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UNDERSTANDING DIABETIC FOOT ULCER: PATHOGENESIS AND ITS MANAGEMENT

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ABSTRACT: *Diabetic Foot Ulcers (DFUs) carry enormous disease burden which affects 15% of diabetic population and the annual population-based lifetime incidence may be as high as 25%. DFUs are the leading cause of most costly and feared consequence-limb amputations; where eight out of ten nontraumatic amputations follow a foot ulcer. Presently, foot problems account to be more than 20 percent of the annual diabetic-related hospitalizations. Nearly 50 percent of the 120,000 non-traumatic, lower-extremity amputations each year result from complications of diabetes Even more deadlier is the mortality following amputation which ranges from 13% to 40% at 1 year, 35% to 65% at 3 years, and 39% to 80% at 5 years—worse than for most malignancies. A cascade of mechanisms at cellular level including decreased growth factor response diminished peripheral blood flow and decreased local angiogenesis, contribute to lack of healing. Consequently diabetic foot ulcers are often recalcitrant to treatment. A systematic review is being done to focus the causes and precautions to be taken for overcoming foot ulcers. The best outcome can be attained by optimizing expert multidisciplinary services and most importantly, ensuring its rapid access.*

Key words: Diabetes, Diabetic Complications, Management, Foot ulcer, Pathogenesis.

INTRODUCTION:

The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity. DFUs are the leading cause of most costly and feared consequence-limb amputations; where eight out of ten nontraumatic amputations follow a foot ulcer. Presently, foot problems account to be more than 20 percent of the annual diabetic-related hospitalizations. Nearly 50 percent of the 120,000 non-traumatic, lower-extremity amputations each year result from complications of diabetes.[1,2,3] Estimates of current (2000) and future (2030) global prevalence of diabetes (for all age-groups) have been published in World Health Organization's 'Global Burden of Disease Study'[4] which was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.[5] Neuropathy, mechanical stresses and angiopathy (ischemia) are the major causes of foot ulcers in diabetic patients; however, a number of other factors have been cited (5-9). Patients with diabetes are at risk for developing serious health problems that may affect the eyes, kidneys, feet, skin, and heart, out of which foot ulcerations are the most common. DFU typically results from peripheral neuropathy (and/or large vessel disease). DFU remains the leading cause of hospital admissions for people with diabetes in the developed world and often leads to pain, suffering, and a poor quality of life. An ulcer can be defined as an area of discontinuation of the surface epithelium. A leg ulcer usually occurs around the ankle or on the foot.

Diabetic Complications:

DFU is a complication of diabetes when three things come together at one time; this is known as Diabetic Foot Triad (Fig.: 1). The three components are:

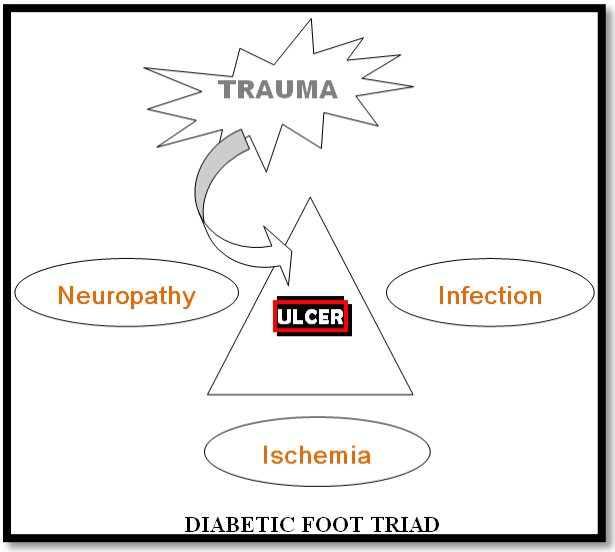
1. Ischemia, (poor circulation)

2. Neuropathy, (nerve disease)

3. Infection, with a precipitation factor

e.g. ongoing trauma or insult

Fig.: 1



1. Ischemia:

Ischemia, is a symptom of Peripheral Vascular Disease and/or calcification of the arteries, in the foot (Macrovascular disease-atherosclerosis), caused by an abnormally high Glucose level for a long term; another cause can be Microangiopathy (Microvascular disease). Due to sufficiently reduced blood supply, body is not able to respond to any injury; consequently the wounds may not heal. (Fig.2).

2. Neuropathy

It affects peripheral sensation, innervation of the small muscle of the foot, and fine vasomotor control of the pedal circulation.

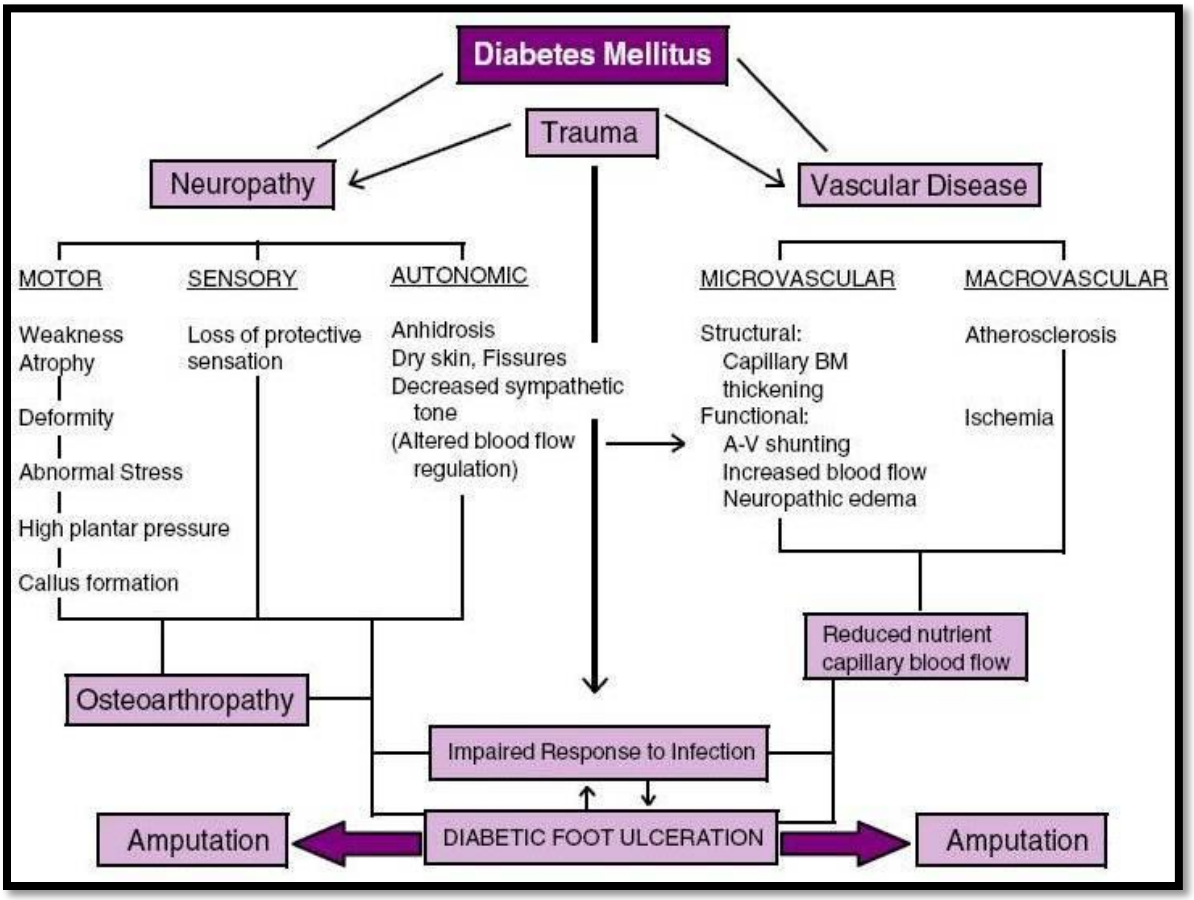
a. **Sensory neuropathy-**It is a loss of protective sensation which leads to lack of awareness of incipient or actual ulceration

b. **Motor neuropathy-**It affects the muscle requires for normal foot movement, altering the distribution of forces during walking and causing reactive thickening of skin (callus) at sites of abnormal load.

c. **Arteriolar-venular shunting-**It is a dysfunction of microcirculation with reduced distribution of blood.

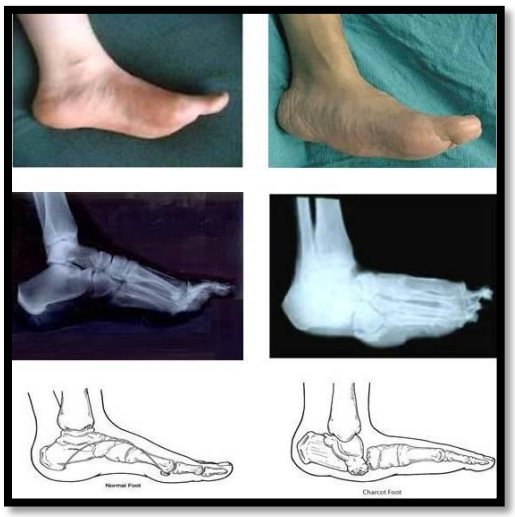
d. **Vasomotor (autonomic) neuropathy-**It affects peripheral nerve functions.

Fig. 2[2]-Contributing factors in the pathogenesis of ulceration



1. **Charcot foot:** It is a spontaneous or traumatic dislocation or collapse of one or more joints on the foot primarily due to osteopenia (resulting from arterio-venular shunting). If predisposed to trauma, it results into fracture of the weakened bone which leads to increased load on adjacent bones, followed by gross destruction[14].

Fig.3[10]-Normal Foot compared with a Charcot Foot



3. Infection

If the precipitating factors are not controlled, infection can occur.

Precipitating Factors:

It can be any ongoing insult to the foot like repeated trauma caused by abnormal pressure in the foot like ingrown toenails constantly digging into the flesh; abnormal shoe pressure; burns caused by heating pads etc.

CHRONIC ULCER:

A chronic leg ulcer is more difficult to define but many people consider ulceration of more than 4-6 weeks duration as being chronic. Chronic ulcers results when sequel of repair is disturbed at one or more stages of inflammation, proliferation, re-epithelialization, remodelling. Common organisms colonizing the ulcers are Staph aureus, Strep pyogens, Strep fecalis and E coli.

A. **Venous Ulcers**

Usually ankle pressure while standing is 125 cms H2O; however on walking the action of calf muscles surrounding the vein pushes the blood out of the leg and

reduces the pressures to about 40 cms of H2O.

Etiology

⇒ PI / Patient recruitment (call center)- Increased pressure at ankle

⇒

⇒ Swelling of the tissues

⇒ Widening of endothelial gap junctions

⇒ Sequestration of the RBCs, WBCs, Proteins

Proposed Theories on the Events Leading To Dermal Disruption:

i. Fibrin Cuff Theory:

Venous hypertension causes increase in the size of the capillary pores which allows the passage of red blood cells and protein (fibrinogen) into the interstitial spaces. Fibrinogen changes to fibrin and forms cuffs around the capillary wall which blocks the diffusion of oxygen and nutrients to the epidermis, thus forming an ulcer.

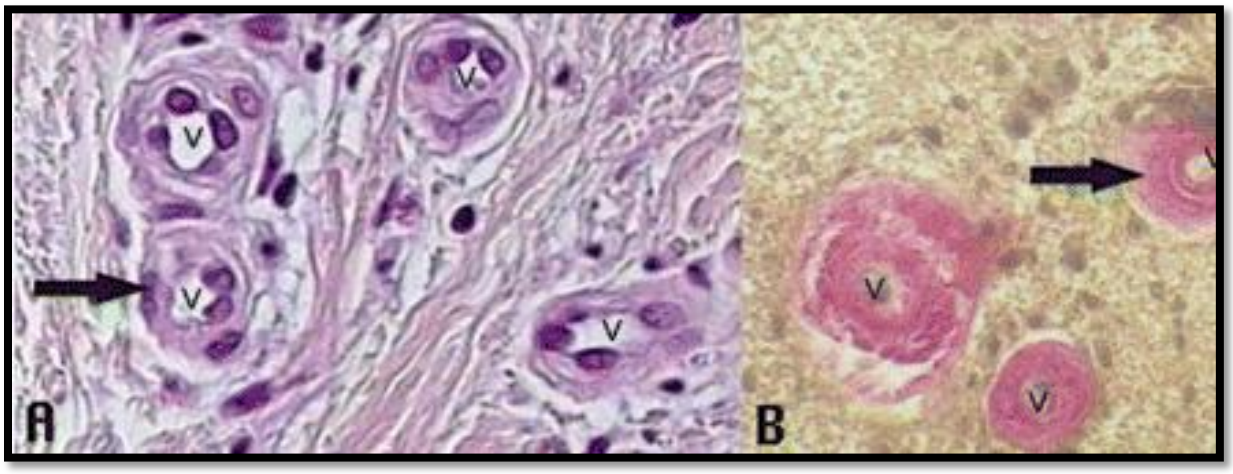


Fig4[11]-Panel A, classic fibrin cuffs (arrow) thicken veins (v) in a venous ulcer bed, 40 x. Panel B, fibrin cuffs (arrow) encircles proliferated thick walled veins (v) in a peri-ventricular MS plaque, 30 x. (Panel A is courtesy of Professor Caggiati, Rome, Italy. Panel B is modified from Adams CW. A Colour Atlas of Multiple Sclerosis. London: Wolfe Med, 1989).

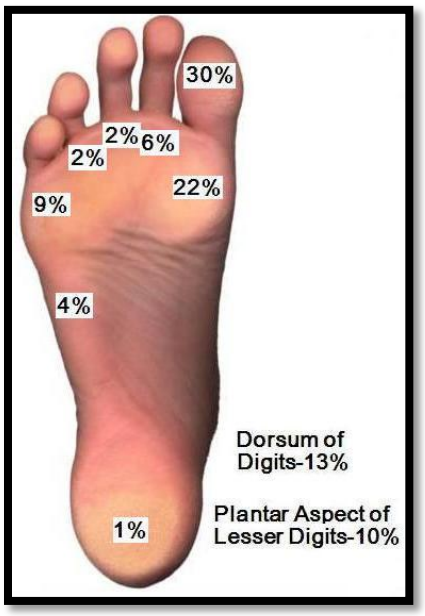
ii. Leukocyte Migration Theory:

This theory is thought to be the best explanation of venous ulceration. Leukocytes adhere to the capillary wall due to reduced blood flow during venous hypertension. Tissue damage is caused by leukocyte-blocked capillaries and also by migrated leukocytes which release proteolytic enzymes, oxygen free radicals, and inflammatory mediators out into the tissues.

B. Arterial Ulcers

Arterial Ulcers indicate the presence of severe occlusive disease; atherosclerosis, vasospasm, inflammatory vascular disease. Loss of nutrients and oxygen lead to tissue break down. Arterial ulcers are common in the feet, head of the 1st and 5th metatarsals (for other wound location see Fig.: 3)

Fig. 5[12]- Wound Locations



Principles of management:

- Treat all infections
- Establish whether any associated ischemia is amenable to revascularisation
- Keep forces applied to the ulcerated part to a minimum
- Improve the condition of the wound/ulcer by wound-bed preparation, topical applications, and removal of callus
- Prevention of ulcer recurrence

Table 1: **Evaluation of ulcer formed during the progression of diabetes by using the diagnostic values and also by examination[10].**

EVALUATION OF ULCER	
By Examination	**By Diagnostic Value**
Site	FBC, ESR, Renal & Liver functions
Size	Wound swab and qualitative cultures
Shape	Duplex studies of the venous system
Number	Connective disease profile
Floor	X-ray of the long bones
Edge / margin	Angiography
Base	Biopsy of the ulcers (Marjolins ulcers)
Surrounding skin	ABI = highest ankle pressure/ Highest brachial pressure
Examination of the arterial. Venous , Lymphatic , Neurological system	For screening of the arterial disease
Evaluation of the nutritional status and underlying medical conditions that prolong wound healing	For compression therapy

Management

- Debridement – Mechanical / surgical / biological / enzymatic

- Off loading foot wear
- Antibiotics
- Appropriate wound care

Fig. 6[10]- Types of Offloading Foot Wears

A-Normal Shoe; B- Orthowedge Healing Shoe; C-Total Contact Cast (TCC)

Properties of an ideal dressing agent

- Protect from bacterial invasion
- Maintain optimum humidity
- Absorb serum from wound site
- Protect granulation tissue
- Reduce pain

Dressing agents not to be used due to toxicity are:

- Hydrogen peroxide
- Boric acid
- EUSOL
- Dakin solution (hypochlorite)
- Iodine

Table:2 Different Dressing Agents used in the treatment of Diabetic Foot ulcers

DRESSING AGENTS

Poly urethane films
- Transmit water vapour, oxygen, carbon dioxide
- Non absorbent
- Useful for healing wounds with minimal drainage

Foams and Hydrocolloids
- Permeable, easy to apply, minimum re-injury
- 60-95% water content maintains the moist atmosphere

Alginates
- Sea weed preparation
- Absorb exudates
- Useful for exudative wounds

Cultured Keratinocytes
- Cells are cultured and transferred to petroleum gauze
- Labour intense and expensive

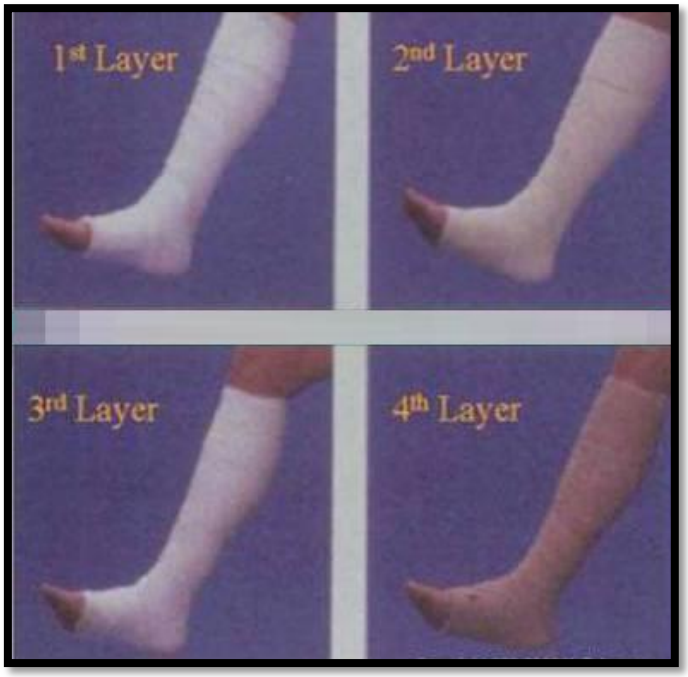
Compression therapy
- Developed by the Charing Cross group
- Different sizes for various ankle diameters
- Main stay of the venous disease
- prevention and treatment
- <0.8 ABI will need further assessment
- Improves healing rate compared to no compression therapy
- Multi layer better than single layer
- Higher the pressure better the healing rate

Profore
- Light and high compression layers
- 0.6 – 0.7 ABI – use 'Profore Lite'
- Multiple layer bandage for the venous hypertension
- ABI <0.5 contraindication for the compression therapy

Growth factors and Wound Healing

Poly-peptides, which stimulate wound healing, promote chemotaxis, miotgenesis of fibroblasts and smooth muscle cells (e.g. Platelet Derived Growth Factor (PDGF), Insulin Like Growth Factor (IGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Transforming Growth Factor-1 (TGF-1)

Fig.7[13]- Application of a multilayer compression system



Role of antibiotics:

- Bacteria can secondarily colonize the wound and general tendency is to over treat
- Not necessarily indicate infection
- Wound bacteria may be transient and may not be detected on random swabs
- Fever /erythema /swelling / increased pain / leucocytosis

Management issues:

- 20% chances of recurrences
- Nutrition-proteins, Zinc, Vitamin C
- Pain management
- Change of dressings
- Removal of slough - Hydrogels, Varidase
- Decrease the bacterial load – Iodoflex
- Reduction of exudates - Alginates
- Odour – Iodoflex, Silver, Metronidazole
- Eczema – Steroids
- Long term use of compression therapy is useful in preventing the recurrences
- Below knee stockings are as good as above knee stockings (replace every 6 months)
- To be used for the day time and foot care at night
- Keep foot end elevated
- Education
- Avoid standing for long duration
- Walking/Keep physically active
- Care of foot

Surgery for lower limb ulcers:

Venous

- Varicose vein – Sapheno Femoral Junction (**SFJ**) / Sapheno Popliteal Junction (**SPJ**) ligation, Great Saphenous Vein (**GSV**) stripping, avulsion of varicosities
- Sub fascial perforator surgery
- Deep vein reconstruction

Arterial

- Angioplasty
- Bypass procedures

THE PROMISE OF THE FUTURE

Synergistic technologies at the molecular and cellular level can be used for analyses and therapeutic purposes. This can be used to prevent wound progression and promote rapid healing. The promising technologies are:

- Systems for molecular analyses-genomics, proteomics, transgenic mice
- Systems for sustained topical delivery-polymers and adenovirus vectors
- Tissue engineering-human skin engineering, cellular matrices, and bone marrow–derived cell therapy
- Disease molecular pathogenesis-studies of patient biopsies and animal models
- Molecular targeting-antisense oligonucleotides, siRNA, and antibodies
- Stem Cell Research

CONCLUSION:

Diabetic foot complications cannot be prevented but it is indeed possible to dramatically reduce their incidence through appropriate multidisciplinary approach and also management of foot ulcers can be achieved by favourable rates of limb salvage in the high risk diabetic patients. Many lesions in the diabetic foot ulcers are preventable or treatable with patient education, properly designed and fitted orthoses and footwear and careful periodic monitoring of the case or complication. A diabetic foot program based on assessment of risk factors-especially sensory loss, deformity, joint limitation and poor circulation-provides a database for early and appropriate management of foot problems is the need of the hour. Further there is a compelling need to develop new technologies towards effective therapy and also focus on complete understanding of the molecular and cellular etiologies of DFU will help the patients to overcome the disease and lead a safe and better life.

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