DIABETIC FOOT ULCERS

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Abstract: Diabetes mellitus is a group of common metabolic diseases characterized by hyperglycemia. Due to multiple and prolonged complications, diabetes affects almost all systems of the body. In diabetes mellitus, cells fail to metabolize glucose in the normal manner, and effectively become starved. The long-term effect of diabetes mellitus includes progressive development of the specific complications of retinopathy, Potential blindness, and neuropathy with a risk of foot ulcer. DFU comprises a full-thickness wound involving the dermis, located in the weight-bearing or exposed area below the ankle. Infection is present, as defined by the presence of local swelling or induration, erythema, local tenderness, or pain. Successful treatment of diabetic foot ulcers consists of debridement, offloading, and infection control.

Keywords: Hyperglycemia, Diabetic foot ulcer, Complications, Callus formation, subcutaneous hemorrhage, Wagner grades.

Introduction:

Diabetes is a severe chronic disease that requires special attention and is also described as a “Global Epidemic”. About 415 million people have diabetes globally which accounts for 1 in 11 people. India has the world’s second largest diabetic population with approximately 69 million people with diabetes. Diabetes prevalence is increasing in developing and developed countries worldwide [1]. Diabetes mellitus is a group of common metabolic diseases characterized by hyperglycemia. Due to multiple and prolonged complications, diabetes affects almost all systems of the body [2].

The medical condition known as diabetes mellitus, or DM, is often called "sugar." It is the most common endocrine disorder and occurs when there is a shortage or absence of insulin, or sometimes when insulin activity is impaired (known as insulin resistance) [3]. The pancreas produces two hormones, insulin, and glucagon. Insulin is secreted by the beta (ß) cells and glucagon is secreted by the alpha (α) cells, both located in the islets of Langerhans. Insulin decreases blood glucose levels by promoting glycogenesis and transporting glucose into muscles, liver, and adipose tissue. Neural tissue and erythrocytes do not require insulin for glucose utilization. Alpha (α) cells play a crucial role in controlling blood glucose levels by producing glucagon, which increases blood glucose levels by accelerating glycogenolysis [4].

Classification of Diabetes Mellitus

The first mostly accepted classification of diabetes mellitus was published by WHO in the year 1980 and, it is modified in the year 1985[5,6].

Classification of diabetes mellitus is described below:

1. Insulin Dependent Diabetes Mellitus (Type1 IDDM)

This type of diabetes mellitus is also called autoimmune diabetes and was previously known as juvenile-onset or ketosis-prone diabetes. The individual may also seek other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease [7]. Type I diabetes mellitus is also known as insulin-dependent diabetes mellitus (IDDM), this occurs mainly in children and young adults; the onset is usually sudden and can be life-threatening. The exact cause of diabetes mellitus is still unknown, although, in most people, there is evidence of an autoimmune mechanism involving auto-antibodies that destroy the beta islet cells [8]. Type 1 diabetes (due to the destruction of B-cells which is usually leading to absolute insulin deficiency) (American Diabetes Association, 2014). The rate of destruction of beta cells is quite variable; it can occur rapidly in some individuals and slowly in others [9].

2. Non-Insulin Dependent Diabetes Mellitus (Type2 NDMM)

Type 2 diabetes mellitus is also known as adult-onset diabetes. The progressive insulin secretary defect on the background of insulin resistance (American Diabetes Association, 2014) [10].

3. Gestational Diabetes Mellitus

The glucose intolerance occurring for the first time or diagnosed during pregnancy is referred to as gestational diabetes mellitus (GDM) [3]. Gestational diabetes mellitus may develop during pregnancy and may disappear after delivery; In the longer term, children born to mothers with GDM are at greater risk of obesity and type 2 diabetes in later life, a phenomenon attributed to the effects of intrauterine exposure to hyperglycemia.

4. Other Specific Type [Monogenic Types]

The most common form of monogenic type of diabetes is developed with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1a. They are also referred to as genetic defects of beta cells. These forms of diabetes are frequently characterized by the onset of hyperglycemia at an early age (generally before the age of 25 years). They are also referred to as maturity-onset diabetes in the young (MODY)[6]. Some drugs are also used in combination with the treatment of HIV/ AIDS or after organ transplantation.

Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. They comprise less than 10% of DM cases [11].

COMPLICATIONS

In diabetes mellitus, cells fail to metabolize glucose in the normal manner, and effectively become starved. The long-term effect of diabetes mellitus which includes progressive development of the specific complications of retinopathy with,

- Potential blindness
- Gluconeogenesis from amino acids and body protein causes muscle wasting, and tissue breakdown and further increases the blood glucose level.
- Catabolism of body fat, releasing some of its energy and excess production of ketone bodies.
- Nephropathy that may lead to renal failure.
- And neuropathy with risk of foot ulcer [3].

PATHOPHYSIOLOGY

DFU comprises a full-thickness wound involving the dermis, located in the weight-bearing or exposed area below the ankle. The Wagner system aids in categorizing the severity of the ulcer, ranking it on a scale of 1 to 5 (Table 1). The pathologic mechanisms of DFU are described in terms of a triad. This triad includes neuropathy, vascular insufficiency, and secondary infection due to trauma of the foot [12].

First, the lack of protective sensation in the feet predisposes patients with diabetes to develop trauma and ulcers. This sensory impairment occurs due to hyperglycemia-induced upregulation of aldose reductase and sorbitol dehydrogenase, which in turn increase the production of fructose and sorbitol. These glucose products accumulate and induce osmotic stress, thereby reducing nerve cell myoinositol synthesis and nerve conduction [13].

Also, from a pathological stance, advanced glycation end-products (AGEs) must be considered. AGEs are non-enzymatic proteins, amino acids, and DNA adducts that form dicarbonyls from glucose. AGE formation is enhanced in diabetes and is associated with the development of diabetic complications [14].

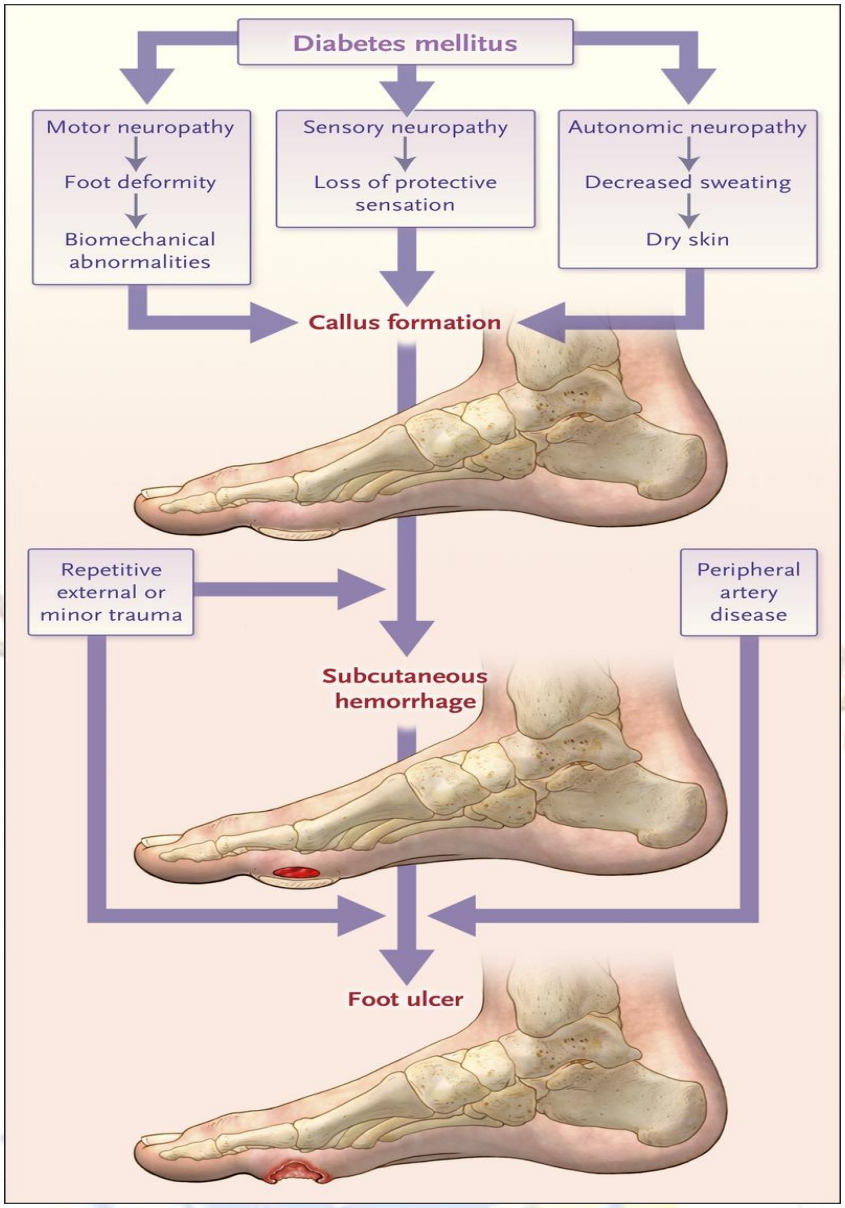

Fig: Pathophysiology of foot ulcer

In addition to sensory neuropathy, diabetes can induce neuronal autonomic dysfunction that results in impaired sweat production, leaving the foot susceptible to dryness, skin cracking, and fissuring [15]. Furthermore, motor neuron dysfunction can give rise to muscle wasting and structural abnormalities of the foot [16]. This causes focally elevated pressures at various zones of the plantar foot and increases the risk of ulceration [17]. In addition to the triad, impaired wound healing has been established as a key means of DFU progression. Importantly, molecular changes at the site of DFU precede the grossly visualized tissue abnormalities. The route from hyperglycemia to DFU involves complex molecular dysfunctions in wound healing. Ordinarily, wounds undergo several healing stages involving homeostasis, inflammation, proliferation, and remodeling. Acute wounds advance linearly through these stages; however, chronic nonhealing DFUs stall in 1 or more phases. In the early phases of wound healing, neutrophils normally release granular molecules to kill foreign pathogens in a process known as neutrophil extracellular traps (NETosis) [18].

However, in a diabetic microenvironment, NETosis becomes dysregulated, causing a proinflammatory cascade and overproduction of cytokines and superoxide, which delay wound healing. Moreover, hyperglycemia induces the formation of AGEs that cause structural and functional changes in key proteins. Specifically, AGEs can bind to the receptor of advanced glycation end-products (RAGE), which is normally minimally expressed in normoglycemic conditions [19]. This in turn activates the nuclear factor kappa-B (NF-κB). Ultimately, cytokine release is enhanced with a self-sustaining cascade that prolongs inflammation and favors apoptosis [20].

Overall, hyperglycemia induces a proinflammatory environment largely due to the dysregulation of cytokine release, NETosis, and AGE production.

Table 1 Wagner's classification of diabetic foot ulcers

Grade	Characteristic
Wagner grade 1	Partial- or full-thickness ulcer (superficial)
Wagner grade 2	Deep ulcer extending to ligament, tendon, joint capsule, bone, or deep fascia without abscess or OM
Wagner grade 3	Deep abscess, OM, or joint sepsis
Wagner grade 4	Partial-foot gangrene

OM: Osteomyelitis

Along with inflammation, substantial alterations of the extracellular matrix (ECM) also play a significant role in perpetuating the non-healing DFU. In cases of normal wound healing, the production and degradation of ECM proteins such as collagen and fibrin are tightly regulated. Collagen comprises most of the soft tissue ECM, and thus, abnormalities of collagen metabolism have significant consequences on wound healing. Specifically, collagen-degrading enzymes known as matrix metalloproteinases (MMPs) become hyperactive, resulting in a highly-proteolytic environment with reduced collagen content. Overall, the ECM becomes disorganized and insufficient to support wound healing. Alongside elevated MMP activity, the accumulation of AGEs results in a reduction of fibroblast. Alongside elevated MMP activity, the accumulation of AGEs results in a reduction of fibroblast growth factor (FGF) and transforming growth factor-beta. This has a similar effect of reducing the collagen content *via* the induction of fibroblast apoptosis.

Lastly, impaired angiogenesis plays a key role in the disruption of diabetic wound healing. Angiogenesis ordinarily occurs during the proliferative phase of wound healing and is responsible for both the formation of granulation tissue and the delivery of nutrition and oxygen to the wound. In the case of DFU, there is a reduction of angiogenic growth factors such as vascular endothelial growth factor (VEGF) 20 and FGF-2. Essentially, VEGF initiates angiogenesis and mediates endothelial cell proliferation while FGF-2 facilitates migration of new blood vessels through the ECM. When VEGF and FGF-2 expression is compromised

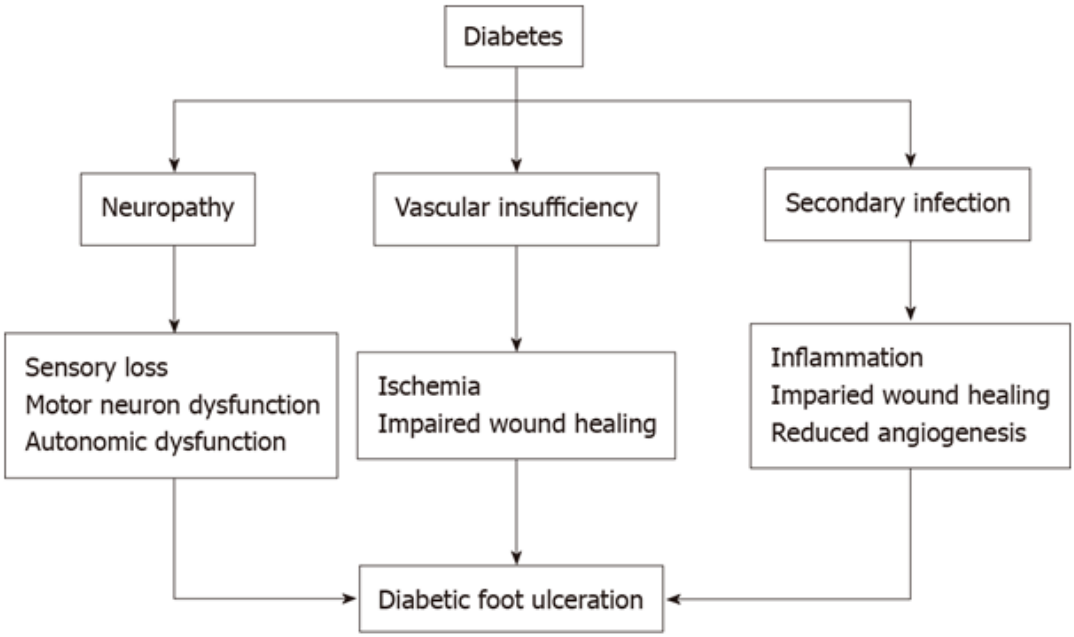

Figure 1 Flow chart of diabetic foot ulceration.

wound healing declines. Furthermore, endothelial progenitor cells (EPCs) have been implicated as an expression of proangiogenic factors and receptors including VEGF and FGF [21].

A deficiency of function and number of EPCs has been demonstrated in patients with type 2 diabetes mellitus, which is attributed to AGE accumulation. Overall, the dysfunction of EPCs and circulating growth factors contribute significantly to the development and progression of DFU by way of disrupting angiogenesis.

Clinical manifestation

Clinical manifestation of infection

Infection present, as defined by the presence of at least 2 of the following items:

- local swelling or induration
- erythema
- local tenderness or pain

- local warmth purulent discharge (thick, opaque-to-white, or sanguineous secretion)
- Local infection involving only the skin and the subcutaneous tissue (without the involvement of deeper tissues and without systemic signs as described below). If erythema must be > 0.5 cm to ≤ 2 cm around the ulcer.

  Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis)
- Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis), and no systemic inflammatory response signs (as described below)

Local infection (as described above) with the signs of SIRS, as manifested by ≥ 2 of the following:

- temperature > 38°C or < 36°C
- heart rate > 90 beats/min
- respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- white blood cell count > 12,000 or < 4000 cells/μL or ≥ 10% immature (band) forms.

Abbreviations: PaCO2, partial pressure of arterial carbon dioxide; SIRS, systemic inflammatory response syndrome

Treatment

Successful treatment of diabetic foot ulcers consists of addressing these three basic issues: debridement, offloading, and infection control.

Debridement

Debridement consists of the 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. After debridement, the wound should be irrigated with saline or cleanser, and a dressing should be applied. Dressings should prevent tissue desiccation, absorb excess fluid, and protect the wound from contamination

There are hundreds of dressings on the market, including hydrogels, foams, calcium alginates, absorbent polymers, growth factors, and skin replacements. Becaplermin contains the -chain platelet–derived growth factor and has been shown in double-blind placebo-controlled trials to significantly increase the incidence of complete wound healing. Its use should be considered for ulcers that are not healing with standard dressings. In case of an abscess, incision, and drainage are essential, with debridement of all abscessed tissue. Many limbs have been saved by timely incision and drainage procedures; conversely, many limbs have been lost by failure to perform these procedures. Treating a deep abscess with antibiotics alone leads to delayed appropriate therapy and further morbidity and mortality.

Offloading

Having patients use a wheelchair or crutches to completely halt weight bearing on the affected foot is the most effective method of offloading to heal foot ulceration. Total contact casts (TCCs) are difficult and time-consuming to apply but significantly reduce pressure on wounds and have been shown to heal between 73 and 100% of all wounds treated with them. Armstrong et al.4 have achieved similar healing rates with an "instant TCC," made by wrapping a removable cast walker with a layer of cohesive bandage or plaster of Paris. Inappropriate application of TCCs may result in new ulcers, and TCCs are contraindicated in deep or draining wounds or for use with noncompliant, blind, morbidly obese, or severely vascularly compromised patients. Clinicians often prefer removable cast walkers because they do not have some of the disadvantages of TCCs. Removability is an advantage in that it allows for daily wound inspection, dressing changes, and early detection of infection. But removability is also the greatest disadvantage in that studies have
shown that patients wear them only ~ 30% of the time they are walking (usually to and from the doctor's office).5Postoperative shoes or wedge shoes are also used and must be large enough to accommodate bulky dressings. Proper offloading remains the biggest challenge for clinicians dealing with diabetic foot ulcers.

Infection control

Limb-threatening diabetic foot infections are usually polymicrobial. Commonly encountered pathogens include methicillin-resistant *staphylococcus aureus*, -hemolytic streptococci, Enterobacteriaceae, *pseudomonas aeruginosa*, and enterococci. Anaerobes, such as *Bacteroides*, *streptococcus*, and *peptostreptococcus*, are rarely the sole pathogens but are seen in mixed infections with aerobes. Antibiotics selected to treat severe or limb-threatening infections should include coverage of gram-positive and gram-negative organisms and provide both aerobic and anaerobic coverage. Patients with such wounds should be hospitalized and treated with intravenous antibiotics. Mild to moderate infections with localized cellulitis can be treated on an outpatient basis with oral antibiotics such as cephalexin, amoxicillin with clavulanate potassium, moxifloxacin, or clindamycin. The antibiotics should be started after initial cultures are taken and changed as necessary.

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