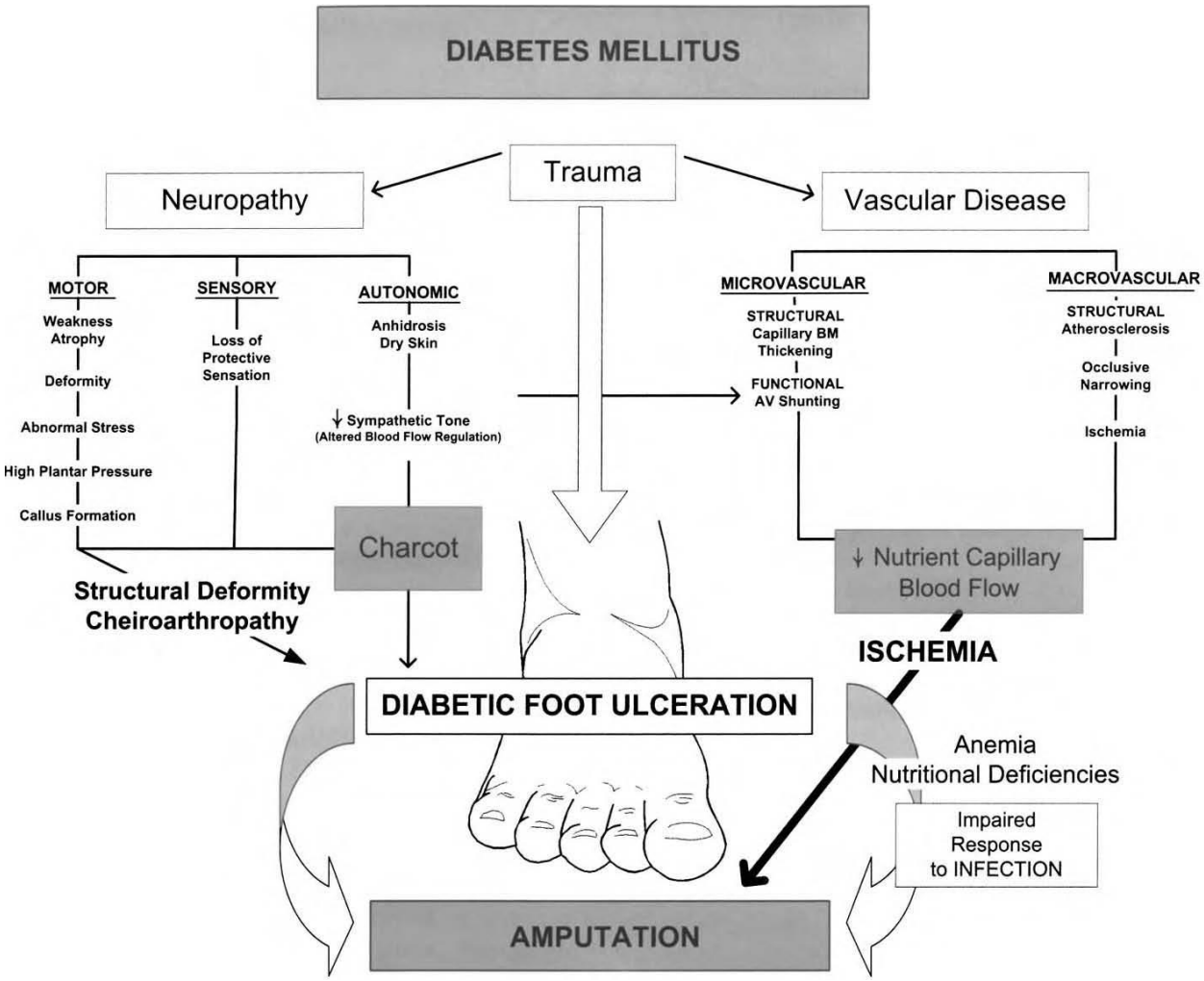

Figure 3 Diabetes mellitus is responsible for a variety of foot pathologies contributing to the complications of ulceration and amputation. Multiple pathologies may be implicated, from vascular disease to neuropathy to mechanical trauma. [19]

RISK FACTORS:

Table 1: The risk factors for diabetic foot ulcer[4]

General / systemic Contributions	Local issues
Uncontrolled Hyperglycaemia	Peripheral neuropathy
Duration of diabetes > 10yrs	Structural foot Deformity
Peripheral vascular disease	Trauma/ ill fitted shoes
Blindness or visual loss	Callus
Chronic renal disease	History of prior ulcer/ Amputation
Older age	Prolonged elevated Pressures
High body mass index	Limited joint mobility

CLASSIFICATION OF DIABETIC FOOT:

There is no one universally accepted classification system. Most systems employ a matrix of grades based upon depth and size of wound.[20]There are threemain diabetic foot classification system are discussed that are commonly used in clinical diagnosis of diabeticfoot. [21]

These were
a) Wagner-Meggitt Classification
b) Depth-Ischemic classification
c) University of Texas classification

Wagner Meggitt Classification:

One of the oldest well-known classifications was proposed by Wagner and Meggitt in the 1970s. Thisclassification is most commonly known as the ―Wagner Classification‖ in the United States and its uses six grades in classifying diabetic foot lesions. [22] This system is basically anatomical with gradations of superficial ulcer, deep ulcer, abscess osteitis, gangrene of the fore foot, and gangrene of the entire foot. Only grade 3 addresses the problem of infection. In this system foot lesions are divided into different grades starting from grade 0to grade 5. Grade 0 includes high risk foot but no active lesion and grade 5 includes gangrene of entire foot. But this system does not mention about ischemia or neuropathy and that is the drawback of this system (Table 2). [21]

Table 2: Wagner-Meggitt Classification System.

Grade	Lesion
Grade0	No open lesion
Grade1	Superficial ulcer
Grade2	Deep ulcer to tendon or joint capsule
Grade3	Deep ulcer with abscess, osteomyelitis and joint sepsis
Grade4	Local gangrene -fore foot or heel
Grade5	Gangrene of entire foot

Depth-Ischemic Classification:
This classification is a modification of Wagner–Meggit system. The purpose of this classification system is to make the classification more accurate, balanced and easier to distinguish between wound and vascularity of foot, to elucidate the difference among the grades 2 and 3, and to advance the correlation of treatment to the grade (Table 3). [23]

Table 3:Depth-Ischemic Classification.

Depth Grade	Definition	Ischemia Grade	Definition
0	At risk, foot with previous ulcer that may cause new ulcer	A	No ischemia
1	Superficial non-infected ulcer	B	Ischemia no gangrene
2	Deep ulcer with tendon or joint exposed (+/ _ infection)	C	Partial forefoot gangrene
3	Extensive ulcer with bone exposed or deep abscess	D	Total foot gangrene

Texas Classification:
A more recently proposed and popularized DFU classification is the University of Texas Health Science Center San Antonio (UT) classification system. This system incorporates a matrix structure of four grades of wound depth with subgroups to denote the presence of infection, ischemia or both. Wounds with frank purulence and/or two or more local signs of inflammation such as warmth, erythema, lymphangitis, lymphadenopathy, edema, pain and loss of function may be classified as infected.‘ Lower extremity vascular insufficiency is made by a combination of one or more clinical signs or symptoms of claudication, rest-pain, absent pulses, dependent rubor, atrophic integument, absence of pedal hair or pallor on elevation coupled with one of more non-invasive values such as a transcutaneous oxygen (TCPO2) <40 mmHg, ankle brachial index (ABI) <0.8 or absolute toe systolic pressure <45 mmHg(Table 4). [24]

Table 4: Texas Classification

	Grade 0	Grade 1	Grade 2	Grade 3
Sttage1	Preulcerative or postulcerative lesions completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating tendon or capsule	Wound penetrating to bone or joint
Stage2	Infection	Infection	Infection	Infection
Stage3	Ischemia	Ischemia	Ischemia	Ischemia
Stage4	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia	Infection and Ischemia

DIAGNOSIS OF DIABETIC FOOT ULCER:

Patients with a DFU should be assessed by the team within one working day of presentation or sooner in the presence of severe infection. Patients with a DFU need to be assessed holistically to identify intrinsic and extrinsic factors. This should encompass a full patient history including medication, co-morbidities and diabetes status. [25] It should also take into consideration the history of the wound, previous DFUs or amputations and any symptoms suggestive of neuropathy or peripheral arterial disease. [26]

A) History and Physical examination:

First, the physician enquire patient about their symptoms and will examine them. This examination should include the patient's vital signs (temperature, pulse, blood pressure, and respiratory rate); examination of the sensation in the feet and legs, an examination of the circulation in the feet and legs, a thorough examination of any problem areas.[14]A thorough medical and foot history must be obtained from the patient. The history should address several specific diabetic foot issues (Table 5). [19]

Table: 5 Showing history and medical examination:

Medical History		
Global History	**Foot Specific History**	
	General	**Wound / ulcer history**
• Diabetes-duration • Glycemic management/control • Cardiovascular, renal and ophthalmic evaluations • Other co-morbidities • Treating physicians • Nutritional status • Alcohol, tobacco and drugs • Current medications • Allergies • Previous hospitalizations/ surgery	• Daily activities • Footwear • Chemical exposures • Callus formation • Previous foot infections, surgery • Neuropathic symptoms • Claudication or rest pain	• Location • Duration • Inciting event or trauma • Recurrence • Infection • Hospitalization • Wound care • Off- loading techniques • Wound response • Patient compliance • Interference with wound care (family or social problems for patient) • Previous foot trauma or surgery • Presence of edema • Charcot foot- previous or active • Charcot treatment

b) X-rays:

X-rays studies of the feet or legs were performed to assess for signs of damage to the bones or arthritis, damage from infection, foreign bodies in the soft tissues. Gas in the soft tissues, indicates gangrene - a very serious, potentially life-threatening or limb-threatening infection. [14]

c) Examination of ulcer:

A sterile stainless steel probe is used for assessing the ulcer to determine the depth and if there is sinus tracts present. The location, size, shape, depth, base and margins of the ulcer should be examined clinically. Presence of granulation tissue or slough should be looked for in the floor of the ulcer to determine subsequent management. 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. [27]

d) Neurological testing:

Peripheral neuropathy is the most common component cause in the pathway to diabetic foot ulceration. The clinical exam recommended, however, is designed to

identify loss of protective sensation (LOPS) rather than early neuropathy. Five simple clinical tests (Table 6) each with evidence from well conducted prospective clinical cohort studies are considered useful in the diagnosis of LOPS in the diabetic foot. The task force agrees that any of the five tests listed could be used by clinicians to identify LOPS, although ideally two of these should be regularly performed during the screening exam-normally the 10-g monofilament and one other test. One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS. However, identification of the patient with LOPS can easily be carried out without Biothesiometer or other expensive equipment. [28]

Table 6: Simple bed side clinical tests.

S.No	Clinical tests
1	10-g monofilaments
2	Pinprick sensation
3	Ankle reflexes
4	Tuning fork test
5	Vibration perception threshold testing

e) Ultrasound:
Doppler ultrasound to see the blood flow through the arteries and veins in the lower extremities. The test is not painful and involves the technician moving a non-invasive probe over the blood vessels of the lower extremities. [14]

f) Laboratory investigations:
Clinical laboratory tests that may be needed in appropriate clinical situations include fasting or random blood glucose, glycohemoglobin (HbA1c), complete blood count (CBC) with or without differential, erythrocyte sedimentation rate (ESR), serum chemistries, C-reactive protein, alkaline phosphatise, wound and blood cultures and urinalysis. Caution must be exercised in the interpretation of laboratory tests in these patients, because several reports have documented the absence of leukocytosis in the presence of severe foot infections. A common sign of persistent infection is recalcitrant hyperglycaemia despite usual antihyperglycaemicregimens. [19]

g) Angiogram:
If the vascular surgeon determines that the patient has poor circulation in the lower extremities, an angiogram may be performed in preparation for surgery to improve circulation. With an angiogram, a catheter is inserted through the artery in the groin and dye is injected while x-rays are taken. [14]

MANAGEMENT DIABETIC FOOT ULCERS:

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. [29]

The essential components of management are.
a. Treating underlying disease processes
b. Ensuring adequate blood supply
c. Local wound care, including infection control
d. Pressure offloading. [26]

Debridement:
Debridement consists of removal of all necrotic tissue, peri-wound callus and foreign bodies down to viable tissue. Proper debridement is necessary to decrease the risk of infection and reduce peri-wound pressure, which can impede normal wound contraction and healing. There are different kinds of debridement which includes surgical, enzymatic, autolytic, mechanical and biological. [30]

Autolytic:
Autolytic debridement uses the body‘s own natural enzymes to break down and digest necrotic tissue. Autolytic debridement also involves the use of moisture in semi-occlusive or occlusive dressings to aid in the efficiency of liquefying devitalized tissue. Dressings for autolytic debridement include hydrocolloids, hydrogels and films. The hydrogels were significantly more effective than gauze dressings or standard care in healing diabetic foot ulcers. [31]

Biological:
Sterile maggots of the green bottle fly (Lucilia sericata) are placed directly into the affected area and

held in place by a close net dressing. The larvae have a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue. [32]

Mechanical:
Although it is a simple and an inexpensive tool, it can remove both viable and also non-viable tissues leading to pain in sensate foot. The wet gauze dressing is applied to the wound bed and then kept to dry. The necrotic debris embedded in the gauze is mechanically stripped from the wound bed on gauze removal. [33]

Enzymatic debridement:
Enzymatic debridement speeds up the process and an ointment is applied to the wound, which contains special enzymes to accelerate the removal of the devitalised or dead tissue from the wound bed. [34]

Dressing:
Ideally, dressings should confer moisture balance, protease sequestration, growth factor stimulation, antimicrobial activity, oxygen permeability, and the capacity to promote autolytic debridement that facilitates the production of granulation tissues and the re-epithelialization process. Wound dressing can be categorized as passive, active, or interactive. Passive dressings are used as protective functions and for acute wounds because they absorb reasonable amounts of exudates and ensure good protection. Active and interactive dressings are capable of modifying the physiology of a wound by stimulating cellular activity and growth factors release. The main categories of dressings used for DFU are as follows: films, hydrogels, hydrocolloids, alginates, foams, and silver-impregnated. [6] New advanced dressings are being researched, for example Vulnamin gel made of aminoacids and hyaluronic acid are used along with elastocompression has shown favourable results. Promogran by Johnson and Johnson‘s is a freeze dried matrix composed of collagen and oxidized regenerated cellulose. When in contact with wound exudates, it forms a biodegradable gel that physically binds and inactivates matrix metalloproteases that affects wound healing. [27]

Table 7. Classification of Advanced Wound Dressings Used for Diabetic Foot Ulcers Healing. [35]

Type	Example	Explanation	Advantages	Disadvantages
Hydrocolloids	Duoderm Granuflex Comfeel	Dressings usually composed of a hydrocolloid matrix bonded onto a vapor permeable film or foam backing. When in contact with the wound surface, this matrix forms a gel to provide a moist environment.	Absorbent; can be left for several days; aids autolysis	Concerns about use for infected wounds; may cause maceration; unpleasant odor
Hydrogels	Aquaform Intrasite Gel Aquaflo	These dressings consist of cross-linked insoluable polymers (ie, starch or carboxymethylcellulose) and up to 96% water. They are designed to absorb wound exudate or rehydrate a wound, depending on the wound moisture levels. They are supplied in flat sheets, an amorphous hydrogel, or as beads	Absorbent; donate liquid; aid autolysis	Concerns about use for infected wounds; may cause maceration; using for highly exudative wounds
Foams	Allevyn Cavicare Biatain Tegaderm	These dressings normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface.	Highly absorbent and protective; anipulate easily; can be left up to 7 days; thermal insulation	Occasional dermatitis with adhesive; bulky; may cause maceration
Films	Tegaderm Opsite	Film dressings often form part of the construction of other dressings, such as hydrocolloids, foams, hydrogel sheets, and composite dressings, which are made of several materials with film being used as outer layer.	Cheap; easily manipulated; permeable to water vapor and oxygen but not to water microorganisms	May need wetting before removal; not suitable for infected wounds; nonabsorbent; if fluid collects under film it must be drained or the film replaced
Alginates	Calcium alginate dressing Kaltostat Sorbalgon Medihoney	The alginate forms a gel when in contact with the wound surface, which can be lifted off with dressing removal or rinsed away with sterile saline; bonding to a secondary viscose pad increases absorbency	Highly absorbent; bacteriostatic; hemostatic; useful in cavities	May need wetting before removal
Silver-impregnated	Acticoat Urgosorb Silver	These dressing are used to treat infected wounds, as silver ions are thought to have antimicrobial properties.	Antiseptic; absorbent; reduce odor; improved pain-related symptoms; decrease wound exudates; prolonged dressing wear time	High cost

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.[29]Inadequate offloading leads to tissue damage and ulceration. The gold standard is the total contact cast (TCC). This is a well moulded, minimally padded foot and lower leg cast that distributes

pressures evenly over the entire plantar surface of the foot. It ensures compliance because it is not easy for the patient to remove. Using a TCC in patients with a unilateral uncomplicated plantar ulcer can reduce healing time by around six weeks.[6]Inappropriate application of TCCs may result in new ulcers, and TCCs are contraindicated in deep or draining woundsor for use with noncompliant, blind, morbidly obese, or severely vascularly compromised patients. [30]

Medical treatment:

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. Antibiotics are preferably given intravenously for limb threatening infections. Gabapentin and pregabalin have been used for symptomatic relief for painful neuropathy in DM. Aldose reductase inhibitors are being studied and have shown to be effective in inhibiting progression of peripheral neuropathy. Autonomic dysfunction may require the use of beta-blockers. Medical management of symptoms of vascular insufficiency like intermittent claudication includes Cilostazol or Pentoxifylline besides exercise therapy. [27]

Adjuvant therapy:

Hyperbaric oxygen therapy (HBOT) has shown promise in the treatment of serious cases of non-healing DFU, which are resistant to other therapeutic methods. HBOT involves intermittent administration of 100% oxygen, usually in daily sessions. During each session, patients breathed pure oxygen at 1.4-3.0 absolute atmospheres during 3 periods of 30 min (overall 90 min) intercalated by 5 min intervals in a hyperbaric chamber.[6]Hyperbaric oxygen therapy (HBOT) has the advantage of reduction of tissue hypoxia, edema, increase angiogenesis and erythrocytes deformability, antimicrobial effects and increase fibroblastic activity. HBOT is approved as an adjunctive treatment to be used in chronic non-healing ulcers by the Undersea and Hyperbaric Medical Society.[33]Low energy lasers have also been used as an adjunctive therapy for DFUs. They act by increasing microcirculation and improving healing of the ischemic DFU. Growth factors for example recombinant human platelet derived growth factor (rhPDGF), topical platelets and platelet rich plasma have also been used in treating DFUs and have shown favourable results. [27]

Surgical management:

Revascularization surgery:

As diabetes is chronic and progressive, it makes sense to have conservative surgical approaches that include surgical revascularization. A successful surgical bypass of larger vessel disease may enable more conservative treatment of the diabetic foot.[32]Revascularization by open surgery of occlusive disease of the distal arteries is carried out mainly by bypass with autologous material (preferably saphenous vein). In turn, endovascular surgery techniques mainly include percutaneous transluminal angioplasty (PTA), which may be combined with stenting, laser and plaque volume reduction techniques. The exponential increase of the use of these endovascular procedures, compared with open surgical revascularisation, is primarily due to the greater benefit with respect to the secondary risk of low percentages of morbidity and mortality associated with the percutaneous techniques. Mixed techniques (open + endovascular surgery) may be used. [20]

Wound closure:

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 DFUs with exposed tendon, ligament or bone require coverage with muscle flaps. Flaps can be either local (for smaller wounds) or freeflaps (for large area). Latissimus dorsi, gracilis or rectus abdominis are the commonly used free flaps. The limitations of standard flaps include donor site morbidity, difficulty in shaping the flaps and interference with footwear. [29]

Amputation:

Amputation may be indicated in the following circumstances. Ischaemic rest pain that cannot be managed by analgesia or revascularization. A life-threatening foot infection that cannot be managed by other measures. A non-healing ulcer that is accompanied by a higher burden of disease than would result from amputation. In some cases, for example, complications in a diabetic foot render it functionally useless and a well performed amputation is a better alternative for the patient.Patients at high risk for ulceration (such as patients who have undergone an amputation for a DFU) should be reviewed 1–3 monthly by a foot protection team. At each review patients' feet should be inspected and the need for vascular assessment reviewed. [26]

Table 8.Wound CareTechnologies [35]

Negative pressure wound therapy Standard electrically powered Mechanically powered
Hyperbaric oxygen therapy Topical oxygen therapy
Biophysical Electrical stimulation, diathermy, pulsed electromagnetic fields Pulsed radio-frequency energy Low-frequency noncontact ultrasound Extracorporeal shock-wave therapy
Growth factors Becaplermin: platelet-derived growth factor Fibroblast growth factor Epidermal growth factor Platelet rich plasma
Acellular matrix tissues Xenograft dermis bovine neonatal dermis bovine collagen bovine dermis Xenograft acellular matrices small intestine submucosa porcine urinary bladder matrix ovine forestomach equine pericardium Human dermis Graftjacket dCELL DermACELL TheraSkin
Human pericardium
Placental tissues Amniotic tissues/amniotic fluid Umbilical cord Dehydrated human amnion chorion
Bioengineered allogeneic cellular therapies Bilayered skin equivalent Dermal replacement therapy
Stem cell therapies Autogenous: bone marrow-derived stem cells Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous Hyalomatrix

NON-PHARMACOLOGICAL TREATMENT:

Having a healthy balanced diet which controls carbohydrate levels in blood, it includes non-fat dairy and lean meats, whole grains, fruits, vegetables, whole grains.

Avoiding too much of pressure on the affected leg. Active lifestyle helps control diabetes and ease stress. Regular reviewing of prescriptions and visiting doctors minimally twice a year especially for eye checkup, foot ulcers and nerve damage.

Management of stress by engaging in yoga, deep breathing, hobbies bringing relaxation and pleasure.

Proper hydration through fluids and urinating frequently.

Washing hands and feet daily with mild soap and lukewarm water, gently drying the feet particularly between toes.
Making use of clean sock and shoes which does not cause too much of pressure on foot.[36]

DIABETIC FOOT CARE GUIDELINES:

Diabetes can be dangerous to your feet—even a small cut can produce serious consequences. Diabetes may cause nerve damage that takes away the feeling in your feet. Diabetes may also reduce blood flow to the feet, making it harder to heal an injury or resist infection. Because of these problems, you may not notice a foreign object in your shoe. As a result, you could develop a blister or a sore. This could lead to an infection or a nonhealing wound that could put you at risk for an amputation.

To avoid serious foot problems that could result in losing a toe, foot or leg, follow these guidelines.
Inspect your feet daily. Check for cuts, blisters, redness, swelling or nail problems. Use a magnifying hand mirror to look at the bottom of your feet. Call your doctor if you notice anything.
Bathe feet in lukewarm, never hot, water. Keep your feet clean by washing them daily. Use only luke warm water—the temperature you would use on a newborn baby.
Be gentle when bathing your feet. Wash them using a soft washcloth or sponge. Dry by blotting or patting and carefully dry between the toes.
Moisturize your feet but not between your toes. Use a moisturizer daily to keep dry skin from itching or cracking. But don't moisturize between the toes—that could encourage a fungal infection.
Cut nails carefully. Cut them straight across and file the edges. Don't cut nails too short, as this could lead to ingrown toenails. If you have concerns about your nails, consult your doctor.
Never treat corns or calluses yourself. No "bathroom surgery" or medicated pads. Visit your doctor for appropriate treatment.
Wear clean, dry socks. Change them daily.
Consider socks made specifically for patients living with diabetes. These socks have extra cushioning, do not have elastic tops, are higher than the ankle and are made from fibers that wick moisture away from the skin.
Wear socks to bed. If your feet get cold at night, wear socks. Never use a heating pad or a hot water bottle.
Shake out your shoes and feel the inside before wearing. Remember, your feet may not be able to feel a pebble or other foreign object, so always inspect your shoes before putting them on.
Keep your feet warm and dry. Don't let your feet get wet in snow or rain. Wear warm socks and shoes in winter.
Consider using an antiperspirant on the soles of your feet. This is helpful if you have excessive sweating of the feet.
Never walk barefoot. Not even at home! Always wear shoes or slippers. You could step on something and get a scratch or cut.
Take care of your diabetes. Keep your blood sugar levels under control.
Do not smoke. Smoking restricts blood flow in your feet.
Get periodic foot exams. Seeing your foot and ankle surgeon on a regular basis can help prevent the foot complications of diabetes. [37]

ROLE OF PHARMACIST IN THE MANAGEMENT OF DIABETIC FOOT ULCERS:

Develop, evaluate and document pharmaceutical care practices in DFU.
Collaborate with other health care professionals to develop treatment guidelines for DFU.
Educate all health professionals who participate in pharmaceutical care.
Participate in health screening for diabetes, and DFU (HbA1c, FBS, PPBS, etc.).
Conducting health promotion and education programs for smoking cessation, obesity control, DFU self-practice; DFU preventive measures DFU awareness camp etc.
Educate and collaborate community pharmacist and their services in the prevention and management of DFU.
Referral for management from counselling centres and community pharmacies.
Research in the field of pharmacotherapeutics; pharmacoepidemiology; pharmacy practice; health economics in diabetes and DFU.
To evaluate and document the results of research in order to improve all aspects of pharmaceutical care.
Participate in the formulation of antibiotic policy and its regulations

Develop professional standards and audit procedures. [38]

CONCLUSION:

Diabetes mellitus is a chronic disease which results in distressing complications like diabetic foot ulcer .It involves management of some etiological factors like vasculopathy,neuropathy and infection .Management involves many advanced techniques like debridement, dressing,offloading which are conservative or limb sparing otherwise surgical management includes revascularization surgery,wound closure and amputation.Guidelines based treatment and multidisciplinary teams would help to improve outcome and minimize amputations.Clinical pharmacist plays a pivotal role in early diagnosis,prevention of further complications and helps in betterment of patient's health.

ABBREVATIONS:

DM - Diabetes mellitus
DFU - Diabetic foot ulcer
HbA1c - Glycosylated hemoglobin
CN - Charcot Neuroarthropathy
RANK - Receptor activator of nuclear factor-κb
RANKL - Receptor activator of nuclear factor-κb ligand
UT - University of Texas Health Science Center San Antonio classification system
TCPO2 - Transcutaneous oxygen
ABI - Ankle Brachial Index
LOPS - Loss of protective sensation
CBC - Complete blood count
ESR - Erythrocyte sedimentation rate
TCC - Total Contact Cast
HBOT - Hyperbaric oxygen therapy
rhPDGF- recombinant human platelet derived growth factor
PTA - Percutaneous transluminal angioplasty

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