"PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS RISK FACTORS LEADING TO AMPUTATION IN DIABETIC FOOT PATIENTS – AT A TERTIARY HEALTH CARE CENTRE IN BELAGAVI"

BY

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS RISK FACTORS LEADING TO AMPUTATION IN DIABETIC FOOT PATIENTS- AT A TERTIARY HEALTH CARE CENTRE IN BELAGAVI"** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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LIST OF ABBREVIATIONS

ABI	Ankle-brachial index
DFU	Diabetic foot ulcer
LEA	Lower extremity amputation
NIDDM	Non-insulin-dependent diabetes mellitus

ABSTRACT

“PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS RISK FACTORS LEADING TO AMPUTATION IN DIABETIC FOOT PATIENTS – AT A TERTIARY HEALTH CARE CENTRE IN BELAGAVI”

Background: Diabetic foot ulcers (DFUs) represent a significant cause of morbidity among individuals with diabetes, frequently leading to hospitalization and non-traumatic lower extremity amputation (LEA). These complications are primarily due to compromised blood supply and neuropathy, which predispose patients to infections and ischemia. To identify and assess risk factors associated with lower limb amputation in diabetic foot patients.

Objective of the study: To predict lower limb amputation occurrence and to determine risk factors leading to amputation in diabetic foot patients

Material and Methods: This prospective observational study included 60 diabetic foot patients admitted to a tertiary healthcare center in Belagavi from January 1, 2023, to December 31, 2023. Patient demographics, comorbidities, history of trauma, and smoking, along with clinical assessments including the Wagner grading system, peripheral neuropathy, and Ankle-Brachial Pressure Index (ABPI), were evaluated. Baseline investigations encompassed “hemoglobin, glycosylated hemoglobin (HbA1c), serum creatinine, total leucocyte count, and fasting blood sugar levels.” Outcomes were measured through the incidence of amputation.

Results: The study included 60 patients with a mean age of 54±12.3 years; 75% were male. Of these, 88.3% had diabetes mellitus alone, while 11.7% had both diabetes and hypertension. Trauma history was present in 68.3%, and 38.3% had a history of

cigarette smoking. According to Wagner's classification, the majority were in grade 2, followed by grades 3 and 4. Peripheral neuropathy was identified in 71.7% of patients, while ABPI was <0.9 in 41.7% and >0.9 in 58.3%. X-rays of foot showed normal findings in 88.3%, with osteomyelitis in 8.3%. Amputation was performed in 43.3% of patients. Significant correlations with higher amputation rates included smoking history (61.5%), higher Wagner grades, peripheral neuropathy, and ABPI <0.9 ($p<0.05$).

Conclusion: The study highlights peripheral neuropathy, smoking, higher Wagner grade, and ABPI <0.9 as significant risk factors for amputation in diabetic foot patients. These findings underscore the necessity for early detection and management of these risk factors to prevent progression to amputation, thereby improving patient outcomes and quality of life.

Keywords: Diabetic foot ulcer, Amputation, Peripheral neuropathy, Wagner grade, Ankle-Brachial Pressure Index, Risk factors

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INTRODUCTION

Diabetes is the most prevalent underlying cause of ischemia, infection, and foot ulcers—three of the most dangerous consequences of the disease that frequently result in hospitalization and non-traumatic lower limb amputation. People with diabetes mellitus are more susceptible to foot infections due to the compromise of blood flow caused by microvascular illness, which is frequently combined with neuropathy-induced loss of feeling.[1]

One of the most frequent diabetes complications that lead to hospitalization is diabetic foot ulcers (DFU). Lower extremity amputation (LEA) is defined by the worldwide lower extremity study group as the total loss of any lower limb component, regardless of the etiology.[2] People with diabetes have a 10–30 times higher risk of LEA (2.8%) than healthy people (0.29%).[3] Diabetes is a common cause of non-traumatic lower extremity amputations, with 15% of diabetics developing foot ulcers and 12–24% of them needing to have their feet amputated. Although there are established risk factors for the development of diabetic foot ulcers, little information is known about the variables that might predict an amputation during an episode of the condition. The research has identified several risk factors for amputations among diabetes. Nonetheless, disparities exist among the research findings.

Assessing the risk factors leading to amputation in diabetic foot patients holds significant scientific importance due to several reasons. First of all, diabetic foot problems are a leading global source of morbidity and death for people with diabetes.

Lower extremity amputations (LEAs) significantly impact the quality of life of affected individuals, leading to disability, reduced mobility, and increased healthcare costs. By identifying and understanding the risk factors associated with amputation in

diabetic foot patients, healthcare professionals can develop targeted interventions to prevent or mitigate these complications. Secondly, diabetic foot ulcers are often complicated by infections, peripheral neuropathy, and peripheral arterial disease, all of which contribute to the progression of tissue damage and increase the risk of amputation. Assessing risk factors allows clinicians to stratify patients based on their likelihood of developing severe complications, enabling personalized treatment approaches and early intervention strategies. [4]

While several categorization systems exist for predicting the fate of diabetic foot ulcers, few research have assessed the external validity or reliability of these systems. These systems of classification are a vital resource for treating patients, making treatment decisions, and enhancing professional communication. Making decisions would therefore be facilitated by a single or streamlined categorization system that incorporates the most accurate predicting criteria for amputation.[3]

Assessing risk factors leading to amputation in diabetic foot patients is crucial for improving clinical outcomes, reducing healthcare burden, and enhancing the overall quality of life for individuals living with diabetes. “Therefore, to predict lower limb amputation occurrence and to determine the factors associated with the risk of amputation in diabetic foot patients, we conducted this study.”

AIMS AND OBJECTIVES

Objective of the study

To predict lower limb amputation occurrence and to determine risk factors leading to amputation in diabetic foot patients

REVIEW OF LITERATURE

Diabetes Mellitus[5]

Diabetes mellitus comes from the Greek "diabetes," which means "to pass through," and the Latin "mellitus," which translates to "sweet." This term was first introduced by Apollonius of Memphis between 250 and 300 BC, influenced by the sweet taste of urine noted by ancient Greek, Indian, and Egyptian cultures. Mering and Minkowski identified the role of the pancreas in diabetes in 1889. Even with substantial advancements in treatment, diabetes remains a widespread chronic illness worldwide.[5]

Epidemiology:

Diabetes has surged into a worldwide epidemic, with India taking the lead as the global hub for the disease, accommodating approximately 41 million diagnosed individuals. Projections indicate that the occurrence of diabetes across all age brackets was expected to climb from 2.8% in 2000 to 4.4% by 2030.[6,7] As per the International Diabetes Federation (2017), the anticipated prevalence of diabetes is projected to increase from 8.8% in 2017 to 11.4% in 2045. Concurrently, the incidence of diabetic eye disease is on the rise.[8] According to the most recent epidemiological data from 2019, India presently counts around 77 million individuals grappling with diabetes, a figure expected to surge to nearly 134 million by 2045. India stands as the second-largest contributor to the global diabetes crisis, trailing only behind China. Among these statistics, 12.1 million individuals are aged 65 or older, and this demographic is projected to expand to 27.5 million by 2045. Additionally, an estimated 57% of diabetes cases in India, approximately 43.9 million people, remain undiagnosed.[9]

Classification of diabetes mellitus

The four types of diabetes mellitus as per new classification identifies.[10] Type 1, Type 2, "Other specific types" and gestational diabetes.

"Type 1: autoimmune β-cell destruction leading to absolute insulin deficiency.

Type 2: (NIDDM / Adult onset) is presents with insulin resistance in peripheral tissues and an insulin secretary defect of the β cells.

Other Specific Types: αβ-cell dysfunction (MODY or Maturity onset Diabetes Mellitus) or with defects of insulin action. Persons with diseases of exocrine pancreas, dysfunction associated with endocrinopathies."

Gestational diabetes refers to diabetes that develops during pregnancy. Although its exact cause remains uncertain, some propose a potential involvement of HLA antigens, particularly HLA DR2, 3, and 4. There's suspicion that excess proinsulin could contribute to gestational diabetes, possibly inducing stress on beta cells. Alternatively, elevated levels of hormones like progesterone, cortisol, prolactin, human placental lactogen, and estrogen are believed by some to disrupt beta-cell function and peripheral insulin sensitivity.[11]

SECONDARY

- Pancreatic disease
- Genetic diseases
- Hormonal abnormalities
- Ingestion of certain drugs or chemical compounds.

Acromegaly, hyperaldosteronism, hyperthyroidism, glucagonoma, Cushing syndrome, and somatostatinomas have all been linked to glucose intolerance and diabetes mellitus, owing to the inherent glucogenic action of the endogenous hormones secreted excessively in these conditions.

Criteria for the diagnosis of Diabetes Mellitus[12]

1) Oral glucose tolerance test: ≥ 200 mg/dl at 2 hours plasma glucose

2) ≥126 mg/dl Fasting plasma glucose.

3) Symptoms associated with > 200 mg/dl plasma glucose concentration

Complications of diabetes mellitus

Diabetes is linked to a range of complications, including acute metabolic problems like hypoglycemia (low blood glucose) leading to loss of consciousness, and diabetic ketoacidosis caused by excessively high blood glucose levels (hyperglycemia). However, the main focus of this discussion will be on the chronic vascular complications of diabetes, which are seen as its most harmful effects. These issues arise, at least in part, from consistently elevated blood glucose levels that harm blood vessels.

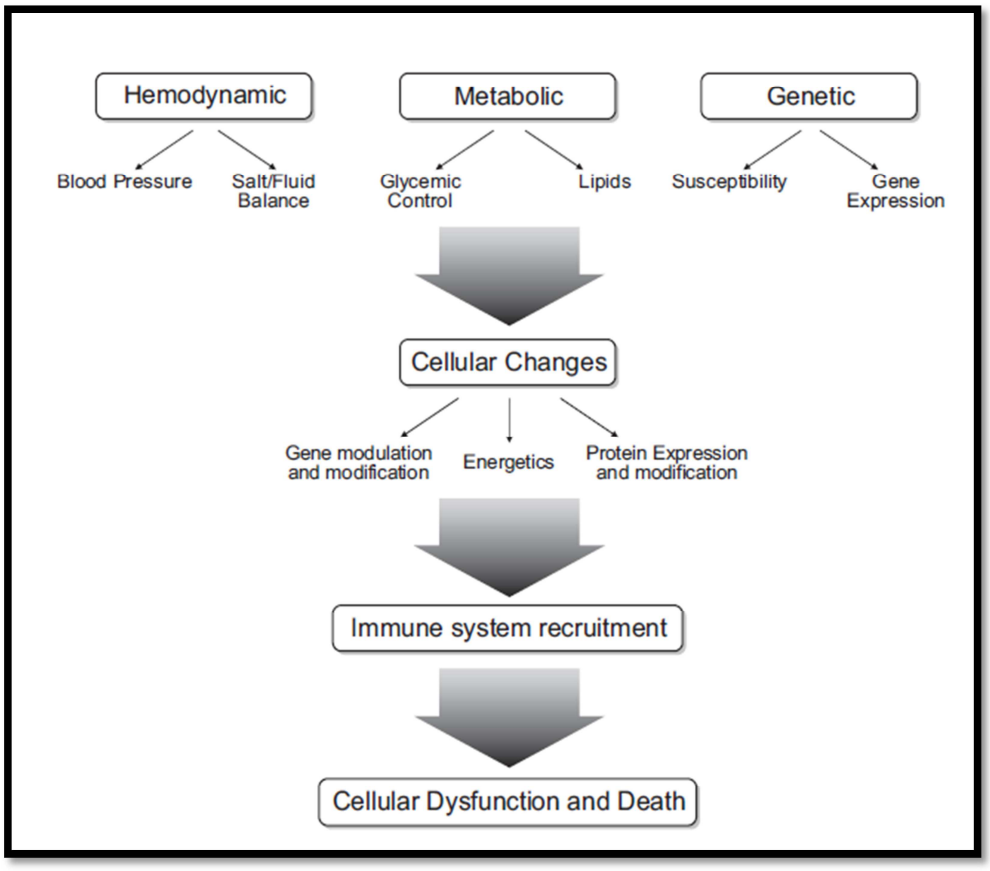


Figure 1: Major pathway showing the complications of diabetes mellitus

Diabetes complications are divided into microvascular and macrovascular diseases. Microvascular problems include eye conditions like retinopathy, kidney diseases termed nephropathy, and nerve damage known as neuropathy. Significant macrovascular complications involve heightened cardiovascular diseases, resulting in events such as heart attacks (myocardial infarction) and stroke (cerebrovascular incidents). Furthermore, myocardial dysfunction linked to diabetes mellitus may develop, partly unrelated to atherosclerosis.

Other chronic complications comprise depression, sexual dysfunction, and dementia.

Diabetic foot ulcers

15% of people with diabetes will develop diabetic foot ulcers at some time in their lives. It is known that amputation may be necessary for 15 to 20% of people with severe foot ulcers. More than 85% of all amputations are due to these ulcers.[13,14] Numerous risk factors contribute significantly to the development of foot ulcers, with peripheral sensory neuropathy being the primary factor, closely followed by peripheral vascular disease. Among individuals with diabetes, the breakdown of neuropathic, neuroischemic, and purely ischemic lesions is approximately 54%, 34%, and 10%, respectively. India experiences an estimated annual total of 40,000 leg amputations, with 75% attributed to neuropathic ulcers that lead to subsequent infections, which could potentially be prevented. Various factors, including walking barefoot, low literacy rates, socioeconomic status, delayed patient presentation, misconceptions about diabetic foot care among primary care physicians, and reliance on alternative medical systems, collectively contribute to this heightened prevalence.[13–15]

History:

Diabetes, an age-old affliction affecting approximately one percent of the global populace, affects both genders equally. Despite being recognized as a distinct medical condition for over 3500 years, its origins remained obscure until the early 20th century. In the 1920s, researchers began suspecting that diabetes stemmed from malfunctions in the digestive system associated with the pancreas gland. Clinical features of the disease were documented by ancient Egyptians around 3000 years ago. The term "diabetes" was coined by Araetus of Cappodocia (18-133 AD), with the addition of "mellitus" (honey sweet) by Thomas Willis of Britain in 1675, inspired by the sweetness of patients' urine and blood, initially observed by ancient Indians. It

wasn't until 1776 that Dobson, also from Britain, confirmed the presence of excessive sugar in urine and blood as the cause of their sweetness.[16]

The understanding of diabetes dates back to ancient civilizations, with significant contributions from various cultures. In India, the Charaka Samhita and writings by Sushruta described symptoms including sweet urine and excessive urination around 500 AD. Avicenna, an Arab physician, provided insights into diabetic gangrene in the 10th century. Ancient Egyptian medical texts like the "Papyrus Ebers" from 1500 BC documented symptoms of frequent urination. The term "diabetes" likely originated around 250 BC by Apollonius of Memphis, with the earliest recorded use of "diabetic" in English appearing in a medical text from around 1425. Thomas Willis added "mellitus" to "diabetes" in 1675 due to the sweet taste of urine. Aretaeus of Cappadocia described the disease as the dissolution of flesh and limbs into urine in the 1st century AD.

The history of diabetic foot ulcers (DFUs) is intertwined with the history of diabetes itself, reflecting advances in medical understanding and treatment of both conditions.

Ancient Civilizations: References to diabetes-like conditions date back to ancient Egypt, India, and Greece, but there is little mention of foot complications specifically related to diabetes.

19th Century: The term "diabetic foot" began to emerge as physicians noticed the association between diabetes and chronic foot ulcers. However, treatments were rudimentary, focusing mainly on wound care and amputation when necessary.

Early 20th Century: Insulin Discovery (1921): The discovery of insulin by Frederick Banting and Charles Best was a significant milestone in diabetes

management, reducing the severity and frequency of complications like DFUs by better controlling blood sugar levels

Basic Foot Care: Early diabetic foot care included basic wound cleaning and bandaging. Podiatry began to establish itself as a distinct medical field, emphasizing the importance of foot care in diabetic patients.

Mid to Late 20th Century: Understanding Neuropathy and Circulation Issues: By the mid-20th century, the role of peripheral neuropathy and poor circulation in DFU development became clearer. Studies highlighted the need for comprehensive foot care, including regular examinations and patient education

Antibiotics and Surgical Advances: The advent of antibiotics improved infection management in DFUs. Surgical techniques also advanced, offering more options for debridement and other interventions.

Late 20th Century to Early 21st Century: Multidisciplinary Approach: The importance of a multidisciplinary approach involving endocrinologists, podiatrists, vascular surgeons, and infectious disease specialists was recognized. This comprehensive care model improved patient outcomes significantly

Recent Advances: Technological Innovations: Recent years have seen the development of advanced wound care technologies, such as bioengineered skin substitutes, negative pressure wound therapy, and hyperbaric oxygen therapy. These innovations have improved healing rates and reduced complications.[68]

Research and Clinical Trials: Ongoing research continues to explore new treatment modalities, including gene therapy, growth factors, and novel surgical techniques like tibial cortex transverse transport to enhance wound healing and vascularization

Current Challenges and Future Directions

- Rising Diabetes Prevalence: With the global increase in diabetes cases, the incidence of DFUs is also rising, presenting ongoing challenges in management and prevention
- Focus on Prevention: Current strategies emphasize prevention through patient education, regular foot examinations, and early intervention to manage risk factors such as high blood sugar and poor circulation

Overall, the history of the diabetic foot reflects significant advancements in understanding, prevention, and treatment, driven by broader developments in diabetes care and medical science

Etiology

The development of diabetic foot ulcers is influenced by several factors, including poor blood sugar control, calluses, foot deformities, inadequate foot care, ill-fitting footwear, peripheral neuropathy, impaired circulation, and dry skin. Neuropathy, which affects about 60% of diabetes patients, substantially increases the likelihood of foot ulcers. Additionally, individuals with flat feet face an increased risk due to uneven pressure distribution, leading to tissue inflammation in susceptible areas.[17]

Epidemiology

The global annual incidence of diabetic foot ulcers varies from 9.1 to 26.1 million cases, affecting approximately 15 to 2 5% of individuals with diabetes mellitus during their lifetime. As the number of new diabetes cases increases annually, the prevalence of diabetic foot ulcers is anticipated to rise. Although these ulcers can

occur at any age, they are most prevalent among individuals aged 45 and older with diabetes. In the United States, Latinos, African Americans, and Native Americans have the highest rates of foot ulcers.[17,18]

Pathophysiology

The progression of a diabetic ulcer typically unfolds in three stages. Initially, a callus forms, often due to neuropathy, which can cause foot deformities and diminished sensation, leading to ongoing injury. Autonomic neuropathy may contribute to skin dryness, exacerbating the problem. Continued trauma to the callus can lead to subcutaneous bleeding, eventually resulting in ulceration. Moreover, individuals with diabetes mellitus commonly experience severe atherosclerosis in the small blood vessels of the lower limbs, reducing blood flow and predisposing them to foot infections. Impaired circulation delays wound healing, ultimately leading to tissue necrosis and gangrene.[18]

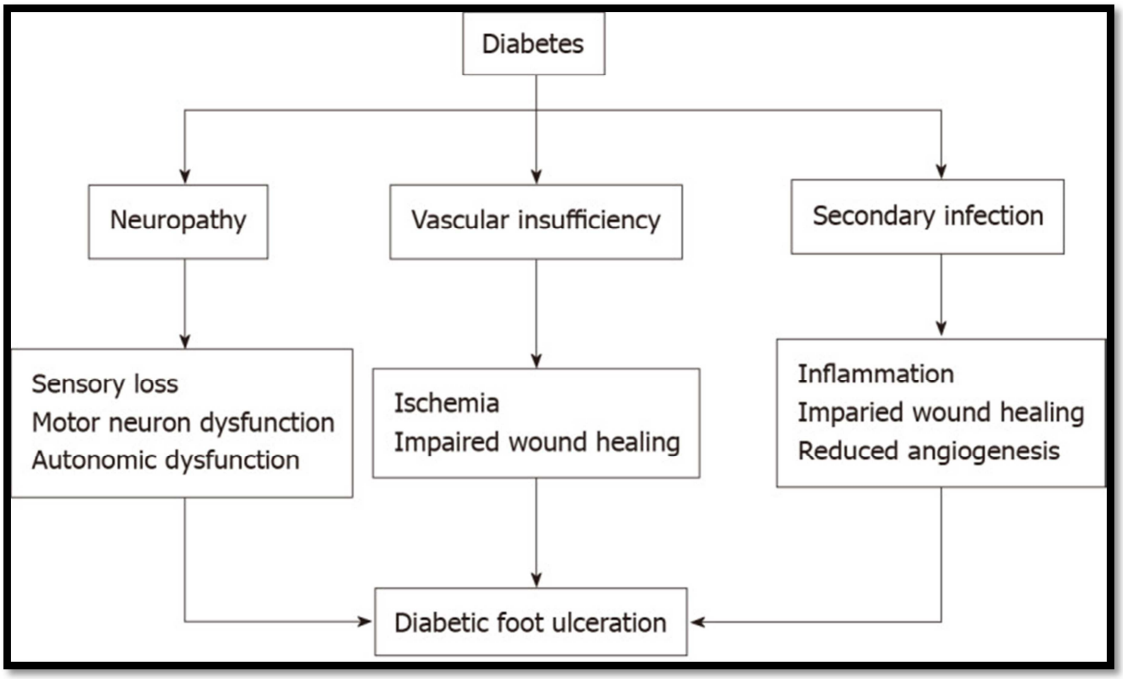


Figure 2 : Diabetic foot ulcer pathogenesis[19]

The pathogenesis of diabetic foot ulcers encompasses a complex interaction of factors involving the vascular, neural, and metabolic systems affected by diabetes.

Peripheral Neuropathy: Diabetic neuropathy, especially peripheral neuropathy, reduces protective sensation in the feet, increasing susceptibility to injuries and ulceration. Studies indicate that oxidative stress and microvascular damage induced by hyperglycemia contribute to nerve fibre degeneration and dysfunction.[20] Diabetic neuropathy presents various symptoms in the diabetic foot due to its involvement of sensory, motor, and autonomic nerve fibres. Peripheral neuropathy affects around 66% of diabetic patients, predominantly in the lower limbs. Distal sensory neuropathy, the most common type, poses a significant risk for foot ulcers in diabetes, displaying a wide spectrum of severity from intense pain to complete insensitivity, leading to ulceration. The distribution of diabetic peripheral neuropathy typically follows a stocking-glove pattern, primarily affecting the lower legs and feet. This condition may also lead to the loss of the Achilles reflex, often an early indicator of neuropathic changes. Structural deformities of the foot, such as the atrophy of certain muscles and increased tension in extensor tendons, can result in a claw-like deformity of the toes. Additionally, sensory neuropathy onset can manifest as vibratory perception, pressure sensitivity, diminished proprioception, and altered gait patterns.[21–23]

Ulceration and infection may result from repetitive trauma, while reduced sensation and proprioception can further increase the risk of injury to skin by causing the atrophy and displacement fat pads in the plantar aspect of foot. Additionally, diabetic autonomic neuropathy can lead to sudomotor dysfunction, contributing to foot ulceration through lack of swaeting, dryness and itchig of skin. Numerous methods have been devised to evaluate sudomotor function, including as the use of indicator plaster, quantitative direct and indirect reflex tests, quantitative sudomotor

axon reflex, and thermoregulatory sweat testing. Among them, indicator plaster, which depends on a color shift in the plantar foot area from blue to pink, provides a quick and simple technique.[24–26]

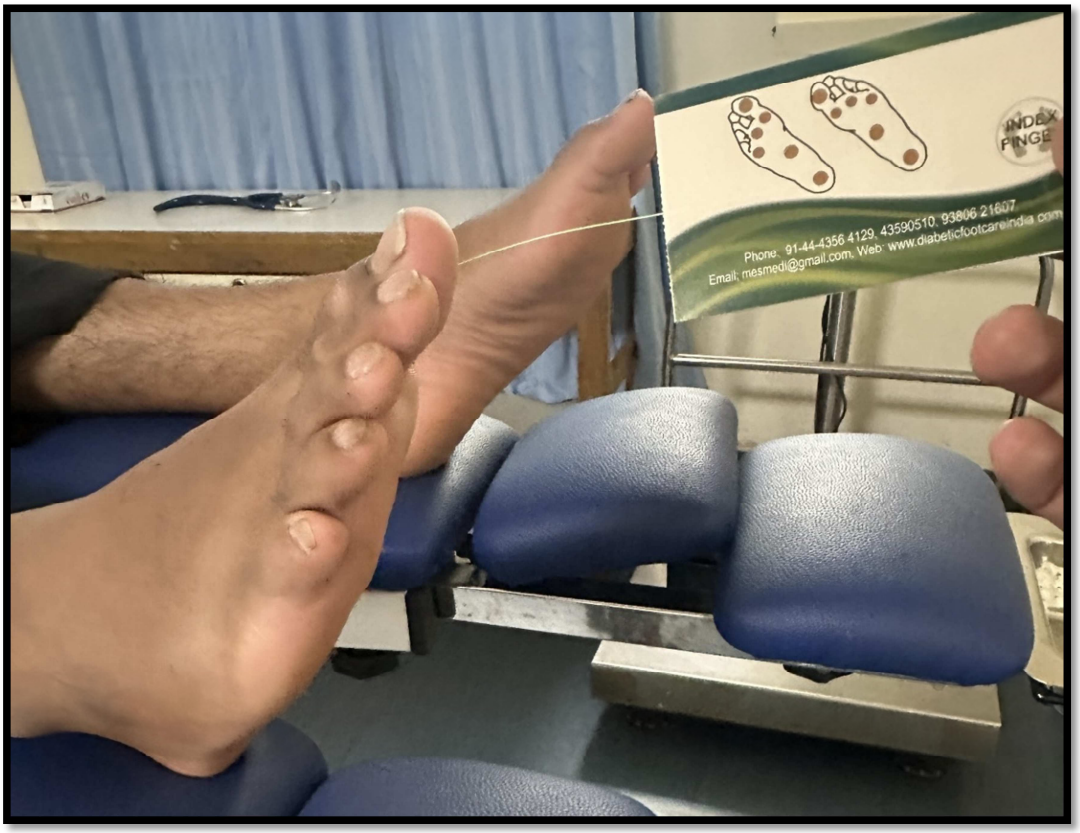


Figure 3: Monofilament test to find out sensory neuropathy [27]

One of the first signs of peripheral diabetic neuropathy is often impairment of vibration perception, or deep sensory impairment. In clinical practice, tuning forks (128 Hz) are frequently used to measure vibration sensitivity on the medial malleolus and other prominences over distal bones, such as the bilateral great toe. However, compared to the monofilament test, tuning forks have a sensitivity of only around 53%, making them less accurate in predicting the development of ulcers in diabetics.[28]

Peripheral Arterial Disease (PAD): Diabetes-related PAD compromises blood flow to the lower extremities, impairing oxygen and nutrient delivery to tissues, which is crucial for wound healing. Chronic hyperglycemia-induced endothelial dysfunction and inflammation contribute to vascular complications in diabetes.[29] During follow-up examinations, pulse palpation on various arteries (posterior tibial, distal pedis, femoral and popliteal) should be done for all diabetic patients. "This clinical examination is simple, cost-effective, and comfortable. Peripheral artery disease may now be diagnosed mostly non-invasively with the use of the ankle-brachial index (ABI).[30] ABI levels between 1.0 to 1.4 are considered typical, with readings less than 0.9 being unmistakably pathological. An artery calcification and stiffness is indicated by an ABI more than 1.4, which is likewise regarded as abnormal. Non-invasive diagnostic methods like computed tomography angiography and Doppler ultrasonography are often employed. Intra-arterial digital subtraction angiography is useful for identifying the smaller arteries in the foot and ankle and has the added benefit of potentially allowing endovascular treatment to be performed concurrently with the surgery. Renal failure patients however, would not benefit from it."[30–32]

Microvascular Damage: Microangiopathy in diabetes leads to capillary basement membrane thickening, endothelial dysfunction, and impaired tissue perfusion. These microvascular changes hinder wound healing by reducing nutrient and oxygen delivery to the wound site.[33,34]

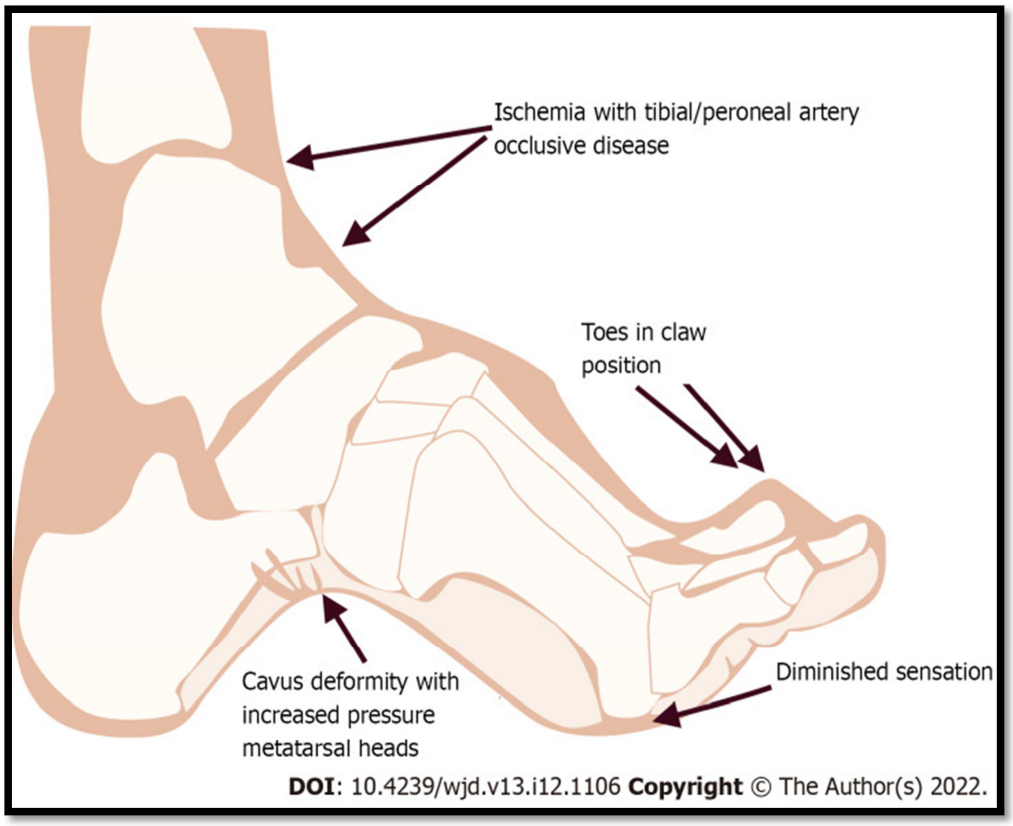


Figure 4: Etiopathogenesis of developing vascular complications in diabetic foot [27]

Foot Deformities and Pressure Points: Structural abnormalities in the foot, such as Charcot arthropathy or hammer toes, increase pressure and friction, predisposing individuals to callus formation and subsequent ulceration. Research highlights the importance of offloading pressure points to prevent ulcer development.[35]

Impaired Immune Response: Diabetes-associated immune dysfunction impairs the body's ability to combat infections, leading to delayed wound healing and increased risk of infection in foot ulcers. Hyperglycemia-induced immune cell dysfunction and impaired cytokine production contribute to impaired host defense mechanisms.

Hyperglycemia: Persistent hyperglycemia disrupts various cellular processes involved in wound healing, including impaired collagen synthesis, reduced

angiogenesis, and dysfunctional inflammatory responses, prolonging the healing process in diabetic foot ulcers.

Poor Foot Care Practices: Neglecting proper foot care, such as wearing improper footwear or failing to inspect the feet regularly, increases the risk of foot trauma and ulceration in individuals with diabetes. Education on foot care and regular foot examinations are essential for ulcer prevention.

Ulcer classification

The first step in "addressing diabetic foot ulcers involves assessing, grading, and categorizing the ulcer. Treatment decisions are based on clinical evaluation, considering factors such as the size, depth, presence of infection or ischemia. It is recommended that all individuals with diabetic foot ulcers undergo measurement of their ankle-brachial index and toe pressure to assess for ischemia."[36,37]

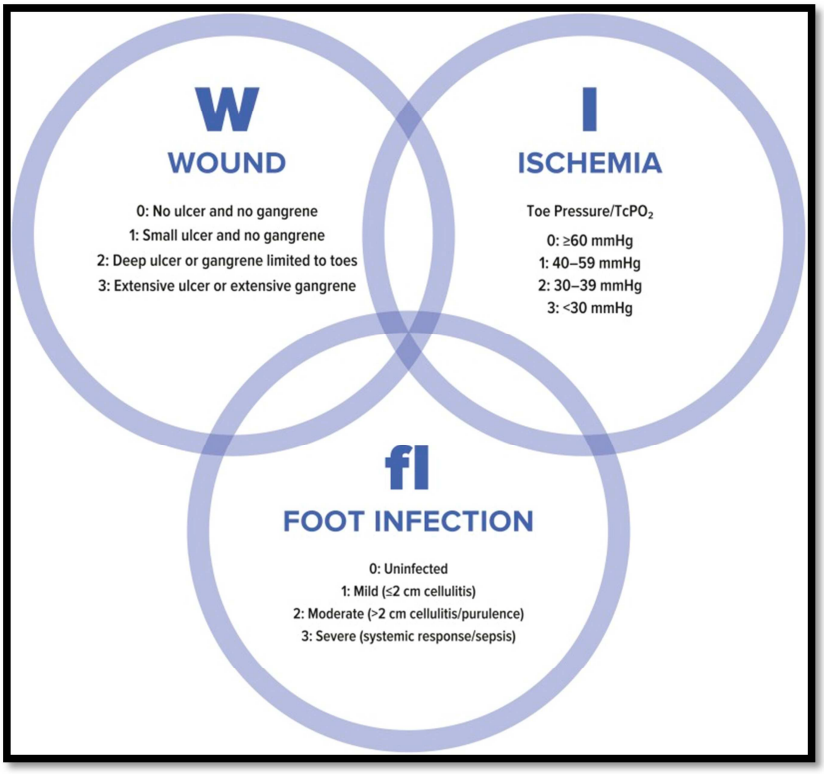


Figure 5: SVS WIfI classification system for risk of foot ulcer

"The University of Texas (UT, San Antonio) in the United States developed a clinical classification system for diabetic foot wounds that considers wound depth, infection, and peripheral artery occlusive disease for each category of wound assessment."[38–40]

Texas ulcer grading

Grade 0: pre or postulcerative

Grade 1: full thickness ulcer not involving the tendon, bone or capsule

Grade 2: tendon or capsular involvement without the bone palpable

Grade 3: probes to bone

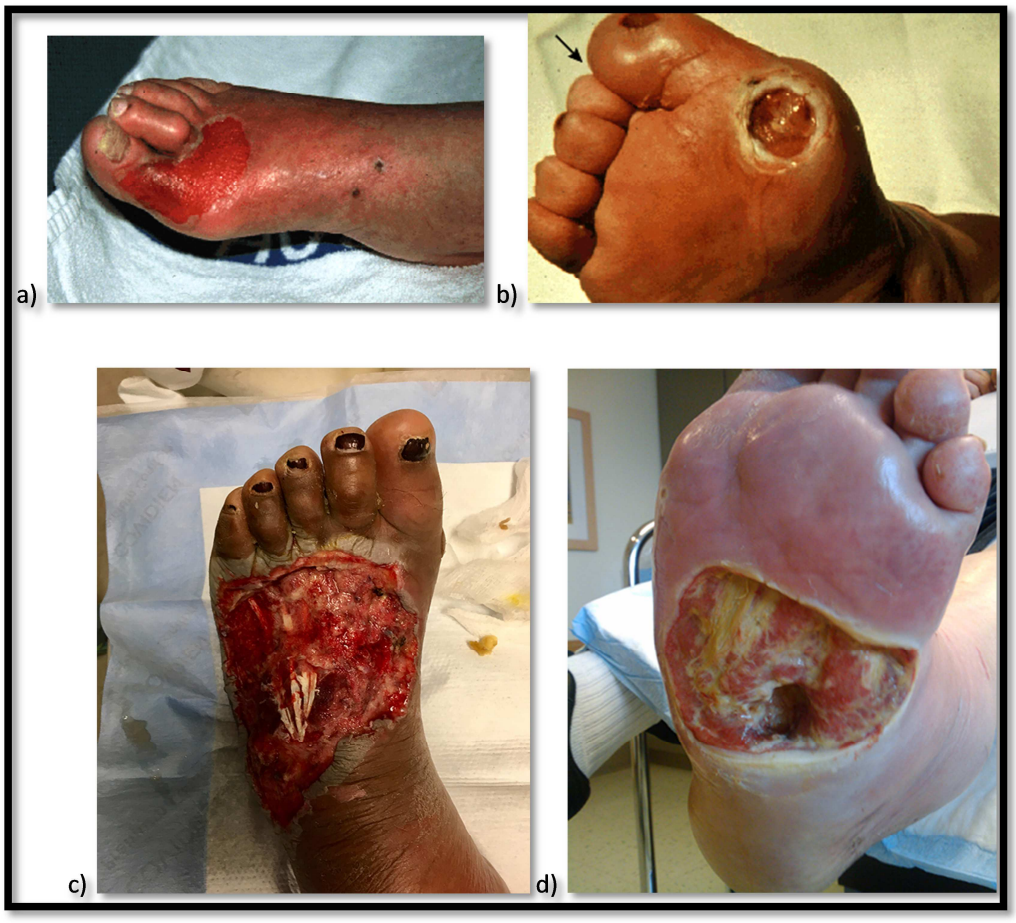


Figure 6: showing the grades of ulcer, a) grade 0, b) grade 1, c) grade 2 and d) grade 3.

Texas ulcer staging:

A. Noninfected

B. Infected

C. Ischemic

D. Infected and ischemic

Wagner, PEDIS and other organizations

Wagner[41] created an early and still widely used classification system at hyperbaric wound healing centres. This classification was only based on clinical evaluation (the depth of the ulcer and the presence of necrosis) and did not take into account diversity in the vascular state of the foot. The ulcers are classified as follows:

- Grade 0 : No lesion
- Grade 1: Superficial ulcer
- Grade 2: Deep ulcer - involves tendon, muscle, joint capsule, or bone
- Grade 3: Deep ulcer - abscess, osteomyelitis, or tendinitis
- Grade 4: Partial foot gangrene
- Grade 5: Whole foot gangrene

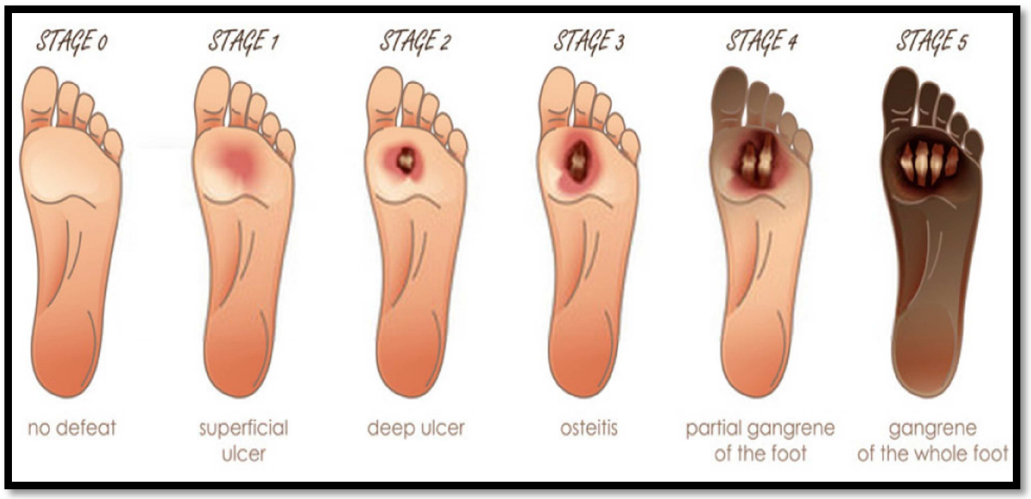


Figure 7: Stage wise evolution of diabetic foot ulcer

Healing of wound

"The response to the injury in healthy individual is inbuilt and is sequentially arranged process that result in the healing of wound with complete re-epithelialization, drainage of resolution and attainment of function to the affected tissue."

Factors effecting the wound healing[42,43]

Local factors

- Hypoxia
- Infection
- Foreign body
- Venous insufficiency

Systemic factors

- Diabetes mellitus
- Obesity
- Disease: jaundice, uremia, anemia, hereditary healing disorders
- Ischemia
- Alcoholism and smoking
- Poor nutrition
- Cancer
- AIDS
- Smoking
- Radiation therapy

Wound healing

The three overlapping stages of wound healing are remodeling, proliferation, and inflammation.[44]

Inflammatory phase: This phase involves hemostasis and inflammation. Upon skin injury, clotting cascades are immediately activated, forming a temporary fibrin blood clot plug at the wound site. Simultaneously, vasoconstriction occurs in the wounded area for 5 to 10 minutes, stopping further bleeding and protecting the wound. "The fibrin plug acts as a provisional matrix, aiding the migration of various cells like leukocytes, keratinocytes, fibroblasts, and endothelial cells, and serves as a reservoir for growth factors. Subsequently, vasodilation follows the initial vasoconstriction response, leading to local hyperemia and edema."

Damage that exposes collagen, tissue factor, and sub-endothelium causes platelets to aggregate and degranulate, releasing growth factors and chemotactic factors that finish hemostasis and start inflammation.[45–47]

Within the first twenty-four hours after the injury, neutrophils are drawn to the site and remain there for two to five days. They start the "process of phagocytosis, which macrophages subsequently carry out. Reactive oxygen species (ROS) and proteases are released by these phagocytic cells in order to eradicate nearby microorganisms and cleanse necrotic tissues. Neutrophils release pro-inflammatory cytokines that enhance the inflammatory response and function as chemoattractants for other cells."

After three days of damage, macrophages usually appear. They release a variety of growth factors, chemokines, and cytokines that promote cell division and the production of extracellular matrix (ECM) components.[47,48]

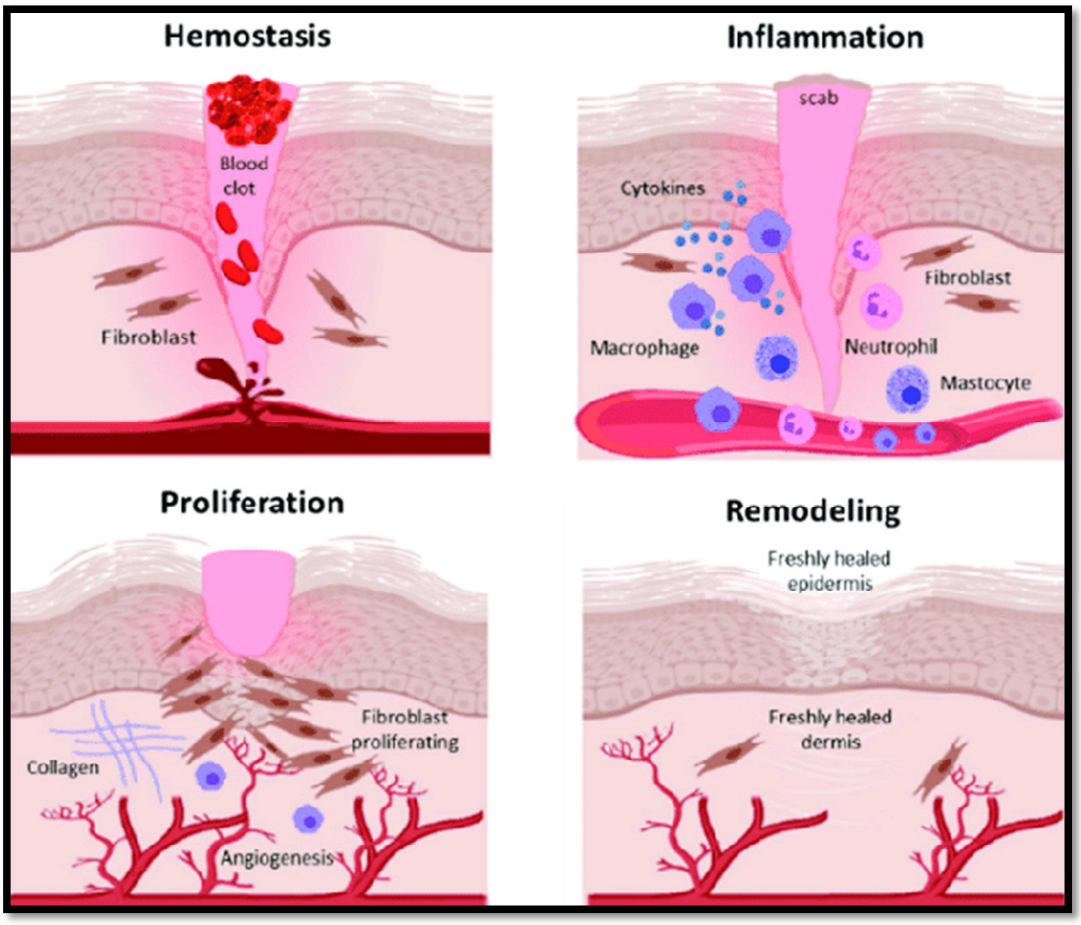


Figure 8: Phases of the wound healing process[49]

Proliferation

The proliferative phase, occurring around 3 to 10 days post-injury, is marked by granulation tissue formation and vascular network restoration. This phase, lasting from days to weeks, relies on various cytokines and growth factors, including members of the TGF-beta family, interleukins, and angiogenesis factors. Fibroblasts and endothelial cells are the key proliferating cells during this stage.

Adequate blood supply is crucial during cell proliferation, prompting an angiogenic response initiated by local hypoxia, VEGF, PDGF, bFGF, and thrombin. Angiogenesis involves the sprouting of new vessels from adjacent mature vessels, while vasculogenesis is a de novo process where endothelial progenitor cells (EPCs)

form new vessels without sprouting. EPC recruitment is initiated by factors like NO, VEGF, and MMPs, especially MMP-9, with SDF1-alpha guiding their homing to ischemic areas. This process ultimately establishes a new vascular network, facilitating nutrient and gas exchange. However, anti-angiogenic drugs like bevacizumab may disrupt this phase, contributing to chronic wound formation.[46,50]

Granulation tissue forms as fibroblasts go to the wound and multiply there in the latter stages of the proliferation phase. "They start forming a temporary matrix made of fibronectin, glycosaminoglycans, and type III collagen. This tissue has a distinctive red appearance because to the loosely distributed collagen bundles, granulocytes, macrophages, capillaries, and fibroblasts." The reason for its great vascularity is continuous angiogenesis.

Remodelling:

The remodelling phase, which marks the final stage of wound healing, typically begins around day 21 and can persist for up to a year.[45,46] During the remodelling phase, a delicate balance between tissue synthesis and degradation is crucial, as any disruption can lead to chronic wounds. As this phase progresses, granulation tissue formation ceases, and the wound enters a maturation phase. Components of the extracellular matrix (ECM) undergo specific modifications to form a stronger and more organized structure. Collagen type III, initially prevalent in the granulation tissue, is gradually replaced by the stronger collagen type I, contributing to increased wound tensile strength. For a minimum of four to five weeks, collagen synthesis persists; nevertheless, the injured region never reaches the same degree of organization as healthy skin. Specifically, hypoxia and a vitamin C deficit can impair wound strength since oxygen and vitamin C are necessary for the production of collagen. Enzymes that modify the matrix, in particular matrix

metalloproteinases (MMPs), play a crucial role in changing the local matrix milieu and promoting angiogenesis, migration, and proliferation of cells. Apoptosis occurs in the surviving cells from previous phases as the remodelling process goes on..[51,52]

After all, the reduction of angiogenic responses, blood flow, and acute metabolic activity in the wound allows the wound to close completely and regain its mechanical strength. Scar formation, which is intimately associated with inflammation, marks the end of wound healing. However, scar tissue typically exhibits certain deficiencies; for example, healed wounds never reach the strength of normal skin, with wound strength at three months and beyond reaching only about 80% of normal skin. Additionally, sub epidermal appendages like hair follicles or sweat glands do not regenerate after severe injuries, and scar tissue lacks rete pegs, which are vital for firm epidermal-dermal connection.[44,46]

Diabetes-related impaired wound healing is a significant problem that can be caused by a number of factors acting independently.

Mechanisms of Diabetes-Related Impairment in Wound Healing:

1. Hyperglycemia: Persistently high blood sugar levels can harm blood vessels, which lowers oxygen and blood flow to the area of wounding.
   - Increased blood sugar levels can also affect white blood cell function, which is crucial for preventing infection and removing debris from wounds.
2. Diabetic neuropathy: a condition that affects sensation distally, causing injuries unnoticeable.
   - Wounds can become worse with repeated impact and pressure on the feet.
3. Peripheral Artery Disease (PAD): Diabetes increases the risk of PAD, which damages blood vessels and decreases blood flow to the extremities, making it more difficult for wound healing agents to supply oxygen and nutrients.

4. Dysfunction of the Immune System: Diabetes impairs immunity, which makes it more difficult for the body to fight infections.
   - Hyperglycemia impairs neutrophils' capacity to carry out phagocytosis and eliminate bacteria.
5. Inflammation: Patients with diabetes frequently experience chronic inflammation, which can impede the natural healing process of wounds.
   - The passage from second to third phase of healing can be slowed down by an excessively vigorous inflammatory response.
6. Collagen Synthesis: Diabetes can affect the production of collagen and the process of cross-linking it, which weakens the healing of wounds.
   - The strength and structural integrity of the repaired tissue depend on collagen.
7. Oxidative Stress: - High blood sugar levels induce more reactive oxygen species (ROS) to be produced, which causes oxidative stress, which harms tissues and cells. The healing process may be further hindered by this oxidative damage.
8. Advanced Glycation End Products (AGEs): AGEs are produced when blood glucose levels are raised and have the potential to stiffen and lessen the flexibility of blood vessels.

AGEs can also obstruct signaling pathways and cellular processes that are essential to the healing of wounds

Management

1. Glycemic Control:
   - Maintaining blood glucose levels within a target range is fundamental to improving wound healing.

2. Wound Care:
   - Regular debridement to remove dead tissue.
   - Appropriate dressings to maintain a moist wound environment and protect from infection.
3. Infection Control:
   - Prompt treatment of infections with appropriate antibiotics.
   - Monitoring for signs of infection and managing promptly.
4. Enhancing Blood Flow:
   - Use of medications or procedures to improve blood flow, such as angioplasty or bypass surgery.
   - Use of vasodilators to improve circulation.
5. Advanced Therapies:
   - Hyperbaric oxygen therapy (HBOT) to increase oxygen delivery to the wound.
   - Growth factors and skin substitutes to promote healing.
   - Negative pressure wound therapy (NPWT) to remove excess fluid and promote tissue growth.
6. Patient Education and Self-Care:
   - Educating patients on proper foot care, including daily inspection and moisturizing.
   - Encouraging lifestyle changes to manage diabetes effectively, such as diet and exercise.
7. Multidisciplinary Approach:
   - Collaboration between endocrinologists, podiatrists, vascular surgeons to provide comprehensive care.

Local care

- Dressing
- Debridement

Adjunctive local therapies

- Negative pressure wound therapy
- Hyperbaric oxygen therapy
- Skin graft and substitutes
- Shock wave therapy
- Growth factors
- Topical oxygen therapy

Preventive care: Because diabetes increases the risk of underlying peripheral vascular disease, diabetic foot ulcers (DFUs) often go unnoticed until they reach an advanced stage, displaying more severe signs and symptoms. Diagnosing DFUs can be challenging due to neuropathy masking ischemia, and vice versa. Therefore, the main preventive measure involves regular screening of diabetic feet to detect DFUs early, allowing for prompt treatment initiation when needed. Early detection and intervention aim to prevent complications like gangrene which prevents amputation. Screening usually includes daily self-checks for trauma or ulceration by the patient and routine examinations during healthcare visits.[53]

The removal of necrotic tissue is critical for ulcer healing. The frequency of examination and correct care may be more important than the type of debridement in wound healing. A study on surgical debridement of chronic wound care among veterans found that when debridement was conducted at 80 percent of visits, the risk of diabetic ulcer healing rose 2.5-fold and doubled when ischemia was measured at the initial visit.[54,55]

Dressings: Following debridement, maintaining cleanliness and appropriate moisture levels in ulcers is crucial, ensuring they are not overly fluid-filled. Dressing selection should be customized based on ulcer characteristics like exudate levels, dryness, or presence of necrotic tissue. Some dressings primarily provide protection, while others promote wound hydration or prevent excessive moisture. Frequently utilized wet-to-dry saline dressings eliminates both viable and nonviable tissue, leaving the wound bed dry. As an alternative, many dressings include antimicrobial ingredients to ward against infection and promote ulcer healing. However, when comparing different dressing types for the treatment of diabetic foot ulcers, there is not enough high-quality data to demonstrate meaningful changes in wound healing results..[56,57]

By containing exudate, preventing infection, keeping the wound moist, and safeguarding it, dressings are essential to the management of DFUs.

The features of the ulcer, such as the quantity of exudate, the existence of infection, and the requirement for debridement, all influence the dressing choice.

Types of Dressings

1. **Hydrocolloid Dressings:**
    - **Composition:** Made from materials like gelatin, pectin, and carboxymethylcellulose that form a gel when in contact with wound exudate.
    - **Indications:** Suitable for low to moderate exudate wounds.
    - **Advantages:**
        - Provide a moist environment that promotes autolytic debridement.

- Can be left in place for several days, reducing the need for frequent changes.
- Offer a cushioning effect, protecting the wound from mechanical trauma.

- **Disadvantages:**
  - Not suitable for heavily exudating or infected wounds.
  - If not properly managed it can lead to skin maceration

2. **Foam Dressings:**
   - **Composition:** Polyurethane foam that absorbs and retains exudate.
   - **Indications:** Used for moderate to heavily exudating wounds.
   - **Advantages:**
     - Highly absorbent, reducing the risk of maceration.
     - Provide thermal insulation and cushioning.
     - Help maintain a moist wound environment conducive to healing.
   - **Disadvantages:**
     - May require frequent changing if exudate levels are very high.
     - Can be expensive compared to other types of dressings.

3. **Alginate Dressings:**
   - **Composition:** Made from seaweed-derived alginic acid, forming a gel upon contact with wound exudate.
   - **Indications:** Ideal for heavily exudating wounds and wounds with minor bleeding.
   - **Advantages:**
     - Highly absorbent, suitable for heavily exudating wounds.

- Promote hemostasis in bleeding wounds.
- Form a gel that maintains a moist wound environment and supports autolytic debridement.

- **Disadvantages:**
  - Require a secondary dressing to hold them in place.
  - Not suitable for dry wounds as they need moisture to activate.

4. **Hydrogel Dressings:**
   - **Composition:** Water-based gels that provide moisture to dry or necrotic wounds.
   - **Indications:** Suitable for dry, necrotic, or eschar-covered wounds.
   - **Advantages:**
     - Rehydrate and soften necrotic tissue, facilitating autolytic debridement.
     - Provide a cooling and soothing effect, reducing wound pain.
     - Promote granulation and epithelialization in dry wounds.
   - **Disadvantages:**
     - May cause maceration if overused.
     - Require frequent changes as they can dry out quickly.

5. **Antimicrobial Dressings:**
   - **Composition:** Contain antimicrobial agents like silver, iodine, or honey.
   - **Indications:** Used for infected or high-risk wounds.
   - **Advantages:**
     - Reduce bacterial load and infection risk.
     - Help manage wound bioburden and prevent biofilm formation.

- Some types, like honey dressings, also promote autolytic debridement.

- **Disadvantages:**
  - Can be expensive.
  - Potential for allergic reactions or sensitivities to the antimicrobial agents.

Debridement

Debridement is a critical step in the management of DFUs, involving the removal of necrotic, infected, or non-viable tissue to promote wound healing and reduce the risk of infection. Several methods of debridement can be employed, each with its specific indications and considerations.

Methods of Debridement

1. **Surgical Debridement:**
   - **Method:** Performed by a healthcare professional using surgical instruments such as scalpels, scissors, and curettes.
   - **Advantages:**
     - Quick and effective at removing large amounts of necrotic tissue.
     - Can be precisely targeted to remove only non-viable tissue while preserving healthy tissue.
     - Often necessary for heavily infected or extensive wounds.
   - **Disadvantages:**
     - Can be painful, requiring local or general anesthesia.
     - Risk of bleeding and damage to healthy tissue.
     - Requires skilled personnel and may need a sterile environment.

2. **Autolytic Debridement:**
    - **Method:** Utilizes the body's own enzymes and moisture-retentive dressings (like hydrocolloids or hydrogels) to break down necrotic tissue.
    - **Advantages:**
        - Non-invasive and less painful compared to surgical debridement.
        - Selective, targeting only necrotic tissue while preserving healthy tissue.
        - Can be performed at home under medical supervision.
    - **Disadvantages:**
        - Slower process, taking days to weeks for effective debridement.
        - Cannot be used for infected wounds as it requires an intact immune response.
3. **Enzymatic Debridement:**
    - **Method:** Application of topical enzymatic agents (e.g., collagenase) that selectively digest necrotic tissue.
    - **Advantages:**
        - Effective and selective, targeting necrotic tissue without harming healthy tissue.
        - Can be combined with other types of dressings to enhance debridement.
    - **Disadvantages:**
        - Expensive, requiring prescription products.
        - May need frequent application and careful monitoring for adverse reactions.

4. **Mechanical Debridement:**
    - **Method:** Involves physical removal of tissue using methods like wet-to-dry dressings, hydrotherapy (whirlpool baths), or ultrasonic devices.
    - **Advantages:**
        - Can be effective for removing loose, non-adherent necrotic tissue.
        - Wet-to-dry dressings are simple and inexpensive.
        - Ultrasonic devices can enhance the debridement process and are less painful.
    - **Disadvantages:**
        - Wet-to-dry dressings can be painful and may also remove healthy tissue.
        - High risk of nfection and maceration.
        - Requires specialized equipment and expertise for ultrasonic devices.

5. **Biological Debridement:**
    - **Method:** Uses sterile maggots (larvae of the green bottle fly) to consume necrotic tissue.
    - **Advantages:**
        - Highly selective, removing only necrotic tissue and leaving healthy tissue intact.
        - Maggots secrete enzymes that break down necrotic tissue and promote healing.
        - Can be effective for wounds with extensive necrosis or infection.

- **Disadvantages:**
    - May be uncomfortable or unacceptable to some patients.
    - Requires a controlled environment and careful management.
    - Less commonly available and may be more expensive.

Adjunct Local Therapy

Adjunct local therapies are extra therapies that can speed up the recovery process of DFUs. These therapies can be used in conjunction with dressings and debridement to optimize wound healing.

Types of Adjunct Local Therapy

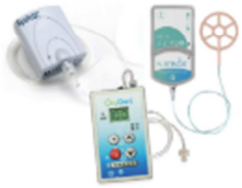
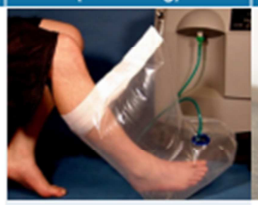
1. **Negative Pressure Wound Therapy (NPWT):**
    - **Method:** Applies controlled negative pressure to the wound via a sealed dressing connected to a vacuum pump.
    - **Advantages:**
        - Promotes granulation tissue formation and wound contraction.
        - Reduces edema and removes excess exudate and infectious material.
        - Enhances perfusion and oxygenation to the wound site.
    - **Disadvantages:**
        - Can be costly and requires specialized equipment and training.
        - Risk of wound desiccation and damage to surrounding skin if not properly managed.
        - Not suitable for all wound types, such as untreated osteomyelitis or exposed organs.

2. **Hyperbaric Oxygen Therapy (HBOT):**
    - **Method:** Involves breathing pure oxygen in a pressurized chamber, increasing oxygen delivery to tissues.
    - **Advantages:**
        - Promotes wound healing by enhancing oxygenation and angiogenesis.
        - Helps fight infection by increasing the efficacy of leukocytes and antibiotics.
        - Can be beneficial for chronic, non-healing wounds.
    - **Disadvantages:**
        - Expensive and time-consuming, requiring multiple sessions.
        - Limited availability, often requiring referral to specialized centers.
        - Potential side effects, including barotrauma and oxygen toxicity.

3. Topical Oxygen Therapy (TOT)

Delivery systems for topical oxygen treatment Three broad categories of TOT delivery systems exist, all of which provide home-based or ambulatory treatment:one that produces continuous oxygen delivery (CDO) at extremely low pressures; two that produce low constant pressure delivery in a confined chamber; and three that produce greater cyclically pressured and humidified delivery in a contained extremity chamber.[32,34].

TABLE 2 Types of Topical Oxygen Devices

CONTINUOUS DELIVERY	LOW CONSTANT PRESSURE (22 mmHg)	CYCLICAL PRESSURE (10–50 mbar)
		
▸ Generally enhanced healing in three formal RCTs ▸ Several case studies ▸ Cohort studies ▸ Tissue studies for cytokine levels	▸ Retrospective database studies ▸ Case series, animal study	▸ Robust sham controlled RCT showing improved healing at both 12 weeks and 12 months ▸ Multiple prospective studies ▸ Real-world evidence showing reduced hospitalizations and amputations at 360 days
▸ Low continuous flow of oxygen (3–15 mL/hour) ▸ Sealed, disposable dressing, changed weekly; low Po_2 diffusion gradient ▸ No compression or humidification, but moisture-retentive dressing	▸ Low oxygen flow and low constant pressure (22 mmHg) ▸ Extremity chamber ▸ Minimal compression ▸ No humidification	▸ High oxygen flow rate and pressure provides deeper oxygen penetration into wound bed ▸ Higher diffusion gradient ▸ Cyclical pressure reduces edema and stimulates angiogenesis, enhances oxygen-dependent enzymes ▸ Cyclical compression ▸ Humidification as needed

CDO devices apply topical continuous diffusion of non-pressurized oxygen through small cannulas to semi-occlusive or proprietary wound dressings. Small, portable, battery-powered electrochemical oxygen generators supply a continuous flow of pure oxygen over the wounds 24 hours per day at a flow rate of up to 15 mL/hour. The low-constant-pressure (22- mmHg) device uses an oxygen concentrator to deliver oxygen in a simple plastic boot that is placed over the extremity with the ulcer. The third system differs from the other devices in being a multimodality approach that applies cyclically pressurized (10–50 mbar) oxygen within a disposable extremity chamber connected to a controller unit and oxygen concentrator. Humidity can be added to this system if required. The higher Po2 produced especially by the latter devices results in a larger pressure gradient that promotes the diffusion of

oxygen molecules into the hypoxic wound tissue, thereby enhancing multiple molecular and enzymatic functions (32, 34).

4. **Topical Growth Factors:**
    - **Method:** Application of growth factors like platelet-derived growth factor (PDGF) to the wound.
    - **Advantages:**
        - Stimulates cellular proliferation, angiogenesis, and wound healing.
        - Can be particularly useful for chronic, non-healing wounds.
        - Some products are available as gels or dressings, making them easy to apply.
    - **Disadvantages:**
        - High cost and limited availability.
        - Potential for adverse reactions or allergic responses.
        - Requires careful selection and monitoring for efficacy.

5. **Antimicrobial Agents:**
    - **Method:** Use of topical antibiotics or antiseptics to reduce bacterial load.
    - **Advantages:**
        - Effective in managing and preventing infection in wounds.
        - Some agents, like silver, have broad-spectrum antimicrobial activity.
        - Can be incorporated into various types of dressings for ease of use.

- **Disadvantages:**
  - Risk of developing antibiotic resistance with prolonged use.
  - Potential for allergic reactions or sensitivities.
  - Requires careful selection to avoid cytotoxic effects on healing tissues.

6. **Electrical Stimulation:**
   - **Method:** Application of electrical currents to the wound to promote healing.
   - **Advantages:**
     - Enhances cell proliferation, blood flow, and collagen synthesis.
     - Can reduce pain and inflammation associated with chronic wounds.
     - Non-invasive and can be combined with other therapies.
   - **Disadvantages:**
     - Requires specialized equipment and expertise.
     - Limited availability and might not be appropriate for every patient
     - Needs regular sessions for optimal results.

7. **Bioengineered Skin Substitutes:**
   - **Method:** Use of synthetic or biological skin equivalents to cover the wound.
   - **Advantages:**
     - Provide a temporary or permanent barrier that protects the wound and promotes healing.

- Can stimulate the body's own healing processes and reduce healing time.
- Useful for large or complex wounds that are difficult to heal with conventional methods.

- **Disadvantages:**
  - Can be expensive and require multiple applications.
  - Risk of rejection or adverse reactions.
  - Need for specialized training and handling.

Amputation in diabetic foot ulcer (DFU) patients is a significant concern due to the complications associated with advanced diabetic complications such as neuropathy, peripheral vascular disease, and impaired wound healing. Here are some scientific details about amputation in DFU patients:

Prevalence and Risk Factors: The prevalence of amputation in DFU patients varies depending on factors such as the severity of diabetes, duration of ulceration, presence of neuropathy, and adequacy of vascular supply to the affected limb. Patients with poorly controlled diabetes, long-standing ulcers, and peripheral neuropathy are at higher risk of requiring amputation. Risk factors for amputation in DFU patients include advanced age, long duration of diabetes, poor glycemic control, smoking, hypertension, renal insufficiency and previous foot ulcers or amputations.

Indications for Amputation: Amputation may be indicated in DFU patients when conservative measures fail to control infection, promote wound healing, or salvage the affected limb. Common indications include extensive tissue necrosis, uncontrollable infection, gangrene, and severe ischemia. The decision for amputation should be made in collaboration with the patient and involve consideration of factors such as overall health status, functional status, and quality of life.

Levels of Amputation: The level of amputation required depends on the extent and severity of tissue involvement. It may range from toe or forefoot amputation to midfoot, hindfoot, or even below-the-knee or above-the-knee amputation in severe cases. The choice of the level of amputation depends on factors such as the extent of tissue involvement, severity of infection, adequacy of blood supply, and functional goals. Partial foot amputations, such as toe or ray amputations, are often considered first-line options to preserve as much foot function as possible.

Surgical Techniques: Various surgical techniques may be employed depending on the extent of tissue involvement and the goal of amputation. These techniques may include guillotine amputation, where the affected part is removed in a single stage, or staged amputation, where multiple procedures are performed to achieve optimal wound healing and functional outcomes.

Post-Amputation Care: Post-amputation care is crucial for optimizing outcomes and preventing complications such as wound infection, delayed healing, and secondary amputations. It involves wound care, pain management, rehabilitation, and patient education on proper stump care and prosthetic use. Pain management is crucial in the post-amputation period to alleviate phantom limb pain and promote patient comfort. Rehabilitation programs focusing on physical therapy, occupational therapy, and prosthetic training are essential to optimize functional outcomes and facilitate adaptation to life with limb loss.

Prognosis and Complications: The prognosis following amputation in DFU patients is variable and depends on factors such as the patient's overall health, comorbidities, and adequacy of post-operative care. Complications may include wound dehiscence, infection, phantom limb pain, and psychological distress.

Preventive Strategies: Given the significant morbidity and mortality associated with amputation in DFU patients, preventive strategies are essential. These may include regular foot examinations, patient education on foot care and diabetes management, early detection and treatment of ulcers, optimization of glycemic control, and multidisciplinary diabetic foot care teams comprising podiatrists, vascular surgeons, endocrinologists, and wound care specialists.

Overall, amputation in DFU patients is a complex clinical decision that requires careful consideration of various factors to achieve optimal outcomes and preserve limb function and quality of life. Early detection, aggressive wound management, and comprehensive multidisciplinary care are key components in reducing the need for amputation and improving long-term prognosis in diabetic foot ulcer patients.

Various studies discussing the risk factors for amputation in diabetic foot:

In a study conducted by Sun JH et al., (2012) to assess the risk factors for lower extremity amputation in diabetic foot disease classified by Wagner classification. Out of 789 participants in the study, 19.9% underwent major lower extremity amputation (LEA) and 22.9% underwent minor LEA. Reduced ankle-brachial index (ABI), elevated Wagner grade, serum albumin, hemoglobin levels, and elevated white blood cell (WBC) count were found to be substantially linked to an increased risk of lower limb amputation (LEA). According to Wagner classification stratification, these risk variables were more prevalent in grade 3 instances associated with estimated glomerular filtration rate (eGFR). For grades 2 and 4, on the other hand, WBC count was the main predictor. The risk factors for LEA are therefore greatly influenced by the Wagner classification, with low ABI, albumin, and eGFR being the most important conventional predictors in Wagner grade 3 patients.[58]

In a study conducted by Pscherer S et al., (2012) to assess the amputation rate and risk factors in T2DM with diabetic foot. The overall occurrence of lower limb amputations linked to diabetes reached 18.2%. Factors such as advanced age, male gender, elevated HbA1c levels, and prolonged diabetes duration, along with other diabetes-related complications, were independently correlated with amputations. Regarding discussion, it's noteworthy that while diabetic foot syndrome can potentially result in lower limb amputation, it's not an inevitable outcome. Given the significant medical and economic strain diabetic complications impose on healthcare systems, early therapeutic measures are crucial for patients grappling with diabetic foot syndrome.[59]

In a retrospective cohort study conducted by Al-Rubeaan K et al., (2015) to assess the diabetic foot complication and risk factors associated with the disorder. The overall prevalence of diabetic foot complications was 3.3%, with foot ulcer, gangrene, and amputation prevalences at 2.05%, 0.19%, and 1.06%, respectively. Prevalence increased with age and diabetes duration, particularly among male patients. Although more common in type 2 diabetes, diabetic foot was found to be more prevalent in type 1 diabetes. Univariate analysis revealed significant risk factors including Charcot joints, peripheral vascular disease, neuropathy, longer diabetes duration, insulin use, retinopathy, nephropathy, older age, cerebral vascular disease, poor glycemic control, coronary artery disease, male gender, smoking, and hypertension, with odds ratios ranging from 1.51 to 42.53. These findings emphasize the need for primary and secondary prevention programs to reduce morbidity, mortality, and economic burden associated with diabetic foot complications, with considerations such as nerve decompression among diabetic patients.[60]

In a case-control study conducted by Kogani M et al., (2015) to assess the risk factors for amputation in patients with DFU. A total of 262 controls and 131 cases were compared. According to the adjusted model, amputation in diabetic patients was associated with sex fewer than two annual hemoglobin A1c (HbA1c) tests, smoking, ill-fitting footwear, and body mass index. In summary, the most important risks linked to amputation were found to be smoking, women, unsuitable footwear, and sporadic HbA1c monitoring. The creation of educational initiatives and initiatives to raise the standard of care for diabetes patients are necessary to address these problems. [61]

In a meta-analysis study conducted by Namgoong S et al., (2016) to assess the risk factors associated with major amputation in DFU patients. Twenty-two of the study's 26 risk variables had significant differences when analysed univariately. Six of them were found to be statistically significant predictors of major amputation in diabetic foot patients by stepwise multiple logistic analysis. The odds ratios that were adjusted for multiple variables were as follows: 11.673 for bone-piercing ulcers, 8.683 for dialysis patients, 6.740 for gastrointestinal issues, 6.158 for ulcers on the back of the foot, 0.641 for low hemoglobin levels, and 1.007 for high fasting blood sugar levels. Thus, the following conditions became important indicators of substantial amputation risk: low hemoglobin, high fasting blood sugar, GI problems, bone-invading ulcers, dialysis, and hind foot ulcers.[62]

In a study conducted by Santos V et al., (2016) to assess the risk factors for primary major amputation in diabetic patients. Age, Wagner grade 5 lesions, ascending lymphangitis, chronic arterial insufficiency without revascularization potential, and duration of diabetes were significant risk factors for severe amputation. The presence of gram-positive germs was associated with the need for major amputation, whereas levels of white blood cells, serum urea, creatinine, and glucose

did not show up as significant risk factors. Finally, age, ascending lymphangitis, calcaneal lesions, vascular insufficiency, Wagner grade 5 lesions, duration of diabetes, and Gram-positive bacteria in cultures were shown to be the main risk factors for amputation.[63]

In a study conducted by Sadriwala Q et al., (2018) to assess the risk factors of amputation in diabetic foot infections. The study comprised 64 patients, "with a 39.1% amputation rate. Statistical significance was found for poor glycemic control, osteomyelitis, vasculopathy, peripheral neuropathy, and Wagner grading. In summary, poor glycemic control, vasculopathy, peripheral neuropathy, and higher Wagner grade were identified as notable risk factors for amputation in diabetic foot infections" based on this study's findings.[3]

In a meta-analysis study conducted by Sen P et al., (2019) to assess risk factors for amputation in diabetic foot infections. In a comprehensive review comprising 2471 potential articles meeting inclusion criteria, 25 articles were included in the final analysis, revealing 6132 patients with diabetic foot infections (DFIs), of whom 1873 underwent amputation. Several risk factors were identified for amputation in DFI patients, including male gender, smoking, history of amputation or osteomyelitis, peripheral arterial disease, retinopathy, and specific grading systems such as IWGDF and Wagner grades. Additionally, gangrene/necrosis, neuroischaemic DFI, severe infection, length of hospitalization, leukocytosis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, tissue culture positivity, and isolation of Gram-negative bacteria were predictors of amputation. These findings underscore the need for tailored risk assessment and management strategies for DFI patients, potentially informing the development of new classification systems to identify high-risk individuals and optimize clinical outcomes.[64]

In a study conducted by Bal BS et al., (2019) to assess the risk factors for lower limb amputation in DFU patients. The majority of patients in group B hailed from rural areas and had a lower socioeconomic status. The duration of diabetes (p=0.017) and diabetic foot ulcers (DFU) was notably longer in group B (P <0.001). Group B also exhibited a significantly higher proportion of patients with Wagner Grade 4 and 5 ulcers compared to group A (P <0.001). Wound infections and presence of maggots were significantly more prevalent in group B, although polymicrobial infections were more common in group A. While biochemical investigations showed abnormalities, the variance between the two groups was not significant. In conclusion, alleviating the socioeconomic burden associated with lower extremity amputations (LEA) can be achieved by enhancing awareness among diabetic patients regarding foot hygiene, ensuring regular medical check-ups for diabetes management and addressing associated complications.[2]

In a study conducted by Umashankar G et al., (2019) to assess predictors for lower extremity amputation in patients with DFU. Study concluded that PEDIS Score > 7 is a highly significant predictor of amputation of diabetic foot ulcer and an integrated risk assessment model including the risk factors which are strongly associated with amputation like PVD, past amputation, nephropathy, past ulceration, ulcer duration, TLC, Hb and serum creatinine and PEDIS Score can be developed to predict adverse outcome(amputation) in diabetic foot ulcer patients which is needed to provide an opportunity to save the limb.[1]

In a meta-analysis study conducted by Lin C et al., (2020) to assess the risk factors for lower extremity amputation in patients with diabetic foot ulcers. This meta-analysis of 21 studies involving 6505 participants, including 2006 patients requiring lower limb amputation, revealed several factors associated with an increased

risk of amputation in diabetic foot ulcer (DFU) patients. These included male sex, smoking history, history of foot ulcers, osteomyelitis, gangrene, lower body mass index, and higher white blood cell count. Notably, age, type of diabetes, hypertension, and HbA1c level were not associated with amputation risk. Gangrene notably escalated the risk of amputation rapidly. These findings underscore the importance of early identification and intervention for DFU patients at heightened risk of amputation, potentially informing targeted preventive strategies to mitigate adverse outcomes. [65]

In a study conducted by Rodrigues B et al., (2022) to assess the prevalence and risk factors associated with lower limb amputation in DFU patients. Sixteen full-text published studies underwent review, revealing a high prevalence of lower limb amputations (LLAs), reaching up to 66%. Using the random-effects model, the combined prevalence was estimated at 19% (95% CI 10–29). Key risk factors (RFs) for LLAs included duration of diabetes mellitus (DM), age, renal impairment, and belonging to an ethnic minority. Particularly among Australians, Indigenous background exhibited a strong association with increased risk of diabetic foot (DF) LLAs. In conclusion, LLAs are notably prevalent among patients with DF, with even higher rates observed among those with multimorbidity.[66]

In a cohort study conducted by Demirkol D et al., (2022) to assess the risk factors for amputation in patients with diabetic foot ulcer. Patients who underwent major or minor amputation exhibited notably “higher mean levels of C-reactive protein (CRP) and White Blood Cell (WBC) compared to those who did not undergo amputation. Additionally, patients with major amputation had significantly elevated mean Neutrophil (PNL), Platelets (PLT), wound width, creatinine, and sedimentation (ESR) values compared to other patient groups. Conversely, increased levels of High-

density lipoprotein (HDL), Hemoglobin (HGB), and albumin were identified as protective factors against amputation risk." Spearman correlation analysis further demonstrated a strong, significant positive relationship between Wagner grades and patients' amputation status. In conclusion, this study delineated specific factors associated with major and minor amputation risk in patients with diabetic foot ulcers (DFUs), highlighting infection markers such as CRP, WBC, ESR, and PNL as prominent indicators in the amputation group. Notably, Meggit Wagner classification emerged as highly correlated with patients' amputation risk, underscoring its importance among the various classification systems for DFUs.[67]

MATERIALS AND METHODS

Source of Data: Study was conducted among patients with diabetic foot at a tertiary health care centre in Belagavi

Study Design: Prospective observational study

Study Period: 1st January 2023 to 31st December 2023

Sample Size: 60

The minimum sample size formula based on prevalence rate is

$$n = \frac{z_\alpha^2 P(1-P)}{d^2}$$

where P is the prevalence rate and d is the percentage likely difference in the prevalence.

z_α is linked with the level of significance. For 5% level of the significance $z_\alpha = 1.96$.

Ref: Prevalence of Foot Complications in People with Type 2 Diabetes Mellitus: A Community-Based Survey in Rural Udupi [9]

The parameter considered in the calculation is the prevalence rate of diabetic foot syndrome which is 51.8%

With P = 51.8% and d = 25% of P = 12.95%, the sample size is 57.

To round of sample size will be increased to 60.

To make the study more consistent the sample size was raised to 60.

Inclusion Criteria: Patients with "diabetes mellitus willing to give written and informed consent, of either sex with foot infections defined as infection of soft tissue in diagnosed case of diabetes mellitus with or without treatment and newly-diagnosed diabetics, of age group 18-70years, were included in the study."

Exclusion Criteria:

- Those suffering from HIV, Hepatitis B, Hepatitis C Positivity, psychiatry disorders
- Pregnant and lactating females
- Patients receiving immunosuppressive therapy and radiotherapy.

Study protocol: After obtaining institutional ethical committee clearance and written informed consent, thorough history and examination findings were obtained. The demographic information of each patient, such as age, gender, history of smoking, and any recent foot trauma, were research variables. "The Wagner grading system was used to categorize all illnesses (Figure 1). Hemoglobin (Hb), glycosylated hemoglobin (HbA1c), total leucocyte count (TLC), serum creatinine, and fasting blood sugar levels were measured as part of baseline studies. An X-ray of the foot was taken to evaluate osteomyelitis characteristics. Ankle brachial index (ABI) was calculated using a hand-held doppler to assess peripheral artery disease (PAD). Ankle reflexes, point pressure with 10gm monofilament at 9 locations, and vibration perception [128 Hz tuning fork] at 2 sites were used to assess the existence of neuropathy." The adequacy of arterial blood supply were determined by the palpation of dorsalis pedis and posterior tibial artery pulsations. Patients were followed up every week for at least 3 months or till amputation. Amputation, which is defined as the total loss of any

lower limb portion in the transverse anatomical plane, was the primary outcome factor.

Data collection procedure: The study was conducted among patients with diabetic foot admitted in a tertiary health care centre, Belagavi from 1st January 2023 to 31st December 2023

Does the study require any investigations or interventions to be conducted on patients or other humans or animals? If so, please describe briefly.

Yes

"Baseline investigations including hemoglobin (Hb), Glycosylated hemoglobin (HbA1c), total leucocyte count (TLC), serum creatinine and fasting blood sugar levels.

X-ray of foot

Ankle brachial index (ABI) measurement using a hand held doppler"

STATISTICAL ANALYSIS

The mean and standard deviation for the continuous quantitative variables were computed. When comparing data that has been split into two groups based on a particular qualitative attribute, appropriate statistical procedures such as the student's unpaired t test were used to compare the continuous variables. The student's paired t test was used to compare the pre- and post-treatment measures. Rates, ratios, and percentages were used to express the categorical data. Fisher's exact test, the Chi-square test, or the test of proportion were used to examine the relationship between the result, clinical, and demographic factors. Apart from the above suitable tools like ANOVA, correlation, multivariate regression etc., were used according to the need. For all the tests the value of p less than 5% (0.05) was considered significant.

RESULTS

In present study total of 60 patients fulfilling inclusion criteria were included with mean age of 54±12.3yrs.

Table 1: Showing mean age of patients

	Mean	SD
Age (yrs)	54.0	12.3

Table 2: Gender distribution among patients

		Count	N %
Gender	Female	15	25.0%
	Male	45	75.0%

Among them 75% were male and 25% were female with male preponderance in the study.

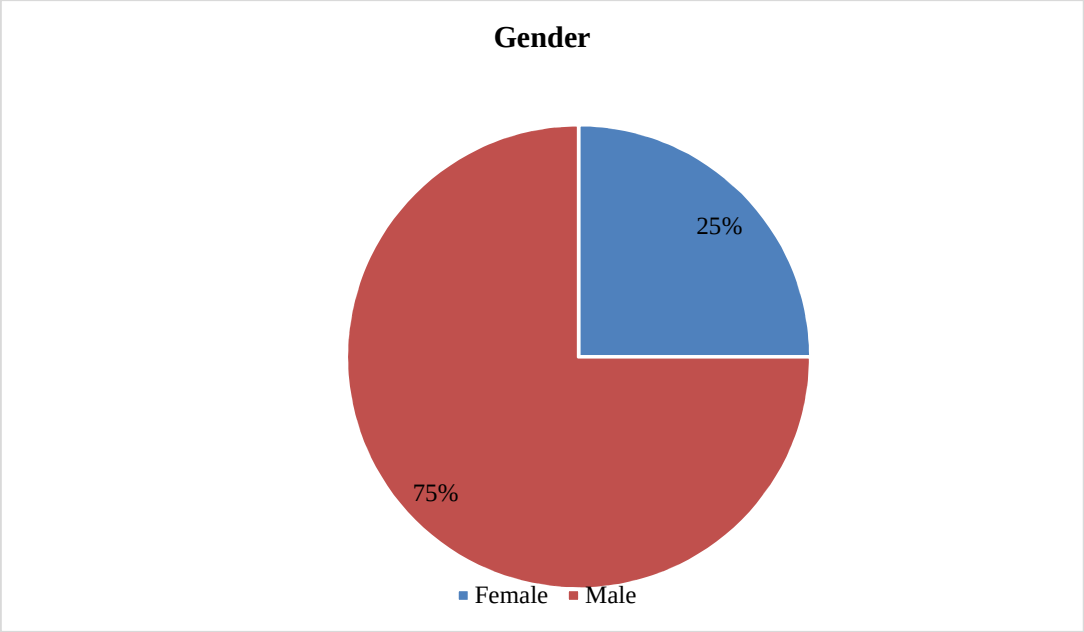


Figure 9: Showing gender distribution

Table 3: Showing presence of comorbidities

		Count	N %
Comorbidities	HTN	7	11.7%
	IHD	4	6.67%
	CVA	1	1.67%

In the study sample population 11.7% had hypertension, 6.67% had ischemic heart disease and 1.67% had history of cerebrovascular accident.

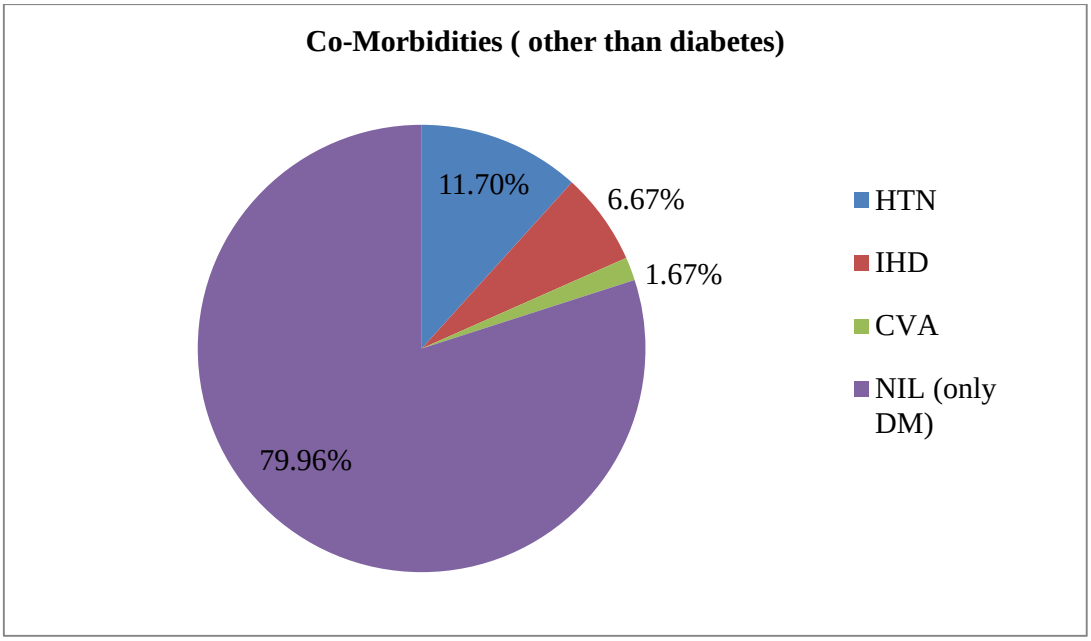


Figure 10: Showing presence of comorbidities

Table 4: Showing history of trauma

		Count	N %
History of trauma	Absent	19	31.7%
	Present	41	68.3%

History of trauma was present in 68.3% of the patients

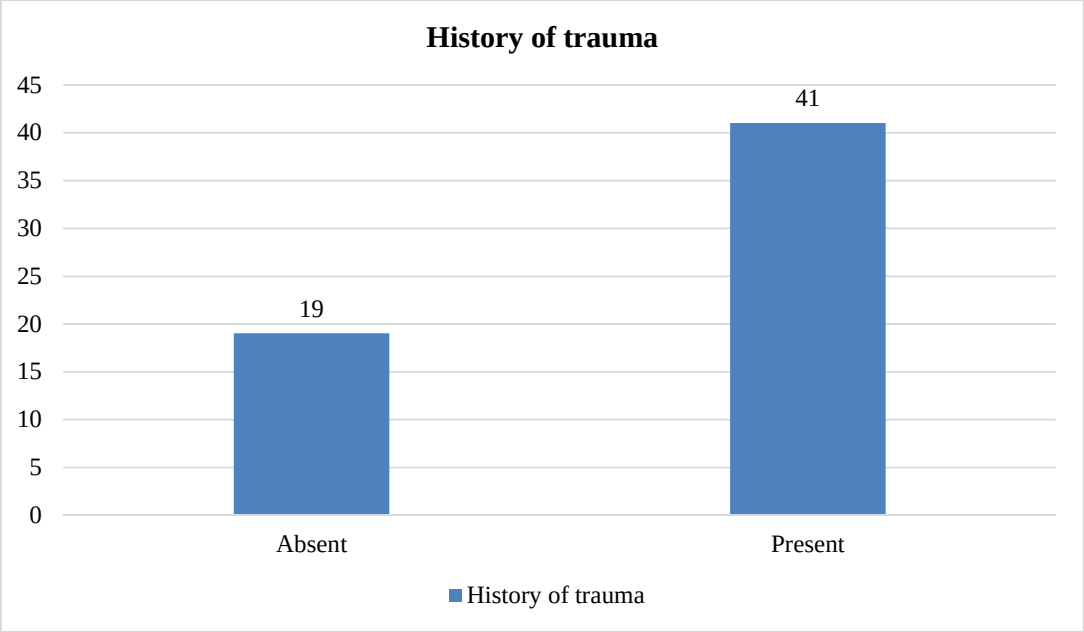


Figure 11: Showing history of trauma

Table 5: Showing presence of smoking history among patients

		Count	N %
Smoker	NO	37	61.7%
	YES	23	38.3%

History of cigarette smoking is present in 38.3% of the patients in this study.

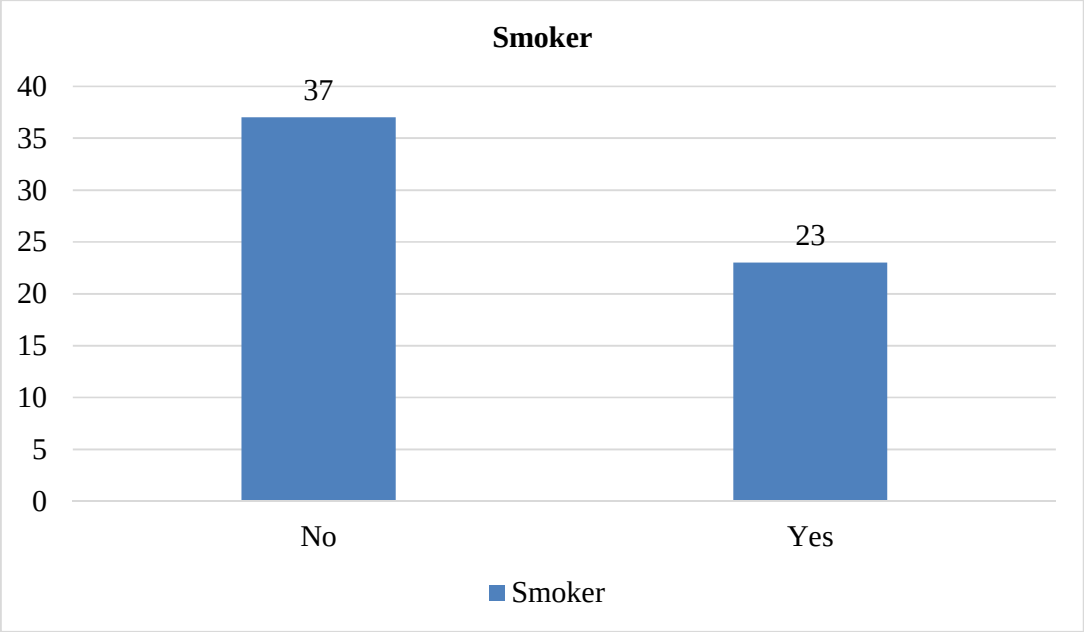


Figure 12: Showing presence of smoking history among patients

Table 6: Showing the Wagner's grade among patients

		Count	N %
Wagner's grade	Grade 2	32	53.33%
	Grade 3	26	43.33%
	Grade 4	2	3.33%

According to wagner's grade, majority were in grade 2, followed by grade 3 and grade 4.

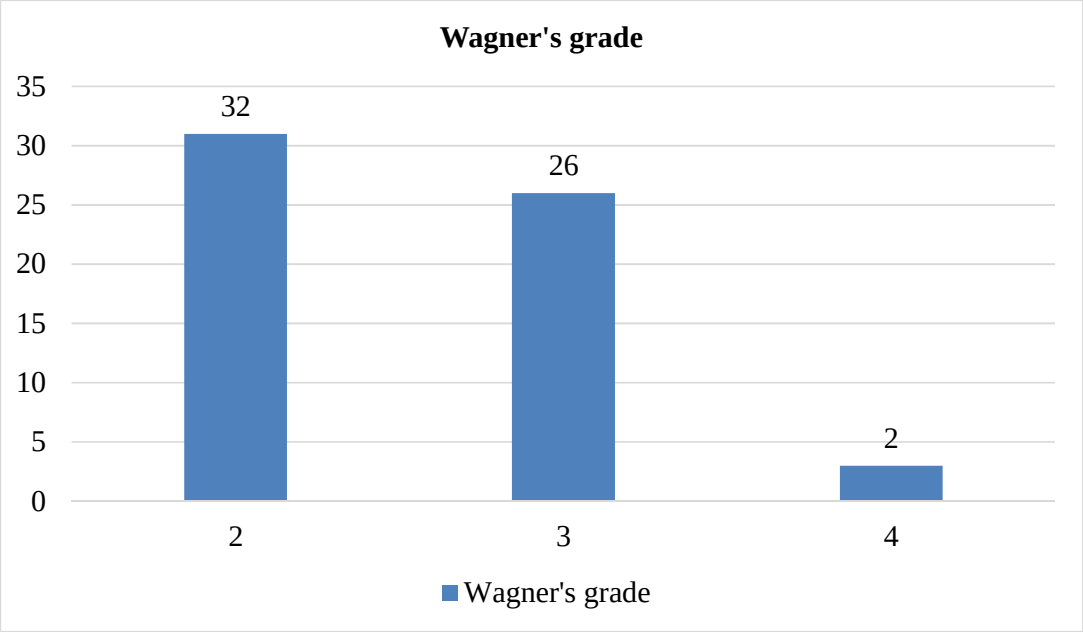


Figure 13: Showing the Wagner's grade among patients

Table 7: Showing presence of peripheral neuropathy among patients

		Count	N %
Peripheral neuropathy	Absent	17	28.3%
	Present	43	71.7%

Peripheral neuropathy was present in 71.7% of the patients.

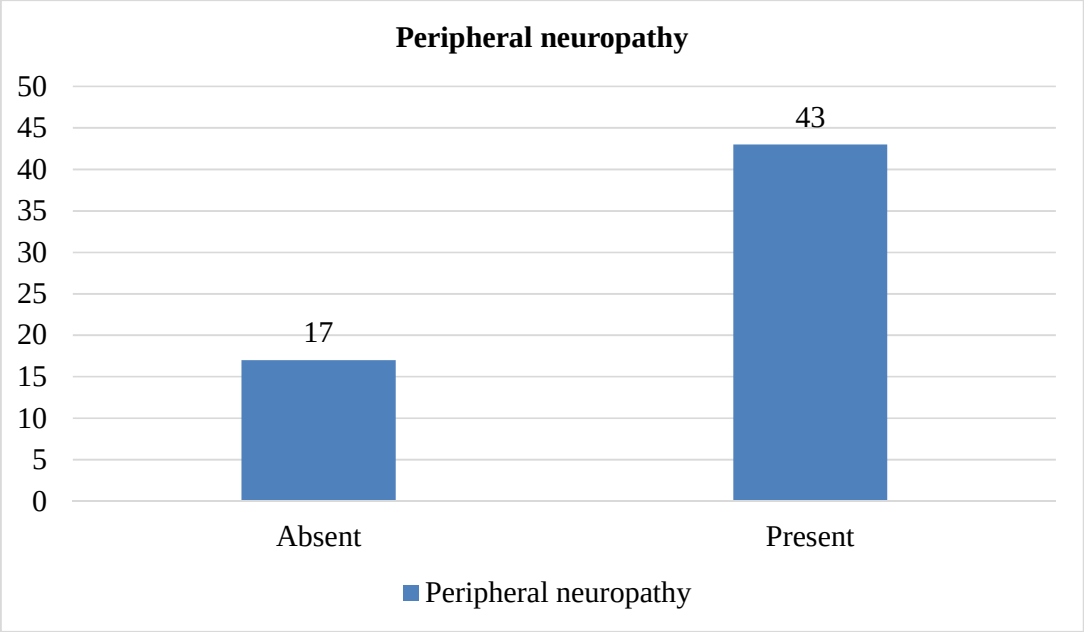


Figure 14: Showing presence of peripheral neuropathy among patients

Table 8: Distribution of patients according to ABPI

		Count	N %
ABPI	<0.9	25	41.7%
	>0.9	35	58.3%

ABPI was <0.9 in 41.7% of the patients and >0.9 in 58.3% of the patients.

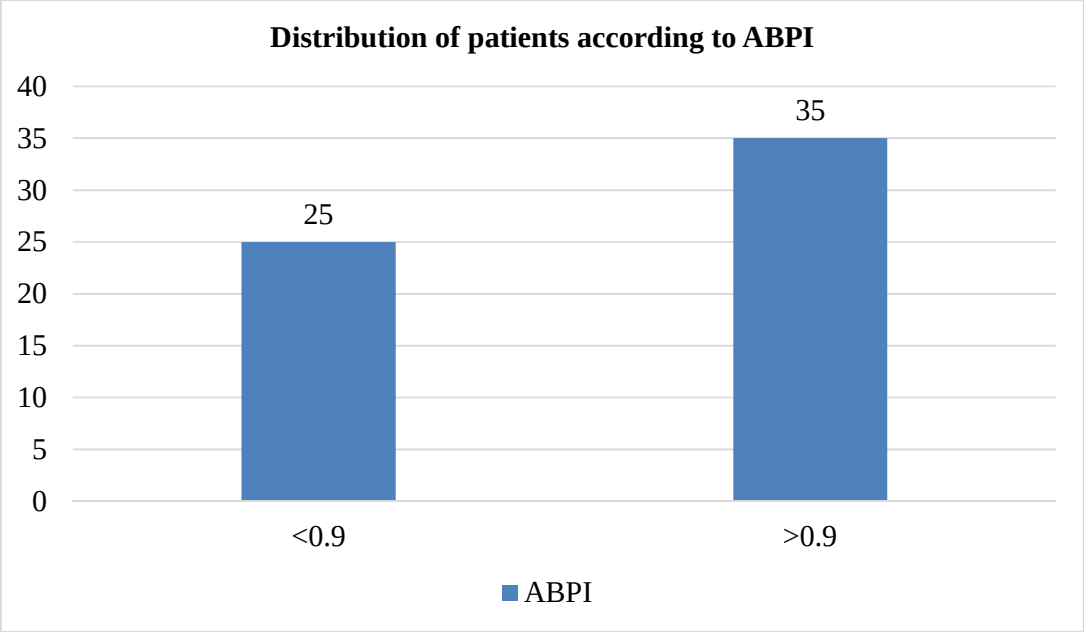


Figure 15: Distribution of patients according to ABPI

Table 9: Showing mean level of the blood parameters among patients

	Mean	SD
Hb	11.3	1.7
TLC	13291.1	6565.0
S. Creatinine	1.38	.71
FBS	152.3	67.6
HbA1C	8.02	1.78

Table showing the blood parameter mean level.

Table 10: Showing X-ray findings among patients

		Count	N %
X-ray foot	Both bone fracture right leg - ORIF plate present	1	1.7%
	Fracture tibia	1	1.7%
	Normal	53	88.3%
	Osteomyelitis present	5	8.3%

Among the patients, x-ray foot showing presence of normal findings in 88.3% of the patients and 8.3% with osteomyelitis findings.

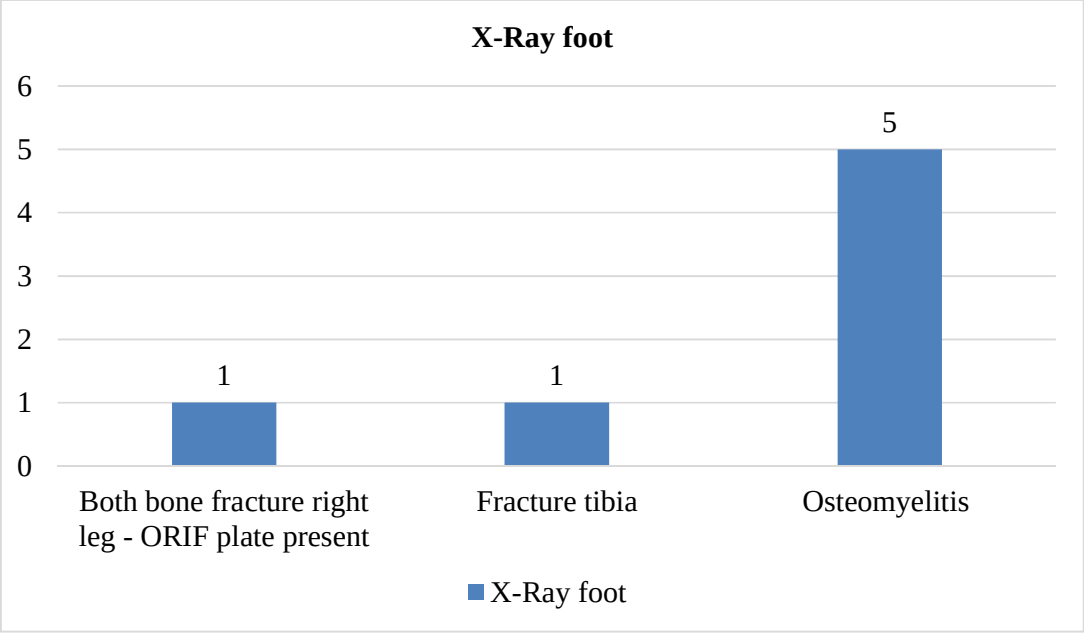


Figure 16: Showing X-ray findings among patients

Table 11: Showing presence of amputation among patients

		Count	N %
Amputation	No	34	56.7%
	Yes	26	43.3%

Amputation was done in 43.3% of the patients.

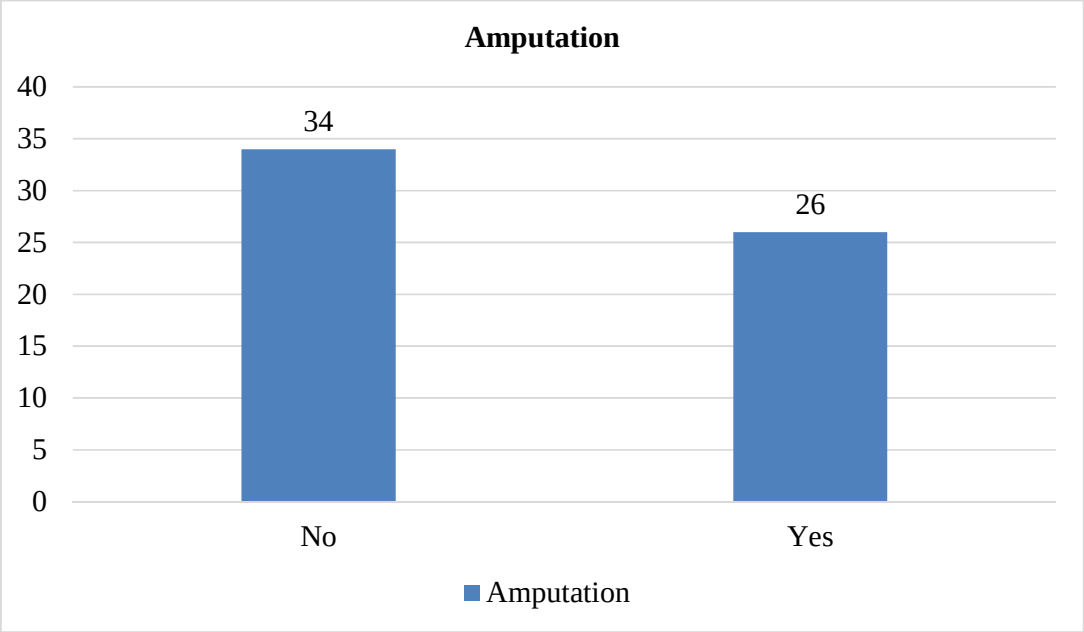


Figure 17: Showing presence of amputation among patients

Table 12: Showing the intervention done in patients

		Count	N %
Intervention underwent	Conservative management	34	56.7%
	above knee amputation	2	3.3%
	below knee amputation	9	15%
	forefoot amputation	15	25%

56.7% of the patients were managed conservatively and 43.3% underwent amputation.

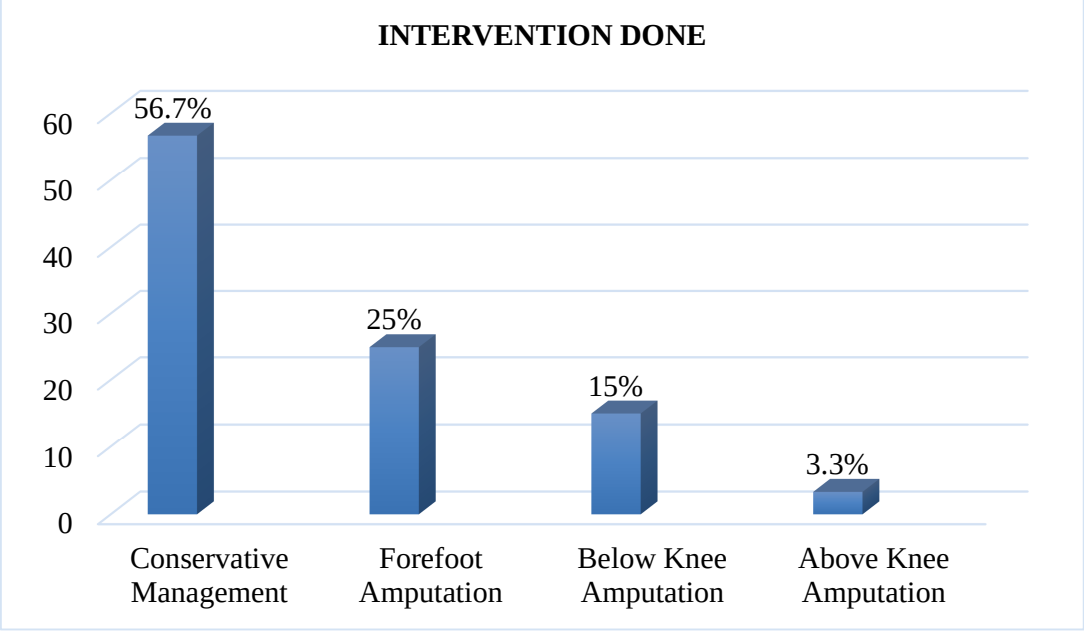


Figure 18: Showing the intervention done in patients

Table 13: Comparison of mean age with amputation in patients

	Amputation				
	No		Yes		p-value
	Mean	SD	Mean	SD	
AGE (years)	53.7	11.4	54.3	13.5	0.65

There is no significant difference in the mean age with the amputation of limb.

Table 14: Comparison of gender with amputation rate in patients

		Amputation				
		No		Yes		Chi-square (p-value)
		Count	N %	Count	N %	
Gender	Female	11	32.4%	4	15.4%	2.26 (0.13)
	Male	23	67.6%	22	84.6%	

There is no significant difference of gender with incidence of limb amputation.

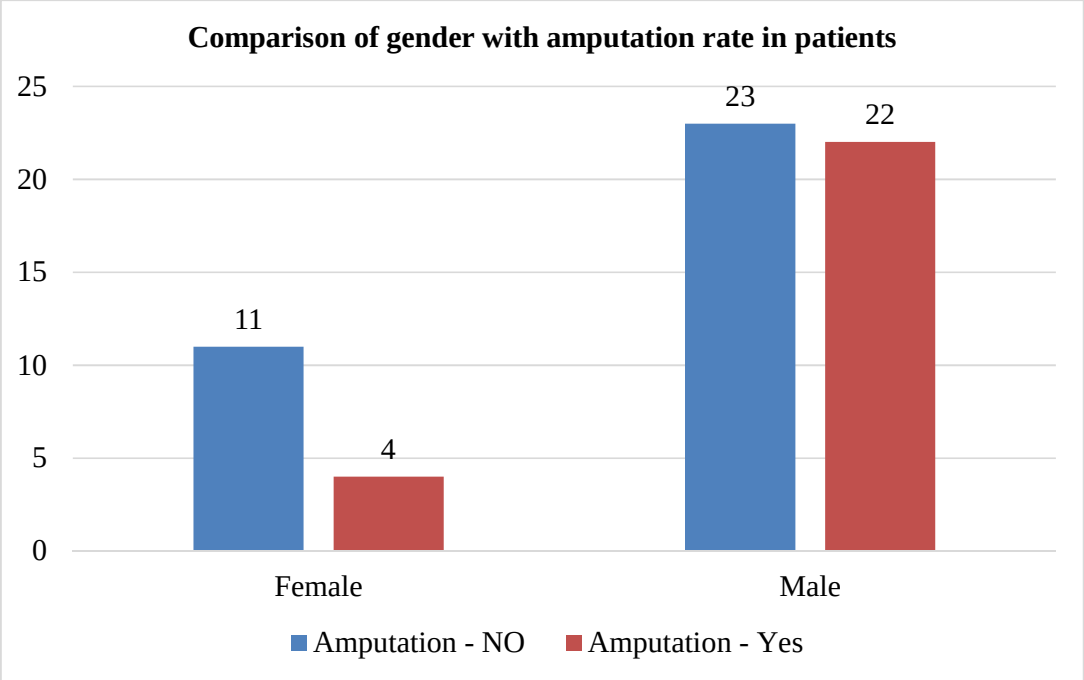


Figure 19: Comparison of gender with incidence of amputation in patients

Table 15: Comparison of comorbidities, trauma and smoking history with incidence of amputation in patients

		Amputation				
		No		Yes		Chi-square (p-value)
		Count	N %	Count	N %	
Comorbidities	HTN	3	8.8%	4	15.4%	0.61 (0.43)
	IHD	2	5.88%	2	7.69%	
	CVA	1	2.94%	0	0%	
History of trauma	Absent	13	38.2%	6	23.1%	1.56 (0.21)
	Present	21	61.8%	20	76.9%	
Smoker	No	27	79.4%	10	38.5%	10.45 (0.01)*
	Yes	7	20.6%	16	61.5%	

There is significant higher incidence of the amputation among the patients with positive smoking history (61.5%). However there was no significant difference with comorbidities and history of trauma with rate of amputation.

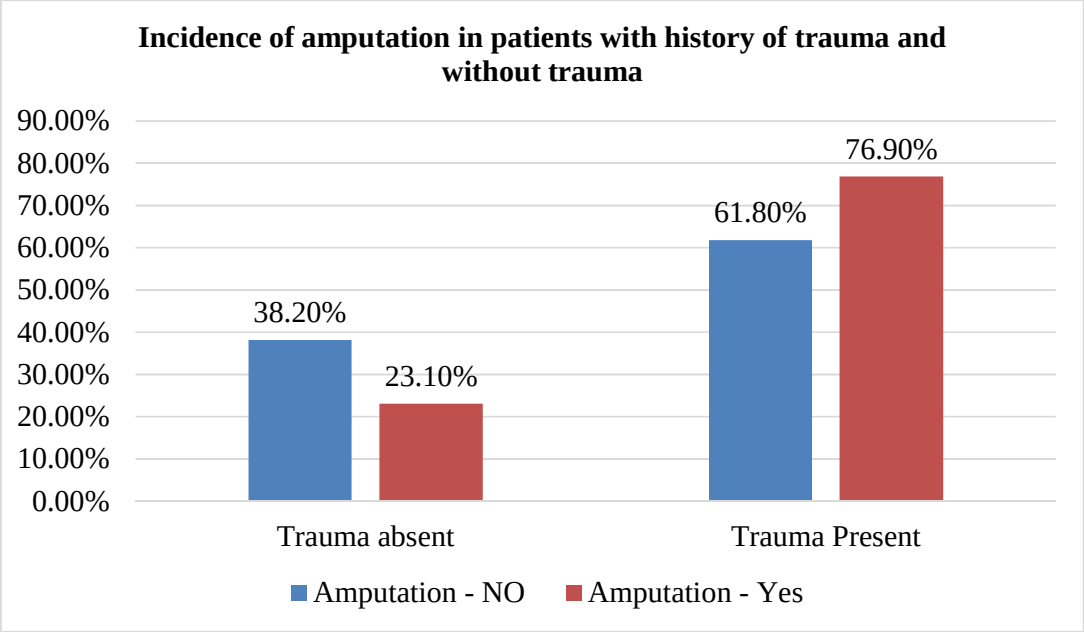


Figure 20: Incidence of amputation in patients with history of trauma and without trauma

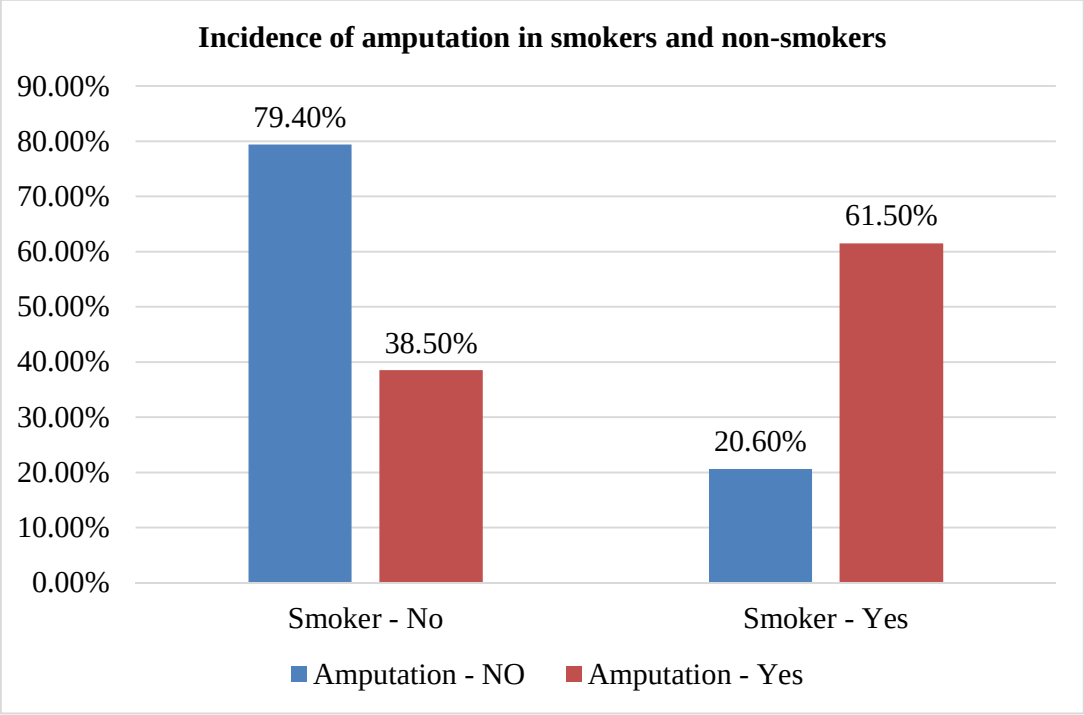


Figure 161: Incidence of amputation in smokers and non-smokers

Table 16: Comparison of the blood parameters with amputation among patients

		Amputation				
		No (34)		Yes (26)		Chi-square (p-value)
		Count	N %	Count	N %	
Hemoglobin	<12	10	11%	21	89%	12.1 (0.62)
	>12	24	70.59%	5	19.23%	
TLC	>11000	7	20.59%	20	76.91%	13.22 (0.01)*
	<11000	27	79.41%	6	23.07%	
Creatinine	>1.2	10	29.41%	6	23.07%	0.32 (0.65)
	<1.2	24	70.59%	20	76.92%	
FBS	>110mg/dl	22	64.7%	20	76.92%	2.66 (0.21)
	<110mg/dl	12	35.29%	6	23.07%	
HbA1c	>8	8	23.52%	9	34.61%	11.03 (0.01)*
	>6.5 -8	12	35.29%	16	61.54%	
	<6.5	14	41.18%	1	3.85%	

There is significant higher incidence of the anemia, elevated leucocyte count and HbA1c among the patients underwent amputation compared to other group.

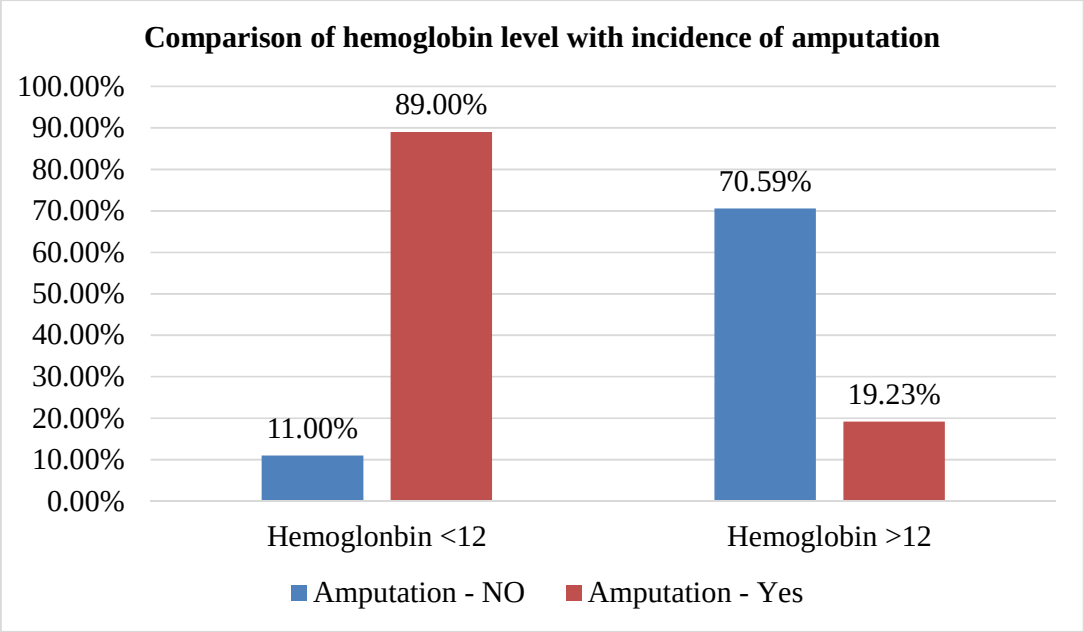


Figure 22: Comparison of hemoglobin level with incidence of amputation

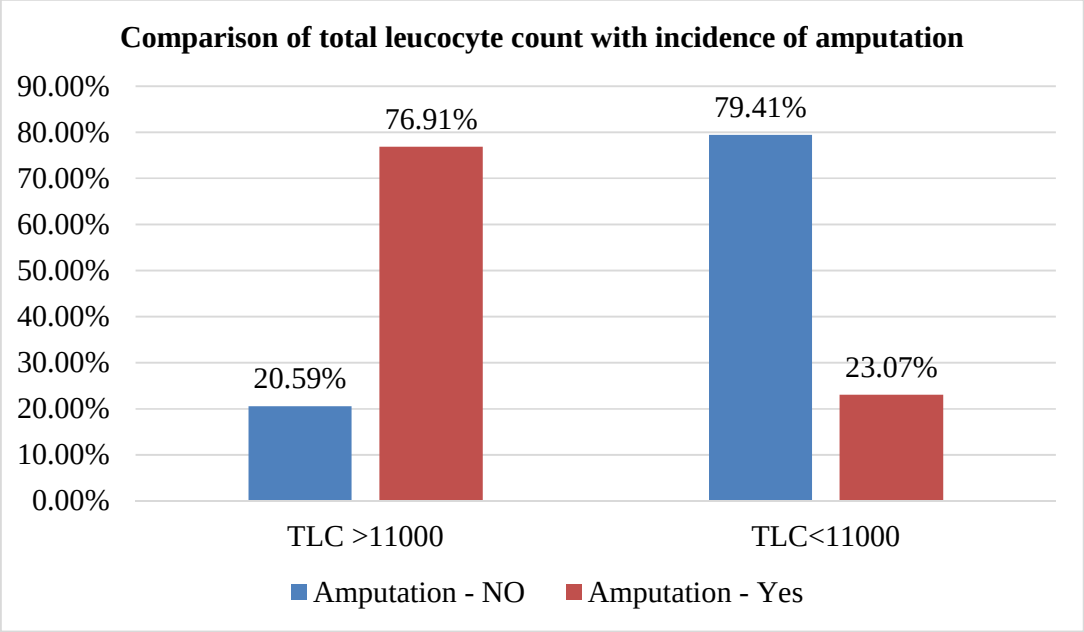


Figure 23: Comparison of total leucocyte count with incidence of amputation

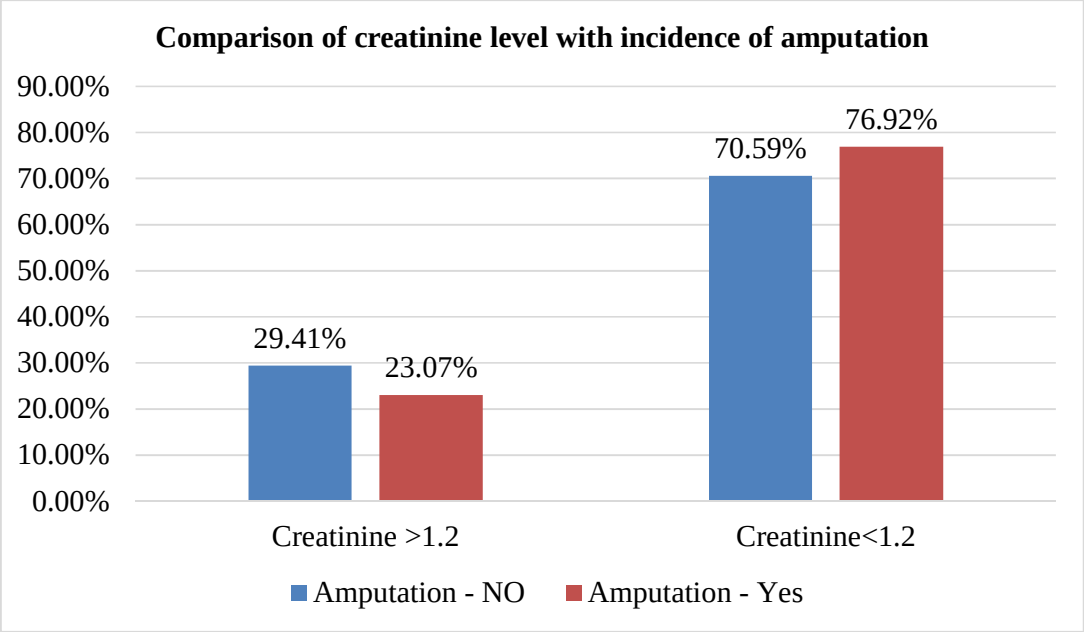


Figure 24: Comparison of creatinine level with incidence of amputation

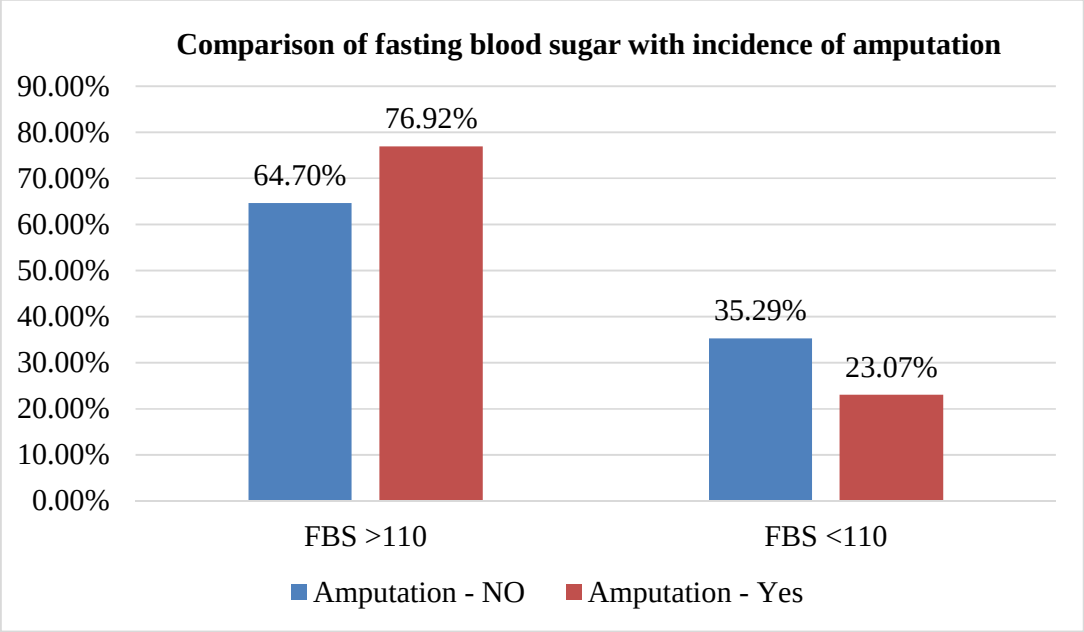


Figure 25: Comparison of fasting blood sugar with incidence of amputation

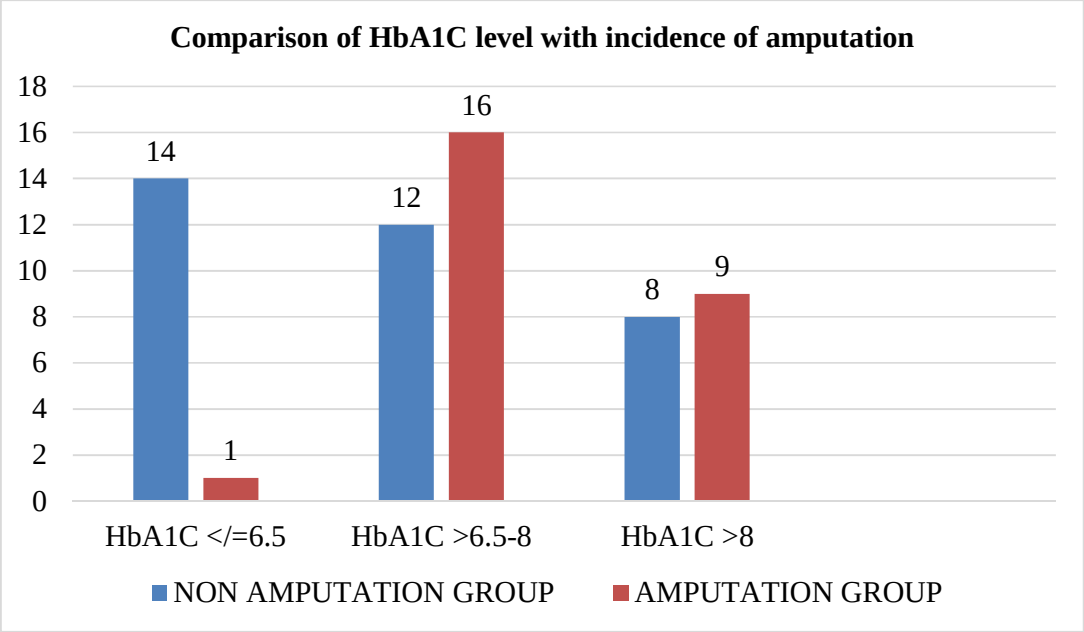


Figure 26: Comparison of the HbA1c level with incidence of amputation

Table 17: Comparison of the Wagner's grade, peripheral neuropathy and ABPI with amputation in patients

		Amputation				
		No		Yes		Chi-square (p-value)
		Count	N %	Count	N %	
Wagner's grade	Grade 2	32	94.12%	0	0.0%	49.7 (0.01)*
	Grade 3	2	5.9%	24	92.3%	
	Grade 4	0	0.0%	2	7.7%	
Peripheral Neuropathy	Absent	14	41.2%	3	11.5%	6.37 (0.01)*
	Present	20	58.8%	23	88.5%	
ABPI	<0.9	4	11.8%	21	80.8%	28.86 (0.01)*
	>0.9	30	88.2%	5	19.2%	

The higher wagner grade showing higher incidence of amputation, similarly the presence of peripheral neuropathy increased significantly incidence of amputation. Also the ABPI of <0.9 had higher incidence of amputation. ($p<0.05$)

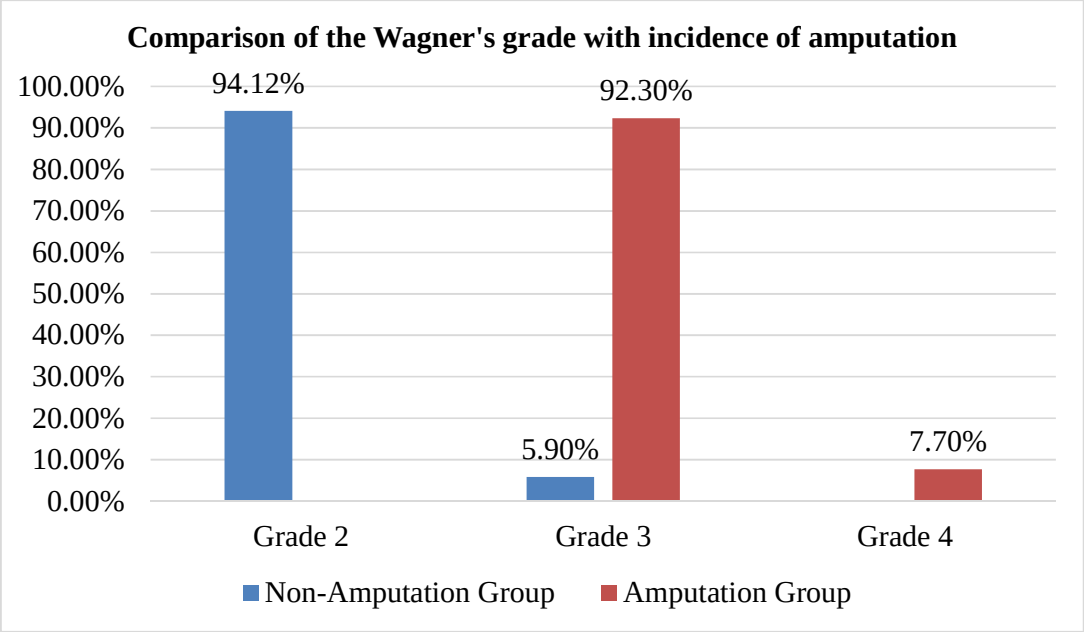


Figure 27: Comparison of the Wagner's grade with incidence of amputation

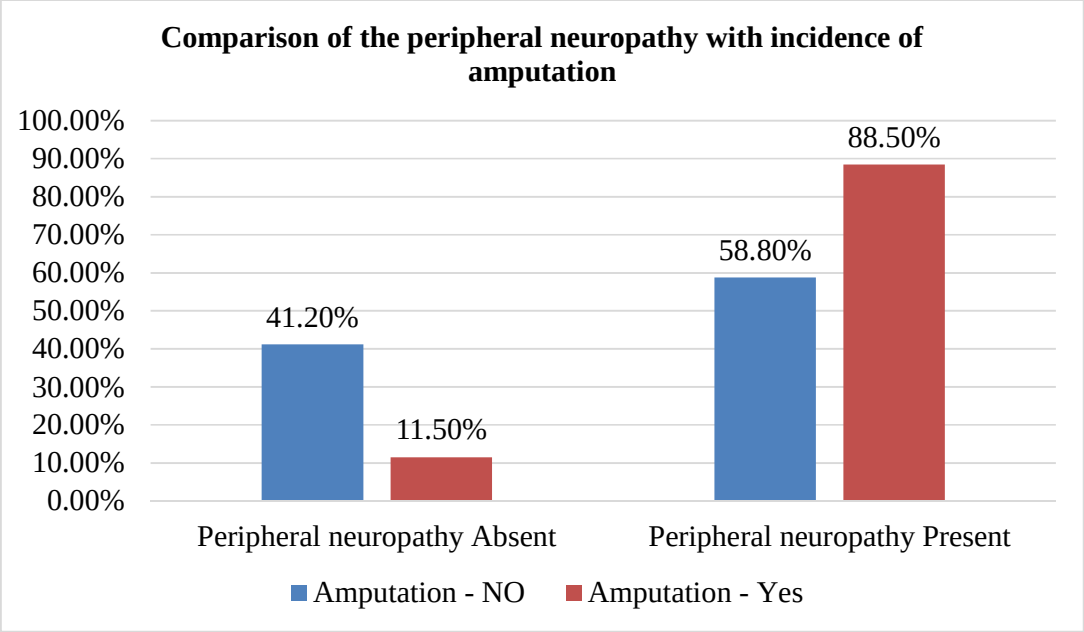


Figure 28: Comparison of the peripheral neuropathy with incidence of amputation

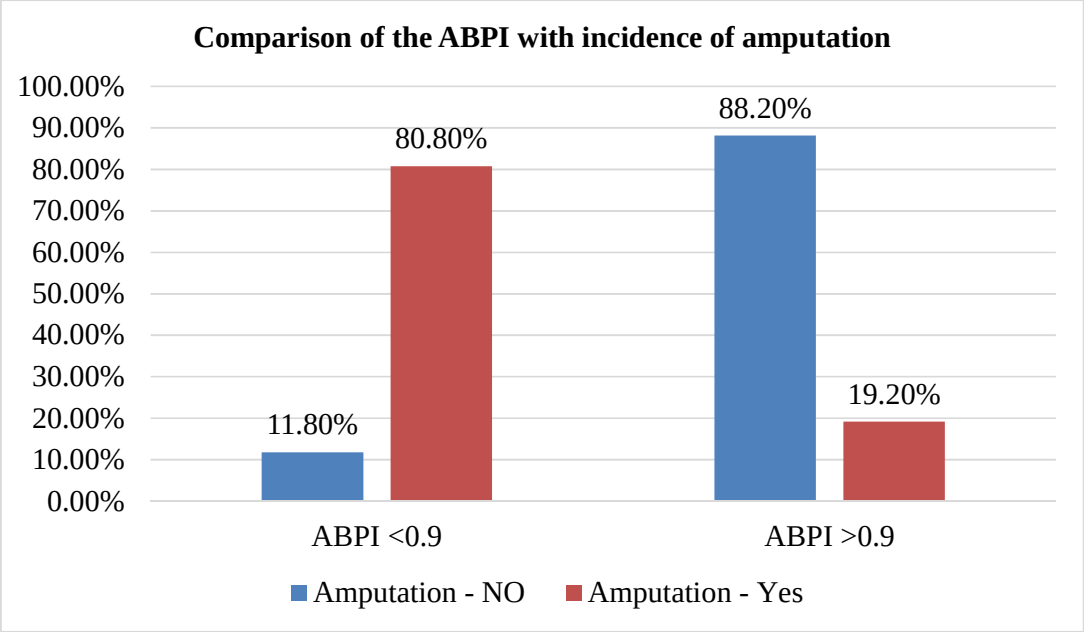


Figure 29: Comparison of the ABPI with incidence of amputation

DISCUSSION

Diabetic foot complications, including ulcers and infections, pose significant challenges due to their potential to progress to lower extremity amputations (LEAs), which severely impact patients' quality of life and incur substantial healthcare costs. Identifying these risk factors is essential for early intervention and personalized treatment strategies aimed at preventing or mitigating the progression to amputation. This discussion explores various factors, from neuropathy and vascular disease to systemic influences, shedding light on the complexities involved and highlighting the importance of targeted clinical management approaches in diabetic foot care. The discussion of risk factors leading to amputation in diabetic foot patients is a critical area of focus within diabetic care and research.

In present study total of 60 patients fulfilling inclusion criteria were included with mean age of 54±12.3yrs. Among them 75% were male and 25% were female with male preponderance in the study. In the study sample population 11.7% had hypertension, 6.67% had ischemic heart disease and 1.67% had history of cerebrovascular accident. History of trauma was present in 68.3% of the patients History of cigarette smoking is present in 38.3% of the patients in study.

In concordance to present study Sadriwala Q et al., documented with mean age of 55.57yrs and among them 80% were male patients.[3] Pscherer S et al., found factors such as advanced age, male gender, elevated HbA1c levels, and prolonged diabetes duration, along with other diabetes-related complications, were independently correlated with amputations [59] , in concordance to present study Umashankar et al., documented mean age of 60yrs with male preponderance in their study.[1] In another study by Bal S et al., documented with male preponderance in their study.[2]

Peripheral neuropathy was present in 71.7% of the patients. ABPI was <0.9 in 41.7% of the patients and >0.9 in 58.3% of the patients. Amputation was done in 43.3% of the patients. There is significant higher incidence of the amputation among the patients with positive smoking history (61.5%). However there was no significant difference with comorbidities and history of trauma with amputation. The higher wagner grade showing higher incidence of amputation, similarly the presence of peripheral neuropathy increased significantly incidence of amputation. Also the ABPI of <0.9 had higher incidence of amputation. ($p<0.05$)

In concordance to current study findings, the ABI of <0.9 was significantly associated with amputation (80%) in study by Sadriwala Q et al. Peripheral neuropathy emerged as a statistically significant risk factor for amputation ($p<0.008$). This condition, resulting from chronically elevated blood sugar levels, leads to vascular and metabolic abnormalities that cause a loss of sensation. Consequently, neuropathic changes such as decreased protective sensation, foot deformity, and skin fissures from diminished sweating predispose individuals to diabetic foot infections. These infections can progress to further tissue damage, ultimately culminating in gangrene and increasing the likelihood of amputation.[3]

Sun JH et al., in concordance to present study documented Wagner classification significantly influenced the identified risk factors for LEA, highlighting distinct predictors across different grades. Traditional predictors for diabetic foot amputation, such as lower ABI, albumin, or eGFR, were predominantly observed in patients with Wagner grade 3. Elevated Wagner grade, lower ABI, serum albumin, and hemoglobin levels, along with increased WBC, were significantly linked to heightened LEA risk [58] Pscherer S et al., documented with the overall occurrence of lower limb amputations linked to diabetes reached 18.2%.[59]

Elevated level of HbA1c, ill-fitting footwear, smoking and body mass index were linked to amputation in diabetic patients. In conclusion, females, irregular monitoring of HbA1c levels, inappropriate footwear, and smoking emerged as the most significant factors associated with amputation. [61] Sadriwala Q et al., documented with 39.1% amputation rate. Poor glycemic control, osteomyelitis, vasculopathy, peripheral neuropathy, and Wagner grading were significantly associated with amputation. [3]

Also, in another study by Santos V et al., Gram-positive microorganisms' presence correlated with major amputation necessity, while serum urea, creatinine, glucose, and white blood cell levels did not emerge as significant risk factors. In conclusion, major amputation risk factors encompassed age, diabetes duration, calcaneal lesions, arterial insufficiency, ascending lymphangitis, Wagner grade 5 lesions, and Gram-positive microorganisms in cultures.[63]

In concordance another study by Umashankar G et al., PEDIS Score > 7 is a highly significant predictor of amputation of diabetic foot ulcer and an integrated risk assessment model including the risk factors which are strongly associated with amputation like PVD, past amputation, nephropathy, past ulceration, ulcer duration, TLC, Hb and serum creatinine and PEDIS Score can be developed to predict adverse outcome(amputation) in diabetic foot ulcer patients which is needed to provide an opportunity to save the limb.[1]

CONCLUSION

Based on the findings of this study involving 60 patients meeting inclusion criteria, several significant observations can be highlighted. Analysis of factors influencing amputation risk showed no significant age or gender differences. However, a striking association was found between smoking history and higher incidence of amputation (61.5%). Wagner grade, presence of peripheral neuropathy, and ABPI <0.9 also significantly correlated with increased amputation rates ($p<0.05$). The study shows a significant risk of amputation rate in patients with uncontrolled diabetes, history of smoking, peripheral neuropathy, Wagner higher grade, ABPI <0.9.

These findings underscore the critical role of early identification and management of risk factors in diabetic foot patients to mitigate the progression to amputation. Tailored interventions addressing smoking cessation, neuropathic complications, and vascular health are essential in improving outcomes and quality of life for individuals affected by diabetic foot complications.

SUMMARY

- In present study total of 60 patients fulfilling inclusion criteria were included with mean age of 54±12.3yrs.
- Among them 75% were male and 25% were female with male preponderance in the study.
- In the study sample population 11.7% had hypertension, 6.67% had ischemic heart disease and 1.67% had history of cerebrovascular accident.
- History of trauma was present in 68.3% of the study sample population.
- History of cigarette smoking is present in 38.3% of the patients in study sample population.
- According to wagner's grade, majority patients in the sample were in grade 2, followed by grade 3 and grade 4.
- Peripheral neuropathy was present in 71.7% of the patients in the total study sample population.
- ABPI was <0.9 in 41.7% of the patients and >0.9 in 58.3% of the patients in the total study group.
- Among the patients in the total study group, x-ray foot showing presence of normal findings in 88.3% of the patients and 8.3% with osteomyelitis findings.
- Amputation was done in 43.3% of the in the total study sample population.
- The intervention was made as conservative in 56.7% of the patients and 43.3% underwent amputation.
- There is no significant difference in the mean age with the amputation of limb.
- There is no significant difference of gender with amputation of the limb.

- There is significant higher incidence of the anemia, elevated leucocyte count and HbA1c among the patients underwent amputation compared to other group.
- There is significant higher incidence of the amputation among the patients with positive smoking history (61.5%). However there was no significant difference with comorbidities and history of trauma with amputation.
- The higher wagner grade showing higher incidence of amputation, similarly the presence of peripheral neuropathy increased significantly incidence of amputation. Also the ABPI of <0.9 had higher incidence of amputation. ($p<0.05$)

STRENGTHS OF THE STUDY

The study employed a prospective observational design, which allowed for real-time data collection and minimized recall bias. Detailed demographic and clinical data were collected from each participant, including comorbidities, history of trauma and smoking, clinical assessments using the Wagner grading system, peripheral neuropathy, and Ankle-Brachial Pressure Index (ABPI). This thorough data collection facilitated a comprehensive analysis of risk factors associated with lower limb amputation.

The study utilized well-established and standardized tools such as the Wagner grading system and ABPI. These tools are widely accepted in clinical practice and research, enhancing the reliability and comparability of the results.

The study investigated a variety of potential risk factors for amputation, including peripheral neuropathy, smoking history, Wagner grade, and ABPI. By analysing multiple factors, the study provided a holistic understanding of the contributors to lower limb amputation in diabetic foot patients.

The findings of the study have direct clinical relevance, highlighting the importance of early detection and management of key risk factors such as peripheral neuropathy and smoking. These insights can inform clinical practice and help in developing targeted interventions to reduce the incidence of amputations in diabetic foot patients.

Conducting the study in a tertiary healthcare centre in Belagavi provides valuable data specific to the local population, which can be used to tailor interventions and healthcare policies to the needs of this community. And the study lays a foundation for future research by identifying critical areas for further investigation. It opens avenues for longitudinal studies to explore the long-term outcomes of interventions targeting the identified risk factors.

LIMITATIONS OF THE STUDY

This study was conducted in a single tertiary healthcare centre in Belagavi, which may limit the generalizability of the findings to other settings or populations. Multi-centre studies could provide more diverse and representative data.

Although the sample size of 60 patients provided meaningful insights, a larger sample size could have increased the statistical power of the study and allowed for more robust conclusions. Future studies with larger cohorts are necessary to validate these findings. Randomized controlled trials would be needed to confirm these causal relationships.

While the study controlled for several variables, there may be other unmeasured confounding factors influencing the outcomes. Factors such as socioeconomic status, access to healthcare, and adherence to treatment protocols were not assessed but could impact the results.

The study was conducted over a one-year period, which may not capture the long-term outcomes and variations in the incidence of amputations. Longitudinal studies with extended follow-up periods would provide a more comprehensive understanding of the risk factors.

The study relied on clinical assessments such as the Wagner grading system and ABPI for diagnosing peripheral neuropathy and ischemia. More advanced diagnostic tools like nerve conduction studies could provide more accurate and detailed evaluations. The study did not include data on specific interventions or treatments received by the patients, which could influence the incidence of amputations. Future research could include a broader patient population to identify additional risk factors

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ANEXURE I - INFORMED CONSENT FORM

KAHERs JNMC, BELAGAVI

"PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS RISK FACTORS LEADING TO AMPUTATION IN DIABETIC FOOT PATIENTS – AT A TERITIARY HEALTH CARE CENTRE IN BELAGAVI "

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Objective: To predict lower limb amputation occurrence and to determine risk factors leading to amputation in diabetic foot patients

Introduction: Diabetes mellitus is a most frequent cause of non-traumatic lower extremity amputation with diabetic foot ulcer being the commonest complication leading to hospitalisation in Diabetic patient. Several risk factors leading to diabetic foot ulcer development are well defined and risk factors for amputation among diabetic foot patient have been cited in literatures assessment of these risk factors which leads to amputation is helpful in risk reduction in diabetic foot patients if detected early which will improve the outcome

Explanation of procedure: After obtaining institutional ethical committee clearance and written informed consent, thorough history and examination findings are obtained. The study factors are demographic details of all patients including age, gender, smoking history, and any recent history of trauma to the foot. All infections were classified according to the Wagner grading system (Figure 1). Baseline investigations including hemoglobin (Hb), Glycosylated hemoglobin (HbA1c), total leucocyte count (TLC), serum creatinine and fasting blood sugar levels were

collected. X-ray of foot was done to assess features of osteomyelitis. Peripheral arterial disease (PAD) was evaluated by measuring ankle brachial index (ABI) using a hand held doppler. The presence of neuropathy will be determined using vibration perception [128 Hz tuning fork] at two sites hallux pulp and malleolus, point pressure using 10gmonofilament at 9 sites and ankle reflexes. The adequacy of arterial blood supply will be determined by the palpation of dorsalis pedis and posterior tibial artery pulsations. Patients will be followed up every week for at least 3 months or till amputation. The main outcome factor was amputation which was defined as the complete loss in the transverse anatomical plane of any part of the lower limb.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: "Name of student/PI, mobile number, email ID" If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights.

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**Prospective observational study to assess risk factors leading to amputation in diabetic foot patients - at a tertiary health care centre in Belagavi"**

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE – II - PROFORMA /

QUESTIONNAIRE TO BE USED FOR DATA COLLECTION

The proposed proforma / questionnaire to be used for data collection for the study titled **"Prospective observational study to assess risk factors leading to amputation in diabetic foot patients at a tertiary health care centre in Belagavi" is as:**

Name:	IP no.:
Sex:	Age:
Address:	Religion:
Education:	Date of admission:
Occupation:	Date of discharge:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING COMPLAINTS:

PAST HISTORY:

PERSONAL HISTORY:

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION:

Built and Nourishment:

Weight:

Pallor / Icterus / Cyanosis / Clubbing / Oedema / Lymphadenopathy

Vital Signs: PR: /min; BP: mm Hg; RR: /min; Febrile/Afebrile

SYSTEMIC EXAMINATION:

Abdomen:

Cardio Vascular System:

Respiratory System:

Local examination:

CLINICAL IMPRESSION:

INVESTIGATIONS:

HEMOGLOBIN:

TLC:

FBS:

HbA1C:

S. CREATININE:

EXAMINATION:

WAGNER GRADE:	LOW GRADE (GRADE 0 TO 2)
	HIGH GRADE (GRADE 3 TO 5)
	XRAY AFFECTED LIMB/FOOT:
SIGNS OF OSTEOMYELITIS	PRESENT / ABSENT
ABPI </=0.9	>0.9

PERIPHERAL NEUROPATHY

SENSORIMOTOR NEUROPATHY

NORMAL STUDY

OUTCOME:

AMPUTATION

NON-AMPUTATION

ANNEXURE – III - MASTERCHART

Sl.No	Age (Yrs)	Sex	Co-Morbidities	History Of Trauma	Smoker	Diagnosis	Wagner's Grade	Peripheral Neuropathy	Abpi	Hb	Tlc	S. Creatinine	Fbs	Hba1c	X-Ray Foot	Intervention Underwent
1	50	F	DM	Present	No	Left diabetic foot with charcots arthropathy	3	Present	>0.9	14.1	16900	1.7	284	8	Osteomyelitis present	Left forefoot amputation
2	44	M	DM	Present	Yes	Right diabetic foot	4	Present	>0.9	11	31000	2.95	408	10.7	Osteomyelitis present	Right below knee amputation
3	42	M	DM	Present	Yes	Right diabetic foot ulcer with degloving injury	3	Present	>0.9	10.9	13700	0.8	189	6.8	Normal	Right forefoot amputation
4	85	M	DM	Present	No	Right diabetic foot with ssi post orif	3	Present	>0.9	14.5	10700	1.4	178	11.2	Both bone fracture right leg - orif plate present	Right above knee amputation
5	52	F	DM, HTN	Present	No	Diabetic foot ulcer with mycetoma right foot	3	Absent	>0.9	9.7	17700	1.09	90	7.8	Normal	Right below knee amputation
6	70	M	DM, HTN, IHD	Present	No	Right diabetic foot ulcer	2	Absent	<0.9	10	10800	1.4	102	6.9	Normal	Conservative management

7	50	M	DM, HTN, IHD	Present	Yes	Right diabetic foot with dry gangrene over 3rd and 5th toes	4	Present	<0.9	12	15780	1.08	136	9.7	Normal	Conservative management
8	56	M	DM	Absent	No	Left diabetic foot ulcer	2	Present	<0.9	13	10000	1.1	109	6	Normal	Conservative management
9	24	M	DM	Present	No	Left diabetic foot ulcer	2	Absent	<0.9	13.6	10600	1.06	98	7.4	Normal	Conservative management
10	42	M	DM	Present	Yes	Right diabetic foot ulcer with gangreneous changes over great toe	3	Present	<0.9	10.2	20200	1.86	198	6.86	Osteomyelitis present	Right forefoot amputation
11	48	M	DM	Present	Yes	Bilateral diabetic foot ulcer with pvd	3	Present	<0.9	8	23000	2.84	216	6.7	Normal	Left below knee amputation
12	75	M	DM	Present	Yes	Left diabetic foot with pvd	3	Present	<0.9	11	12600	1.09	116	9.3	Normal	Left forefoot amputation
13	65	M	DM	Present	Yes	Right diabetic foot abscess+ gangrene	3	Present	<0.9	9.7	34200	1.28	278	11.6	Normal	Left below knee amputation
14	41	M	DM	Present	Yes	Diabetic foot ulcer with fracture tibia	3	Present	<0.9	13.3	11900	0.65	141	6.8	Fracture tibia	Left above knee amputation
15	45	F	DM, HTN	Present	No	Dry gangrene over left forefoot with diabetic foot	3	Absent	<0.9	11.5	8300	0.8	90	6.8	Normal	Left below knee amputation

16	46	F	DM	Present	No	Left diabetic foot wiyth gangrene	3	Present	<0.9	9.6	23900	0.6	64	9.9	Normal	Left forefoot amputation
17	63	M	DM	Absent	No	Left diabetic foot with pvd	3	Present	<0.9	9.2	23000	1.94	118	7.4	Normal	Left forefoot amputation
18	34	M	DM, HTN, IHD	Absent	Yes	Right diabetic foot ulcer with pvd	3	Absent	<0.9	13.5	18900	0.62	114	5.4	Normal	Right forefoot amputation
19	44	M	DM	Present	Yes	Right diabetic foot	3	Present	<0.9	9.7	12700	2.9	96	6.9	Normal	Right forefoot amputation
20	58	M	DM	Absent	Yes	Left diabetic foot with dry gangrene over forefoot	4	Present	<0.9	10.1	5800	1.74	240	8.6	Normal	Left forefoot amputation
21	70	M	DM	Present	Yes	Right diabetic foot with gangrene	3	Present	<0.9	11.4	17200	1.61	89	7	Normal	Right forefoot amputation
22	74	M	DM	Present	No	Right diabetic foot ulcer with dry gangrene over right great toe	3	Present	<0.9	10.8	12600	1.24	177	6.8	Normal	Left forefoot amputation
23	50	M	DM	Absent	Yes	Right diabetic foot with dry gangrene over right foreoot	3	Present	<0.9	10.4	7500	2.8	101	6.8	Normal	Right below knee amputation
24	73	M	DM	Present	No	Left diabetic foot with gangrene over left great toe	3	Present	<0.9	9.3	11500	1.61	187	10.4	Normal	Left forefoot amputation

25	33	M	DM	Present	No	Left diabetic foot with gangrene over left forefoot	3	Present	<0.9	10.5	12800	2.42	204	6.8	Normal	Left forefoot amputation
26	49	M	DM	Absent	Yes	Pvd left lower limb with diabetic foot	3	Present	<0.9	8.3	20100	0.9	134	6.7	Normal	Left below knee amputation
27	66	M	DM	Present	Yes	Right diabetic foot with dry gangrene over dorsum of right foot secondary to pvd	3	Present	<0.9	9.8	26800	0.83	317	13	Normal	Right forefoot amputation
28	50	M	DM, HTN, IHD	Absent	No	Dry gangrene over right forefoot with diabetic foot	3	Present	<0.9	13.5	10500	0.69	128	9.7	Osteomyelitis present	Right forefoot amputation
29	54	M	DM	Present	Yes	Right diabetic foot with gangrene over dorsum of right foot secondary to pvd	3	Present	<0.9	9.8	18700	1.6	210	7.8	Normal	Right below knee amputation
30	60	M	DM	Present	Yes	Pvd left lower limb with diabetic foot ulcer over left heel	3	Present	<0.9	10.5	10000	2.9	290	7.5	Osteomyelitis present	Left below knee amputation

31	46	M	DM	Absent	No	Right diabetic foot ulcer	2	Present	>0.9	12.6	7800	1	98	6	Normal	Conservative management
32	48	M	DM	Absent	No	Left diabetic foot ulcer	2	Present	>0.9	14	9900	0.98	89	6.3	Normal	Conservative management
33	58	M	DM	Absent	No	Right diabetic foot ulcer	2	Present	>0.9	13.4	8790	0.76	90	5.8	Normal	Conservative management
34	57	M	DM	Present	No	Left diabetic foot ulcer	2	Present	>0.9	15	7865	0.68	108	6	Normal	Conservative management
35	52	F	DM	Absent	Yes	Right diabetic foot ulcer	2	Absent	>0.9	13.6	6600	0.9	102	5.9	Normal	Conservative management
36	54	F	DM	Absent	No	Diabetic foot ulcer over sole of right foot	2	Absent	>0.9	12.5	9760	1	96	6	Normal	Conservative management
37	67	M	DM	Present	Yes	Left diabetic foot ulcer	2	Absent	>0.9	12.8	5890	0.94	108	7	Normal	Conservative management
38	48	M	DM	Absent	No	Right diabetic foot ulcer	2	Absent	>0.9	12.8	7980	0.8	129	9	Normal	Conservative management
39	45	M	DM	Absent	No	Left diabetic foot ulcer	2	Absent	>0.9	13.2	8900	1	180	11	Normal	Conservative management
40	66	M	DM	Absent	No	Diabetic foot ulcer over left heel	3	Absent	>0.9	12.4	9200	1.1	156	8.4	Normal	Conservative management
41	50	M	DM	Present	No	Diabetic foot ulcer over right heel	2	Present	>0.9	10.1	10000	0.8	138	6	Normal	Conservative management
42	62	M	DM	Absent	No	Left diabetic foot ulcer with cellulitis	2	Present	>0.9	12	18000	0.93	173	8.6	Normal	Conservative management

43	52	M	DM	Present	Yes	Diabetic foot with necrotising fascitis	3	Absent	>0.9	9.3	18700	3.48	149	10.1	Normal	Conservative management
44	60	M	DM	Present	No	Left diabetic foot ulcer	2	Absent	>0.9	12.3	4800	1.7	121	6.8	Normal	Conservative management
45	53	M	DM	Present	Yes	Right diabetic foot ulcer	2	Present	>0.9	10.9	5500	2.89	156	6.6	Normal	Conservative management
46	61	F	DM	Absent	No	Right diabetic foot ulcer	2	Present	>0.9	8.1	7500	1.83	110	11.2	Normal	Conservative management
47	58	F	DM	Present	No	Right diabetic foot abscess	2	Absent	>0.9	9.6	8200	0.77	225	6.7	Normal	Conservative management
48	45	F	DM	Present	No	Left diabetic foot ulcer	2	Absent	>0.9	8.6	29200	1.03	286	9.1	Normal	Conservative management
49	44	F	DM, HTN, CVA	Present	No	Left diabetic foot ulcer	2	Absent	>0.9	10.4	11000	0.63	126	9.2	Normal	Conservative management
50	61	F	DM	Present	No	Left diabetic foot ulcer	2	Absent	>0.9	9.4	16400	1.32	142	7.2	Normal	Conservative management
51	37	M	DM	Present	No	Diabetic foot ulcer over sole of left foot	2	Present	>0.9	12.2	10700	2.08	183	7.1	Normal	Conservative management
52	55	M	DM	Absent	No	Left diabetic foot ulcer	2	Present	>0.9	10.8	9200	1.85	138	8.6	Normal	Conservative management
53	63	F	DM	Present	No	Diabetic foot ulcer over heel of right foot	2	Present	>0.9	13.1	9000	0.89	158	9.5	Normal	Conservative management
54	75	M	DM	Present	No	Left diabetic foot ulcer	2	Present	>0.9	12.1	10700	1.1	128	10.2	Normal	Conservative management

55	63	M	DM	Present	Yes	Right diabetic foot ulcer	2	Present	>0.9	10.8	10800	0.9	109	11	Normal	Conservative management
56	43	M	DM	Absent	No	Right diabetic foot ulcer	2	Present	>0.9	12	9800	1	116	9.6	Normal	Conservative management
57	22	M	DM	Present	No	Right diabetic foot ulcer	2	Present	>0.9	10.8	9800	0.96	98	7.1	Normal	Conservative management
58	60	F	DM	Present	No	Diabetic foot ulcer over left 5th toe	2	Present	>0..9	9.8	10700	1.86	101	6.9	Normal	Conservative management
59	60	F	DM	Present	Yes	Right diabetic foot ulcer	2	Present	>0.9	13	17800	1.1	117	7.5	Normal	Conservative management
60	60	F	DM	Present	No	Right diabetic foot ulcer	2	Present	>0.9	12.1	7600	0.9	106	7.8	Normal	Conservative management