“EVALUATE THE ROLE OF TOPICAL OXYGEN THERAPY IN WOUND HEALING DYNAMICS OF DIABETIC LOWER LIMB ULCERS – A RANDOMISED CONTROLLED STUDY”

BY

REG. NO.BH0121009

Dissertation

Submitted to the

KLE Academy of Higher Education and

Research, Belagavi, Karnataka.

In Partial Fulfillment

Of the requirements for the degree of

MASTER OF SURGERY (M.S)

IN

GENERALSURGERY

DEPARTMENT OF GENERAL SURGERY, JAWAHARLAL NEHRU MEDICAL COLLEGE BELAGAVI, KARNATAKA.

DECEMBER 2024/ JANUARY 2025

KLE Academy of Higher Education and Research

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LIST OF ABBREVATIONS

DFU: DIABETIC FOOT ULCER

TOWT: TOPICAL OXYGEN WOUND THERAPY

POD: POST-OPERATIVE DAY

HBOT: HYPERBARIC OXYGEN THERAPY

THO: TOPICAL HYPERBARIC OXYGEN THERAPY

HTN: HYPERTENSION

T2DM: TYPE 2 DIABETES MELLITUS

TOT: TOPICAL OXYGEN THERAPY

MWT: MOIST WOUND THERAPY

SOC: STANDARD OF CARE

CDO: CONTINUOUS DIFFUSION OF OXYGEN

BMI: BASAL METABOLIC INDEX

USG: ULTRASONOGRAPHY

BP: BLOOD PRESSURE

ATP: ADENOSINE TRIPHOSPHATE

CBC: COMPLETE BLOOD COUNT

CNS: CENTRAL NERVOUS SYSTEM

CVS: CARDIOVASCULAR SYSTEM

PVD: PERIPHERAL VASCULAR DISEASE

SPSS: STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES

OHA: ORAL HYPOGLYCAEMIC AGENTS

atm: ATMOSPHERE

mmHg: MILIMETRES OF MERCURY

cm: CENTIMETRE

cm^2: CENTIMETRE SQUARE

Kg/m^2: KILOGRAM PER METER SQUARE

mg/dl: MILLIGRAM PER DECILITRE

PAD: PERIPHERAL ARTERY DISEASE

ROS: REACTIVE OXYGEN SPECIES

PO2: PARTIAL PRESSURE OF OXYGEN

TGF-β: TRANSFORMING GROWTH FACTOR BETA

IGF-1: INSULIN-LIKE GROWTH FACTOR -1

MMP: MATRIX METALLOPROTEINASES

NO: NITRIC OXIDE

PDGF: PLATELET-DERIVED GROWTH FACTORS

VEGF: VASCULAR ENDOTHELIAL GROWTH FACTORS

HIV: HUMAN IMMUNODEFICIENCY VIRUS

AIDS: ACQUIRED IMMUNODEFICIENCY SYNDROME

HbA1c: GLYCATED HAEMOGLOBIN

FBS: FASTING BLOOD SUGAR

C/S: CULTURE AND SENSITIVITY

D 0: DAY ZERO

D 14: DAY FOURTEEN

TWO2: TOPICAL WOUND OXYGEN

M: F: MALE TO FEMALE RATIO

VLU: VENOUS LEG ULCER:

RCT: RANDOMISED CONTROL TRIAL

CAS-HA: CALCIUM SULPHATE-HYDROXYAPATITE

D.O.A: DATE OF ADMISSION

e.g.: FOR EXAMPLE

I.P.: IN PATIENT

i.e.: THAT IS

vs.: VERSUS

ABSTRACT

Background:

Diabetic foot ulcers are a rising complication of diabetes mellitus and a leading cause of morbidity in the world. Even after development and research of multiple modalities of treatment, no single method has been proven to show an economical, safe and effective way of healing these ulcers. After the advent of hyperbaric oxygen therapy, the role of oxygen in healing has been validated worldwide. However, there is a large lacuna in the role of Topical oxygen wound therapy in healing of diabetic foot ulcers. This study aims to fill this lacuna and discuss the efficacy of Topical oxygen wound therapy.

Methodology:

A single centre, randomized controlled study was conducted over one year, involving 60 patients who were divided into two groups of 30 each. One group (Test group) was given topical oxygen therapy for an hour daily in addition to conventional dressing, while the other group (Control group) only received conventional dressing daily. The primary endpoint included the wound area reduction in either group at the end of 14 days.

Results:

The study found a significant difference in between the healing rates of the two groups. The difference in the mean area reduction of ulcers over 14 days in the test group was significantly greater as compared to control group, i.e. 2.31 cm^2 and 1.07 cm^2 respectively (p value = 0.035). The mean percentage area reduction of ulcer in the test and control groups were 3.70% and 1.99% respectively, showing a significant difference in healing rates (p value = 0.002). In adjunct to this, the test group showed more decrease in number of positive wound cultures over study period compared to the control group, indicating the anti-microbial benefits of

topical oxygen wound therapy on DFUs. The study shows no adverse effects in any of the patients receiving Topical oxygen wound therapy.

Conclusion:

In conclusion, addition of Topical Oxygen Wound Therapy for diabetic foot ulcers management has shown to contribute to superior healing rates when compared to conventional dressings alone. It is economical and safe without any adverse effects to the patients. It also shows a potential anti-microbial property. These findings suggest that Topical oxygen wound therapy can be used as a frontline treatment modality locally for diabetic foot ulcers as an adjuvant to conventional dressings.

Keywords: *Diabetic foot ulcers, Topical oxygen wound therapy, conventional dressing, mean area reduction, mean percentage area reduction, anti-microbial effects.*

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF GRAPHS

LIST OT PHOTOGRAPHS

INTRODUCTION

Diabetes mellitus, a common chronic metabolic disorder, is frequently associated with complications, including the diabetic foot [1]. A diabetic foot ulcer (DFU) is one of the hallmarks of this condition, which is the result of diabetic peripheral neuropathy [2]. Infection and injury to the foot are additional potential outcomes of neuropathy. [2]

Complications attributed to diabetes that affect the lower extremities are among the numerous causes of illness and infirmity worldwide. [3] Diabetic foot ulcers (DFUs) are a significant cause of lower limb amputations and mortality [4]. It is possible for up to one-third of individuals with diabetes to develop a DFU at some point in their lifetimes [5].

Diabetic foot is also associated with an elevated risk of lower limb amputation and death [5]. The worldwide prevalence of type 2 diabetes is 6.4%, with Asian countries accounting for 5.5% [6], South Indian states 6.38% [7], and North Indian states 14.30% [8]. The probability of lower extremity amputations increases as DFU becomes more taxing [9, 10]. The repair of DFUs is significantly impeded by their complexity. Even in specialist institutions, the recovery rates for DFUs range from 22 to 30 percent by the 20th week [11, 12].

In most cases, regular wound dressing, wound debridement, skin grafting, revascularization, and amputation are among the numerous surgical and non-surgical methods employed to address this issue. The health-related quality of life of individuals with type 2 diabetes may be enhanced by increasing awareness of the significance of foot care [13].

The primary objective of any therapeutic approach is to expedite the closure of the lesion. The standard treatment regimen entails the removal of infected tissue, the revascularization of ischemic tissues, and the prevention of additional pressure on the lesion. [14]

The complex process of wound healing is characterized by a dynamic network of interactions among local cells, proteins, proteases, growth hormones, and extracellular matrix

components [15]. Local tissue hypoxia, which is a consequence of damaged or impaired vasculature, impedes wound healing [16]. Throughout this process, oxygen is essential for the synthesis of cellular ATP, the proliferation of fibroblasts, the formation of angiogenesis, the deposition of collagen, and the formation of superoxide. Local tissues are capable of resisting infections as a result of these mechanisms [17].

The local healing response may result in increased oxygen requirements and/or arterial flow interruption, which can cause wounds to become hypoxic over time [17, 18]. Wound tissue hypoxia occurs when blood supply is restricted by peripheral vascular diseases (PVDs). An additional contributing factor is the elevated oxygen requirement of regenerating tissue, which is crucial for the synthesis of collagen and angiogenesis. Finally, respiratory surge produces reactive oxygen species (ROS), which are essential for redox signalling and infection control. Therefore, oxygen serves as the primary energy source and also facilitates cell signal transduction and cell cycling through Transforming Growth Factor (TGF) -β and Matrix Metalloprotease (MMP) -1 and 2. [19]

Even in the absence of peripheral artery disease (PAD), hypoxia may develop in the wound microenvironment [20]. This is due to the fact that metabolically active cells require a significant amount of oxygen. Consequently, remedies that are designed to enhance the passage of oxygen to the affected area may facilitate the healing of chronic lesions more rapidly. Oxygen is the primary factor responsible for enhancing the wound healing process, as evidenced by the implementation of simple and secure techniques to increase the adoption of treatment options for individuals with DFU.

Hyperbaric oxygen treatment, which entails the administration of oxygen through this method, has experienced a significant increase in popularity and interest. Hyperbaric oxygen therapy (HBOT) has been demonstrated to facilitate wound healing; however, there is some

evidence that it may be linked to high treatment costs, oxygen toxicity, and barotrauma consequences [21].

The risk of complications is minimal when using topical oxygen treatment (TOT) or any other topical delivery technique. When topical oxygen is administered directly to the wound site without invasively circumventing the oxygen transport system, a wound bed environment with elevated pH levels and a high concentration of oxygen can aid in the treatment of infection. TOT has the potential to enhance the quality of wound healing and expedite the healing process when used in conjunction with other methods for treating chronic, nonhealing diabetic foot ulcers [22].

Topical oxygen therapy has supplanted hyperbaric oxygen treatment as the preferred method for wound healing. This is due to the hyperbaric oxygen therapy (HBOT)'s systemic adverse effects and exorbitant cost, which prevents all hospitals from accessing it. [23] Topical oxygen therapy (TOT) has been adopted by the global wound healing community as an alternative to systemically administered HBOT. Clinical studies that have attempted to demonstrate the efficacy of HBOT in treating chronic DFU have been inconsistent and disappointing, despite the apparent prospective physiologic advantages.[24]

This approach to topical oxygen administration is a substantial enhancement over conventional methods, as it is both practical and effective. Nevertheless, there has been a dearth of academic research on topical oxygen modalities and treatment. Consequently, a randomised controlled study is required to substantiate this innovative method of topical oxygen treatment. Therefore, in order to bolster the use of TOWT as the primary option for advanced wound care in diabetic foot ulcers, a more comprehensive study is necessary, which should include a cost-effectiveness evaluation and standardised care procedures.

AIMS & OBJECTIVES

To compare healing rates of diabetic lower limb ulcers treated with Topical Oxygen Wound Therapy with conventional dressing versus that with conventional dressing therapy alone.

REVIEW OF LITERATURE

DIABETES MELLITUS:

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction and treatment strategies beyond glycemic control.[13] The American Diabetes Association defines diabetes mellitus as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[14]

Diabetes has emerged to be one of the significant causes of morbidity and mortality worldwide in the past few decades. In the year 2019, the global prevalence of diabetes amounted to 463 million people which is estimated to rise to 700 million by 2045. (Figure 1)

Every 1 in 5 of the people who are above 65 years old have diabetes. There were 4.2 million deaths reported due to diabetes in the year of 2019.It has been estimated that 374 million people are predisposed to develop type 2 diabetes as of 2020.15India is the second most affected country by diabetes mellitus after China.[16]

As per the latest International Diabetes Federation Atlas, there are more than 77 million people with diabetes in India as of 2020. (Figure 2) [15]

Nearly 1 million Indians die due to diabetes every year.[17]

According to the Indian Heart Association, India is estimated to have 109 million people with diabetes by 2035.[18]

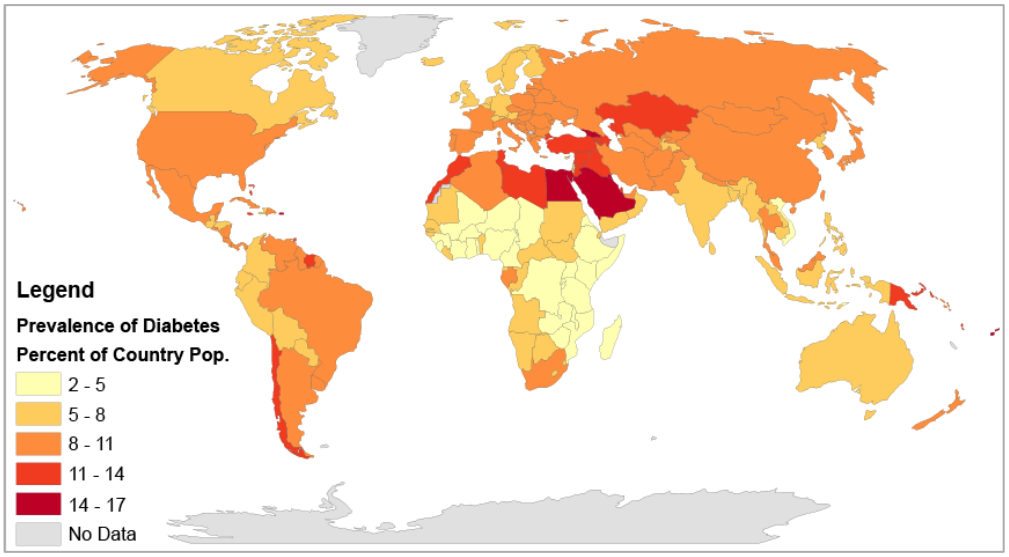


Figure 1. Worldwide prevalence of Diabetes

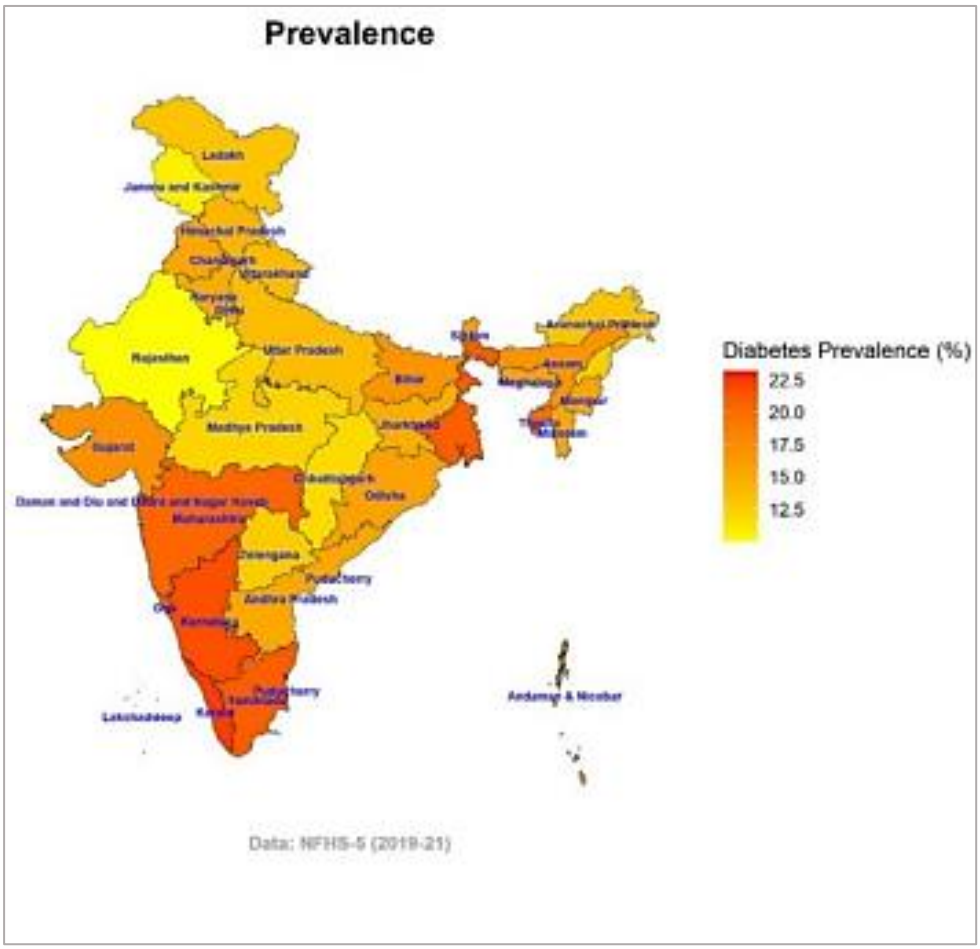


Figure 2. Prevalence of Diabetes in India

ETIOLOGY & RISK FACTORS

Genetic and environmental risk factors affect inflammation, autoimmunity and metabolic stress states at the cellular level. These lead to destruction of beta cell mass affecting insulin production and/or its activity. Inadequate insulin secretion along with diminished tissue response to insulin affects the complex pathways of hormone action at multiple levels. The deficient action of insulin on target tissues forms the basis of abnormalities in carbohydrate, fat, and protein metabolism in diabetes. The chronic hyperglycemia of diabetes consequently leads to long-term damage and dysfunction of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[19]

TYPES OF DIABETES MELLITUS

Diabetes can be classified into the following general categories [14]:

1. Type 1 diabetes (β-cell damage, because of autoimmune mechanisms, leads to absolute insulin deficiency)
2. Type 2 diabetes (β-cell insulin secretion hampered along with insulin resistance)
3. Gestational diabetes mellitus (development of diabetes in the second or third trimester of pregnancy which was not overt diabetes before gestation)
4. Specific types of diabetes:
    - monogenic diabetes syndromes (example- neonatal diabetes and maturity-onset diabetes of the young)
    - diseases of the exocrine pancreas (example- cystic fibrosis and pancreatitis)
    - drug- or chemical-induced diabetes (example- with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

DIAGNOSIS

Diabetes mellitus can be diagnosed based on any of the following four tests (Table 1) [14]:

Fasting plasma glucose	⩾7.0 mmol/l ⩾126 mg/dl	6.1–6.9 mmol/l 110–125 mg/dl
2 h plasma glucose after OGTT	⩾11.1 mmol/l ⩾200 mg/dl	7.8–11.0 mmol/l 140–199 mg/dl
Random plasma glucose	⩾11.1 mmol/l ⩾200 mg/dl	
Glycosylated haemoglobin	⩾6.5%	

*Adapted from World Health Organization and International Diabetes Federation.[6]
DM = diabetes mellitus; OGTT = oral glucose tolerance test.

Table 1. Diagnosis of Diabetes Mellitus

COMPLICATIONS OF DIABETES MELLITUS

Uncontrolled diabetes has certain acute complications such as hyperglycemia with ketoacidosis or the non-ketotic hyperosmolar syndrome. The long-term injurious effects of diabetes are categorized into microvascular and macrovascular complications.

The microvascular complications comprise of diabetic retinopathy leading to progressive loss of vision, nephropathy which is a leading cause of renal failure and neuropathy. Diabetic neuropathy is described the presence of clinical features of peripheral nerve dysfunction in diabetics after eliminating other causes. Peripheral neuropathy in diabetics may manifest in forms such as sensory, multifocal and autonomic neuropathies. Distal sensorimotor symmetric polyneuropathy is considered as the most common type of diabetic neuropathy, leading to foot ulcers, amputations and Charcot joints. Autonomic neuropathy manifests as gastrointestinal, genitourinary and cardiovascular clinical features.

The increased risk of atherosclerosis, platelet adhesion and hypercoagulability in diabetic patients form the basis of macrovascular complications in them. Diabetics are more at risk for cardiovascular, cerebrovascular and peripheral arterial disease. Chronic hyperglycemia leads to impairment of growth and susceptibility to certain infections.

Lower limb complications-

Diabetes leads to a multitude of complications in lower extremities as a result of its microvascular and macrovascular effects. (Figure 3) The combination of distal sensorimotor peripheral and autonomic neuropathy, vasculopathy and infection makes the foot of a diabetic patient susceptible. Consequently, they develop decreased sensations of pain, temperature, proprioception with small muscle wasting leading to foot deformities and dry skin leading to callus formation. All these put the patients' foot at risk for the formation of ulcers. Repetitive trauma to foot due to decreased sensations have a superadded effect on the vulnerable foot for ulcer formation. [20]

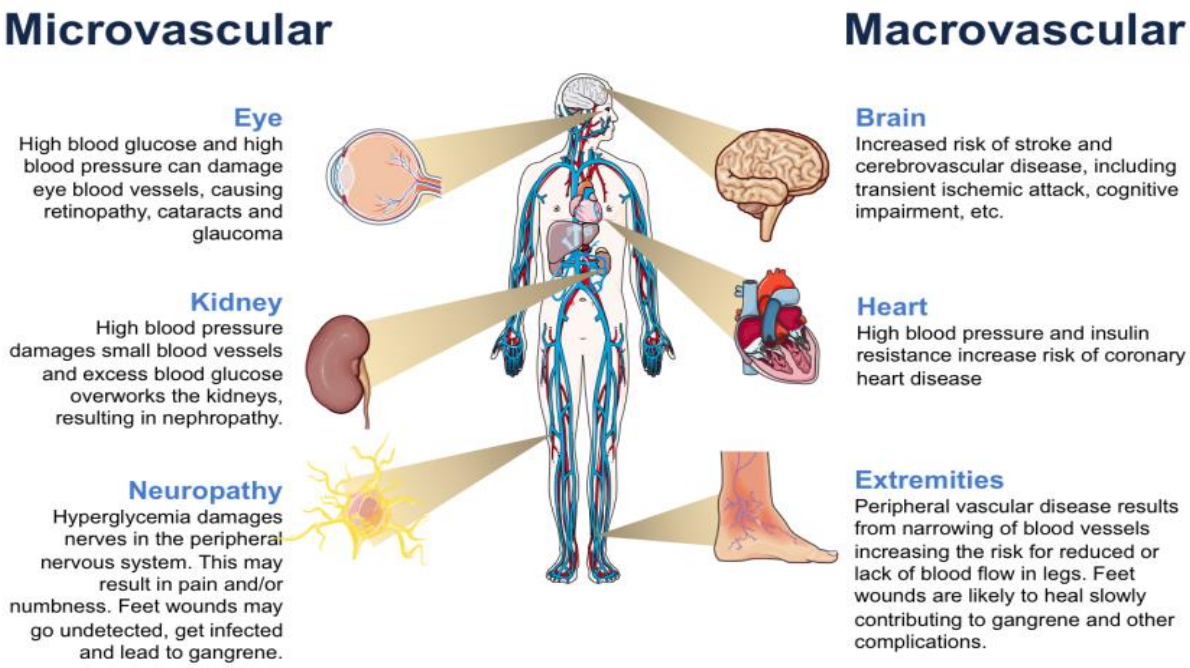


Figure 3. Major microvascular and macrovascular complications associated with diabetes mellitus.

DIABETIC FOOT ULCER

Diabetic foot' is defined as "Infection, ulceration or destruction of tissues of the foot of a person with currently or previously diagnosed diabetes mellitus, usually accompanied by neuropathy and/or peripheral arterial disease in the lower extremity." [21]

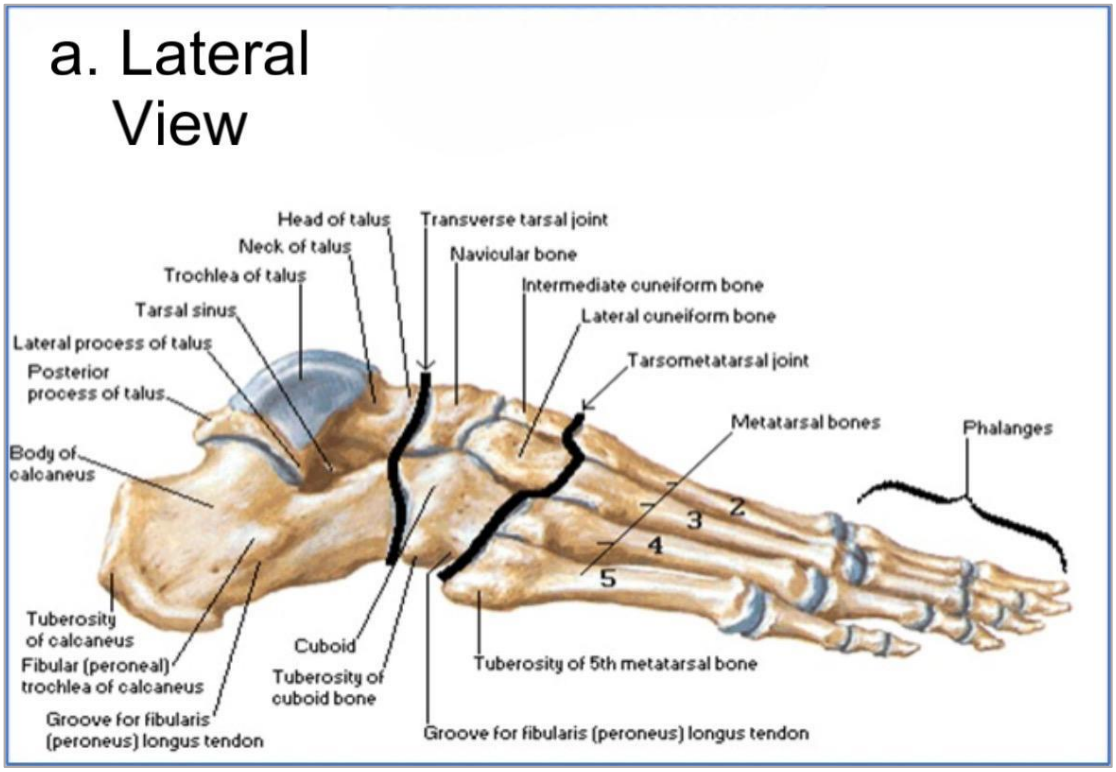
Diabetic foot is one of most common, expensive as well as severe complications of diabetes.

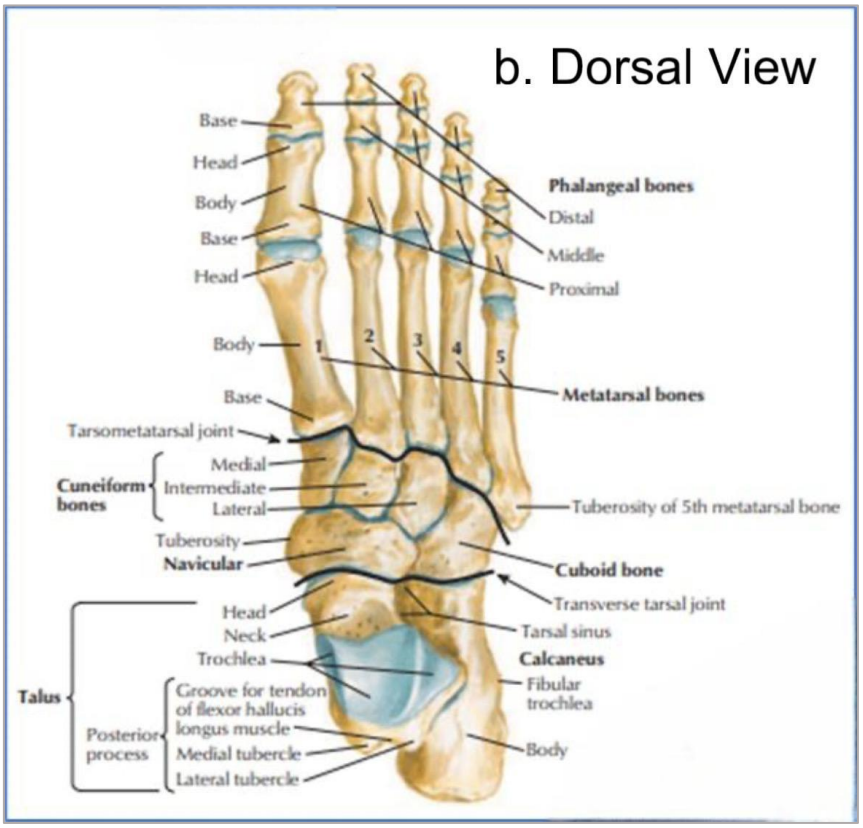
Estimates suggest 15% of diabetics carry a risk of forming diabetic foot ulcers in their lifespan, from where15-20% cases eventually result in need for amputation.[22] Every half minute one lower limb or part of lower limb gets lost worldwide because of diabetes. [23] In India, approximately 40,000 lower limbs are lost in amputation every year. Of these, more than 75% cases are due to neuropathy with superadded infection, which are potentially avoidable. [22]

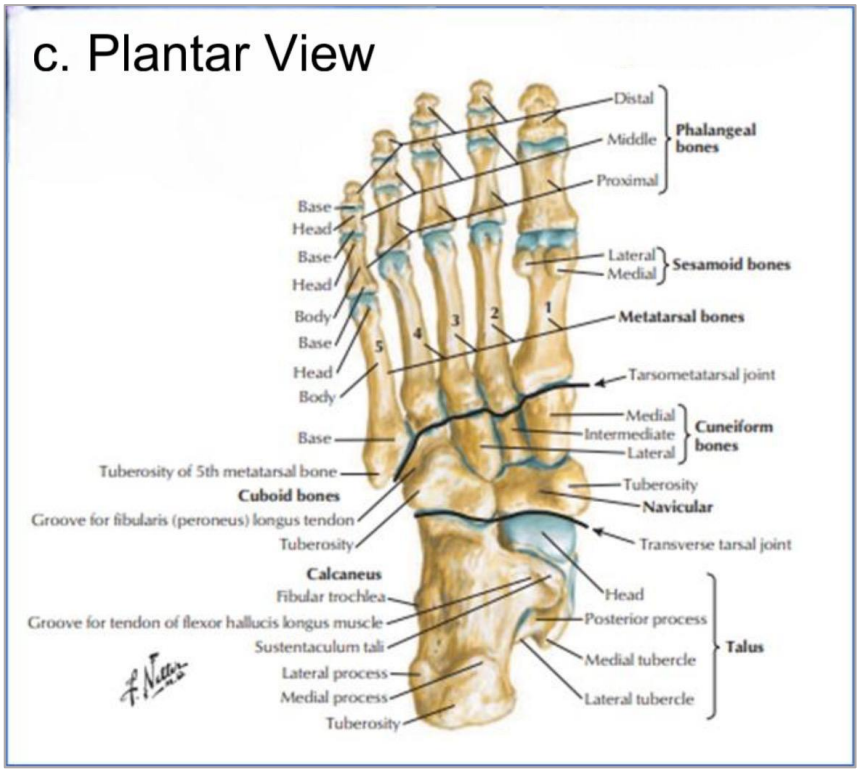
SURGICAL ANATOMY OF FOOT

The foot is an integrated complex of tendons, ligaments, muscles and bones arranged in arches with an intricate neurovascular framework. It provides a pedestal to carry entire weight of body and forms crux of locomotion. The foot skeletal framework comprises of 7 tarsals, 5 metatarsals and 14 phalanges. The hindfoot comprises of talus and calcaneum. The midfoot includes cuboid, navicular and cuneiforms and the forefoot includes phalanges and metatarsals (Figure 4) [25,26,27].

Figure 4. BONES OF FOOT







Skin, Subcutaneous Tissue, and Deep Fascia of the foot

The skin over the plantar aspect or the sole of the foot is thicker and more sensitive than that of the dorsal aspect. The subcutaneous tissue deep to the plantar skin is more fibrous and compact than the loose tissue deep to the dorsal skin. Fibrous septa attach the skin to the plantar aponeurosis preventing excessive movement of skin during walking. This improves the plantar grip during locomotion. These 'modified skin ligaments' also concentrate the subcutaneous fat over the weight bearing areas of heel, sole's lateral margin as well as across plantar aspect of heads of metatarsals. This helps those areas to act as shock absorbing pads. The skin over the sole has characteristic lack of sebaceous glands and hair follicles and marked presence of numerous sweat glands. [25,26]

The deep fascia is a distal extension of the inferior extensor retinaculum over dorsum of foot. This is called 'plantar fascia' over sole of foot, where it has a more complex distribution being thicker in the central area and weaker in the medial and lateral areas. The plantar fascia holds paramount importance in the maintenance of the longitudinal arches of the

foot. It also protects the plantar aspect of foot from injury and keeps the parts of foot intact. The stronger central portion is termed as the 'plantar aponeuroses. It extends from the calcaneum distally and ends within its own modifications namely the 'fibrous digital sheaths' enclosing the 5 flexor tendons and 'superficial transverse metatarsal ligament' over metatarsal heads (Figure 5). [25,26]

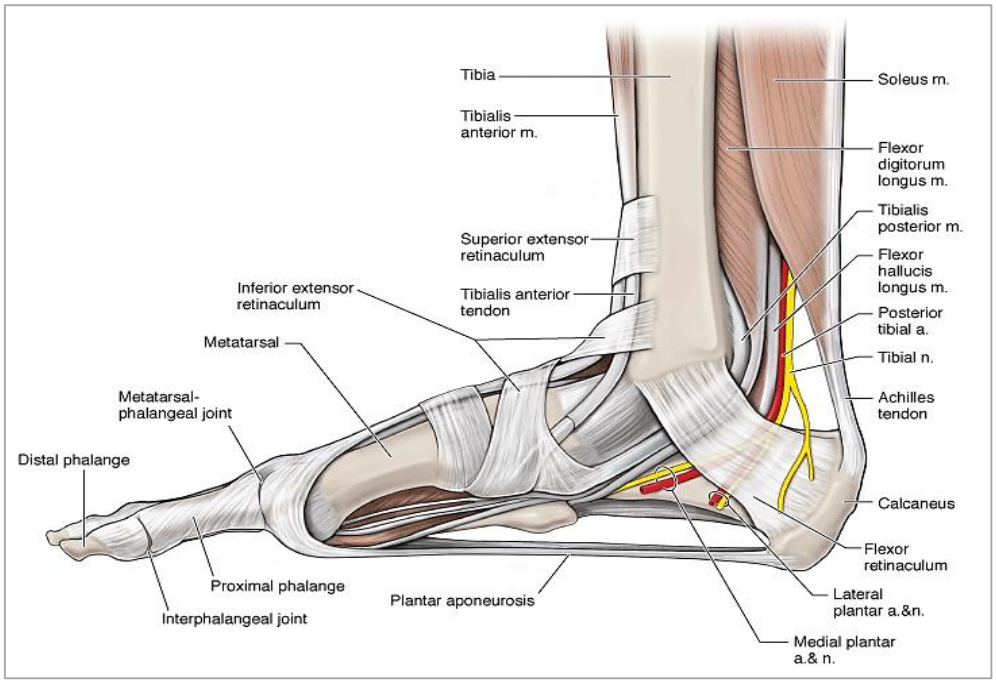


Figure 5. Medial view of the fascia of the right foot.

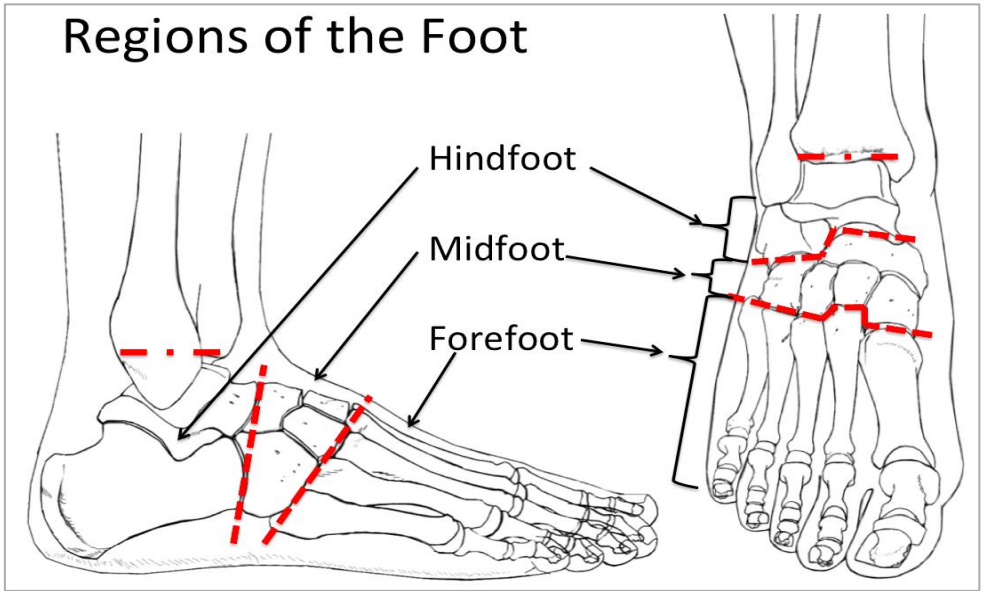


Figure 6. Regions of the foot

Layers of Foot

Each foot comprises of 20 muscles. There are 2 on the dorsal aspect, 4 in the intermediate position and 14 muscles on sole of foot. The muscles of the sole of foot are divided into four layers within four compartments. All the muscles of the sole together stabilize the foot during the support phase of stance by maintaining the integrity of the arches of the foot (Figure 7). [25,26]

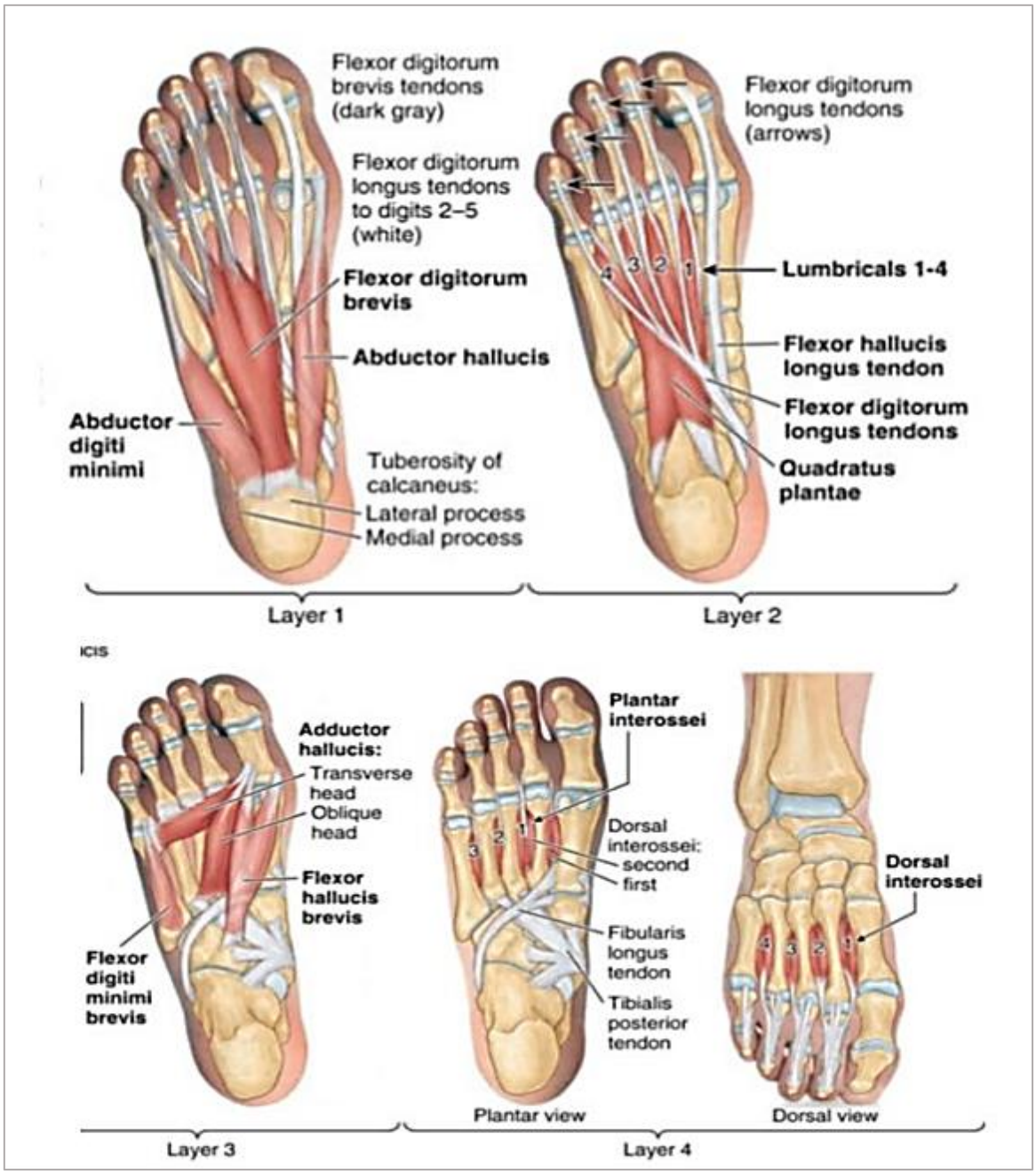


Figure 7. Muscles of dorsum of foot

Innervation of foot

The muscles of sole of foot are innervated by medial and lateral plantar nerves that are tibial nerve's end branches. The Extensor digitorum brevis muscle on the dorsum of foot is innervated by lateral branch of deep fibular nerve (Figure 8).

Cutaneous nerve supply of foot is by the following nerves:

1) Superficial fibular(peroneal) nerve – medial and lateral cutaneous branches
2) Deep fibular(peroneal) nerve
3) Sural nerve
4) Saphenous nerve
5) Medial and lateral plantar nerves

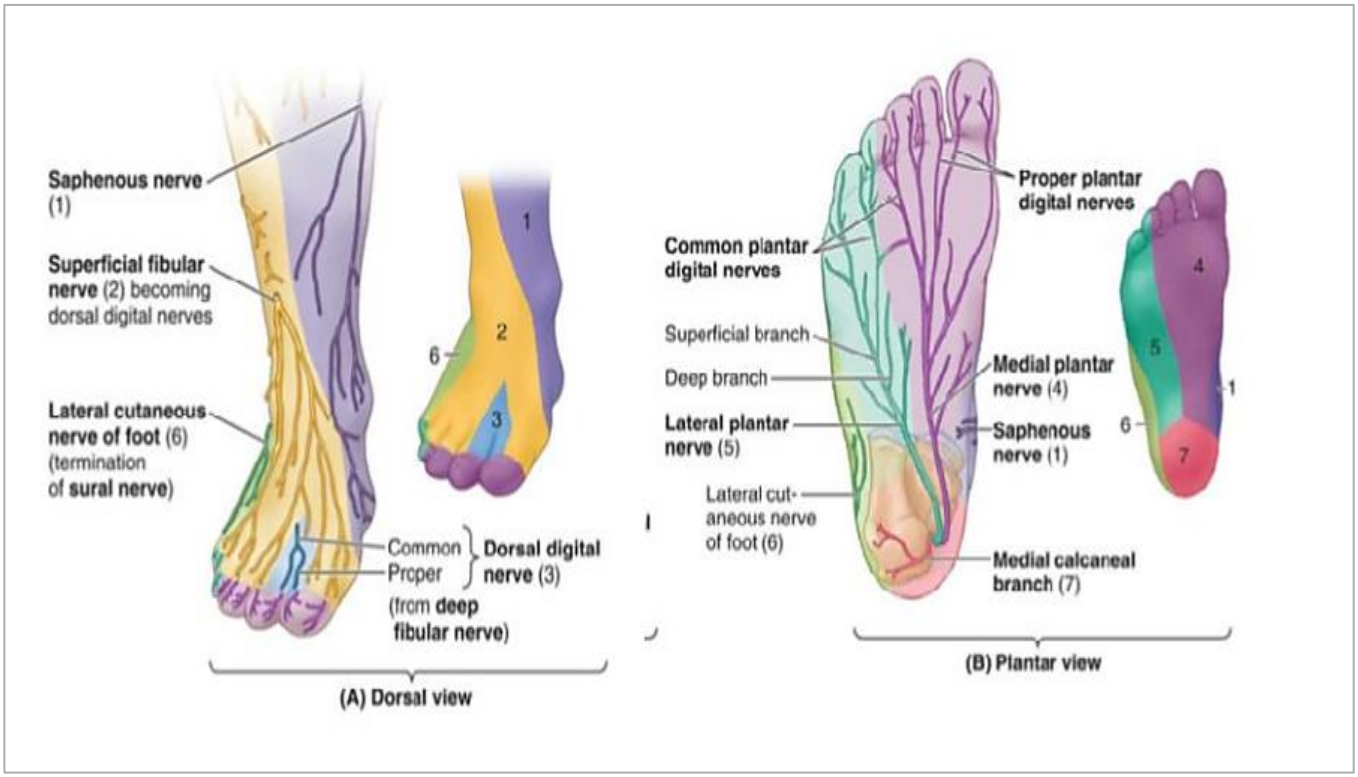


Figure 8. Cutaneous nerve supply dorsum and plantar aspects of foot

Blood Supply of Foot

Dorsum of Foot-

Supply by Dorsalis pedis artery that is the Anterior tibial artery's continuation.

Dorsalis Pedis artery branches (Figure 9) [28]:

- Lateral tarsal artery
- Arcuate artery
- First dorsal metatarsal artery
- Deep plantar artery (terminal branch

Sole of the foot is supplied by end branches of Posterior tibial artery:

- Medial plantar artery
- Lateral plantar artery

Plantar arch that is created by anastomoses between deep plantar artery and lateral plantar artery, gives plantar metatarsal arteries to toes.

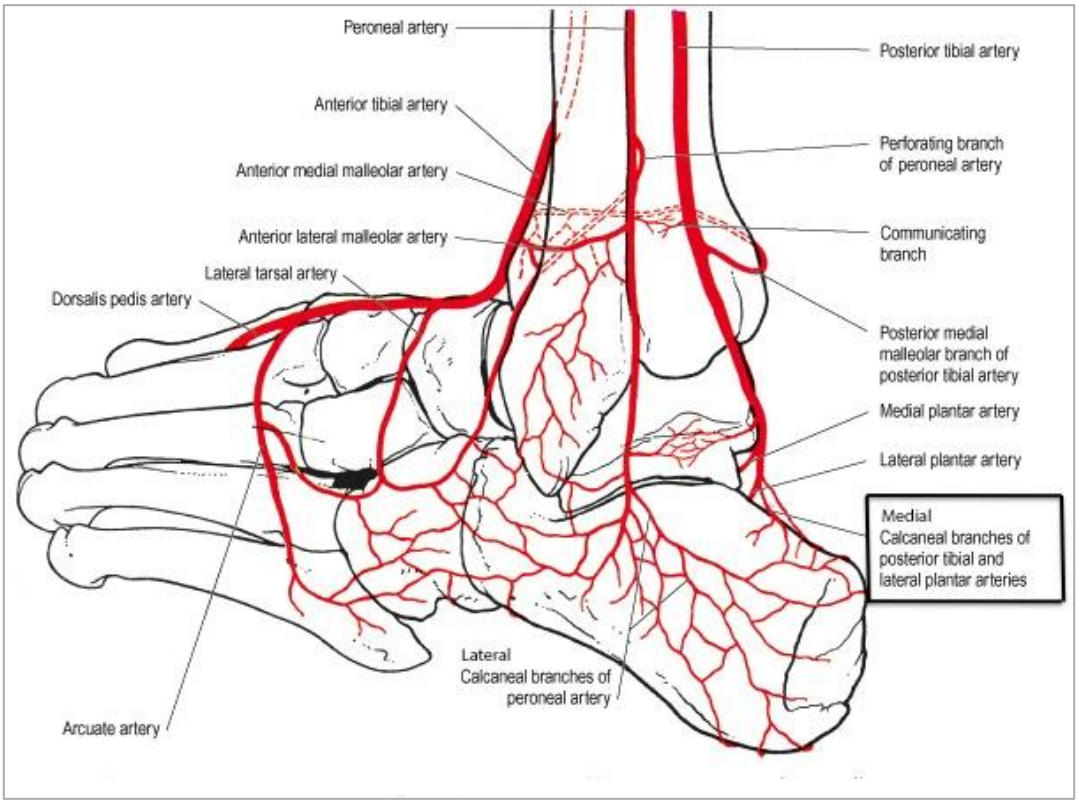


Figure 9. Blood supply to foot

The Dorsal venous arch drains majority of blood in foot through digital veins and communicating veins from sole into great saphenous vein medially and short saphenous vein laterally. On the sole of foot, medial and lateral plantar veins traverse along with their corresponding arteries and ultimately unite to form posterior tibial venae comitantes. (Figure 10) [25,26]

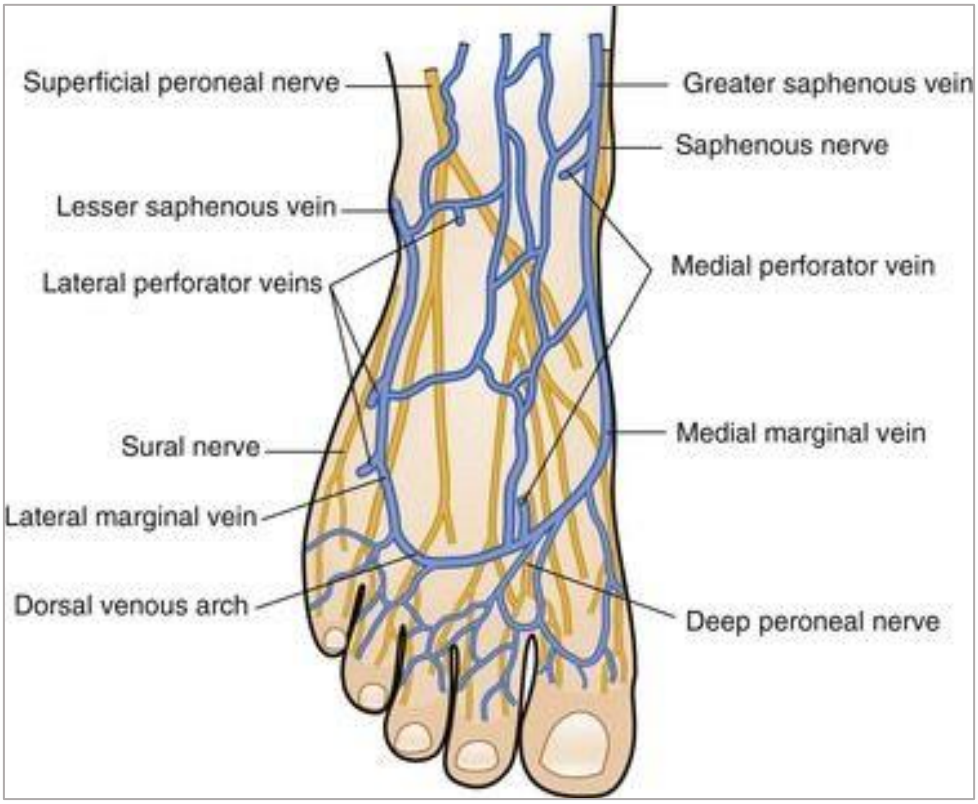


Figure 10. Venous Systems of the foot

Arches of the Foot

Arches of foot comprise of bones of foot held together by ligaments, tendons and muscles forming an intricate elastic structure. These arches allow foot to support entire weight of body. Different arches of foot are as follows (Figure 11) [25,26,29]

- Longitudinal arch. (Medial & Lateral).
- Transverse arch. (Mid-tarsal & Anterior transverse)

Functions of the arches of the foot:

1) Uniform distribution of the weight of the body over the entire foot.

2) To act as a propellant for locomotion.

3) To enable the foot to adapt to changes in surface contour.

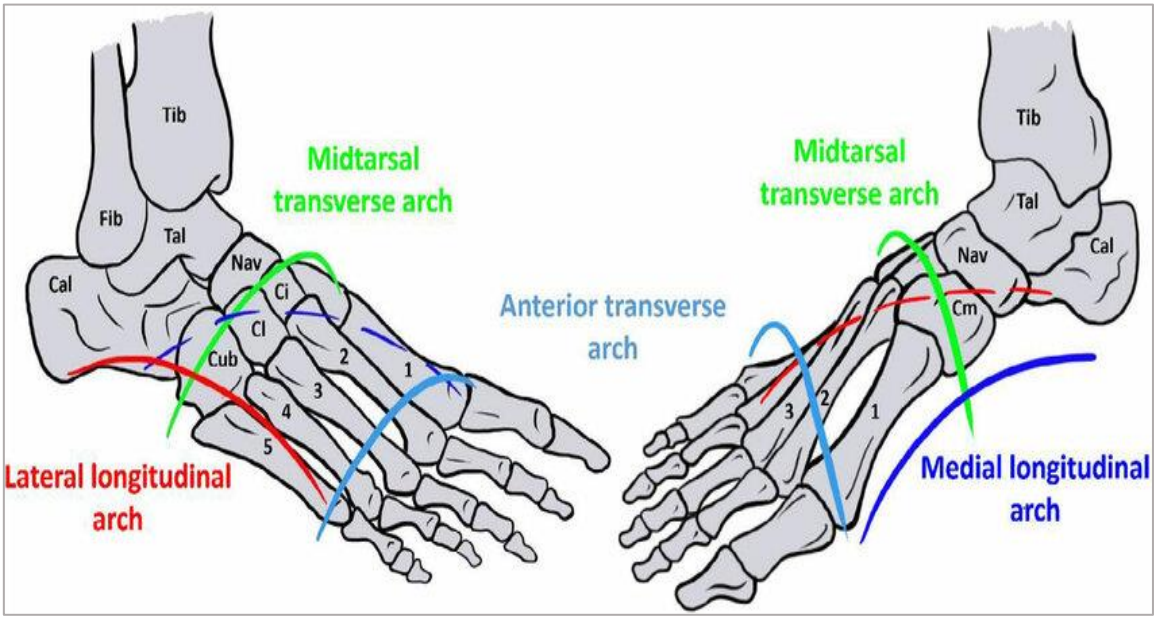


Figure 11. Arches of the foot

The foot arches are supported by (Figure 12) [28]:

A) Passive Supports:

1) Ligaments of the foot

- The most significant in maintaining the arches.
- Plantar Calcaneo-navicular ligament, Short & Long Plantar ligaments.

2) The plantar aponeurosis.

3) The structure of the bones.

B) Dynamic Supports:

1) The action of intrinsic and extrinsic muscles

2) The action of the long tendons extending into the foot - Flexor digitorum longus, Flexor hallucis longus, Fibularis longus, Tibialis posterior.

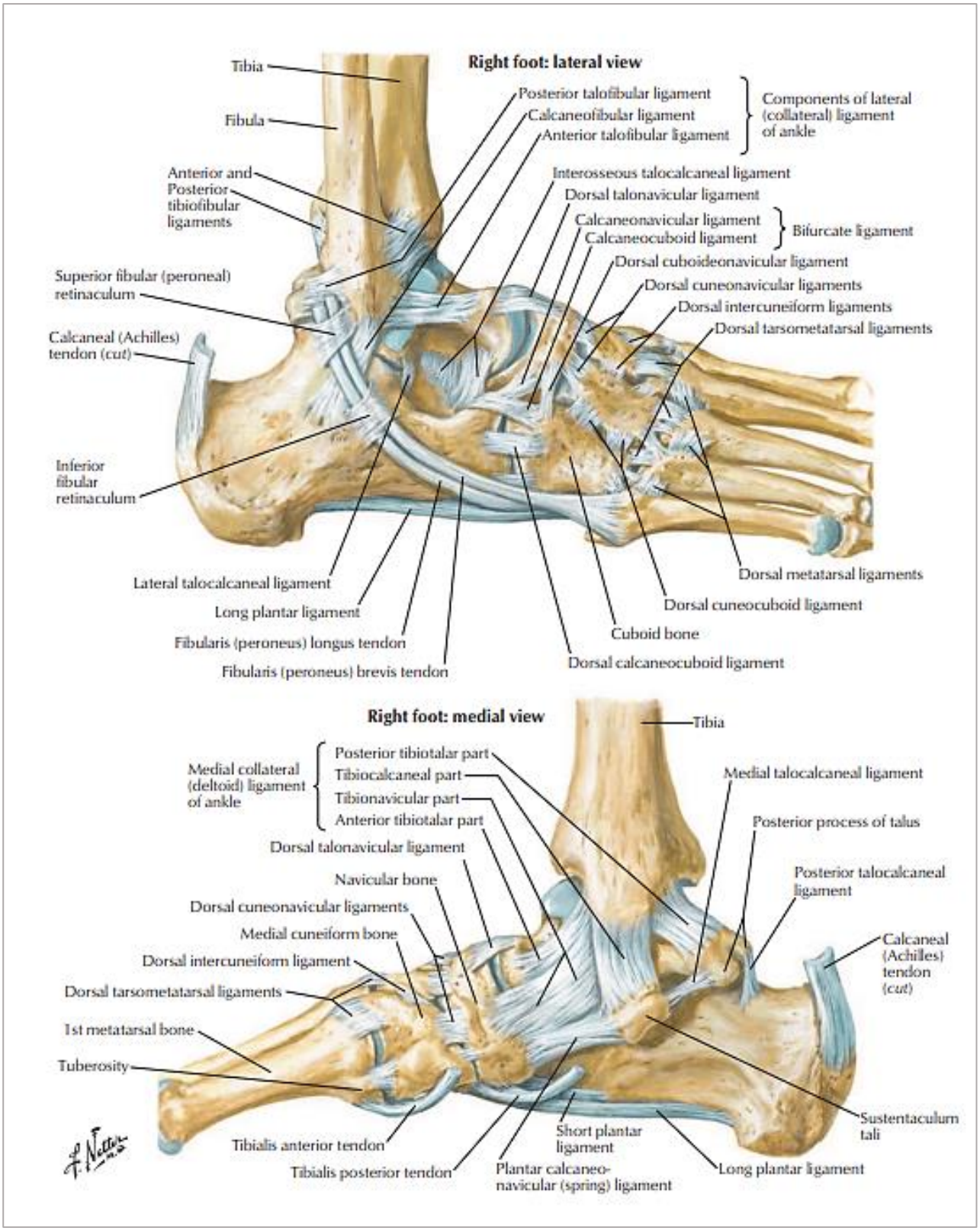


Figure 12. Ligaments and Tendons of Foot

PHYSIOLOGY OF WOUND HEALING

This is an intricate dynamic mechanism that replaces nonviable tissue. Chronic conditions such as diabetes mellitus predispose the skin to impaired wound healing. [24] A thorough understanding of the physiology of wound healing holds paramount importance in dealing with local and systemic factors that hamper the normal healing process. This in turn allows to develop wound healing strategies that allow a faster road to recovery.

Physiological wound healing is described under four distinct phases which progress in a linear fashion (Figure 13 & 14) [30].

1) Phases of Haemostasias

Disruption of tissue integrity leads to vascular injury both at the microvascular and macrovascular level. Damaged arteries constrict by smooth muscle contraction due to rise in cytoplasmic calcium levels. The decreased tissue blood flow due to vasoconstriction cause tissue hypoxia and acidosis. This leads to synthesis and release of vasoactive substances such as nitric oxide and adenosine causing reflex vasodilatation of arterioles and arteries. The process is further accentuated by mast cells which secrete histamine causing vasodilatation and increase in vascular permeability. Thus, a state of increased inflammatory cells in extracellular space is created.

The phase of hemostasis finally leads to clot formation which is supported by the intrinsic and extrinsic pathway along with platelet activation mechanism. The activated platelets also facilitate the wound healing process by releasing more than 300 crucial signalling molecules such as transforming growth factor or TGF, platelet derived growth factor or PDGF and the vascular endothelial growth factor or VEGF. These in turn stimulate other platelets, endothelial cells and leucocytes. The final step of this phase is the derivation of prostaglandins and leukotrienes from arachidonic acid as a result of the

injured cell membrane in wounds. These provide the adequate stimulus to initiate the inflammatory phase. [24,31].

2) Phases of Inflammation

The 'first responders' of this phase are neutrophils, which accelerate a series of events such as the leukotriene stimulation and complement cascade. These in turn lead to 'chemotaxis' or the passage of neutrophils down the chemical gradient toward the wound. Neutrophils further promote the destruction of bacteria by phagocytosis, degranulation and release of toxic products like neutrophil elastase, cathepsin and proteases and finally by production of oxygen free radicals. In diabetics, decreased chemotaxis and phagocytosis has been implicated to impair this phase of wound healing. Macrophages dominate the wound healing cascade by 48-72 hours by releasing products like epidermal growth factor and transforming growth factor. These promote angiogenesis, granulation tissue formation and modulate the inflammatory process. The last contribution in this stage is provided by the lymphocyte after 72 hours. They produce extracellular matrix and remodel collagen thus, regulating wound healing. [24,31]

3) Phases of Proliferation

This step in the wound healing process marks the repair stage of the wound. It comprises of the following stages:

Angiogenesis -The initiating event of neovascularization is the production of transforming growth factor or TGF and platelet derived growth factor or PDGF from platelets once the platelet plug is formed. As a consequence of hypoxia, vascular endothelial growth factor or VEGF is released which together with other cytokines begin genesis of blood vessels and repair of damaged vessels.

Fibroblast migration -The formation of clot stimulates the production of growth factors causing fibroblast proliferation. The fibroblasts lay down extracellular matrix

formed by hyaluronan, fibronectins and proteoglycans and ultimately collagen type 3 which provides the foundation of granulation tissue. The fibroblasts eventually transform phenotypically into myofibroblasts. The latter combine with the extracellular matrix proteins to initiate wound contraction. Collagen is the primary source providing strength to the regenerating tissue.

Epithelialization -This is marked by the proliferation of epithelium over the wound area covering the exposed surface and formation of attachments with the extracellular matrix. The movement of epithelial cells across the wound is supported by the embryological process of 'epithelial-mesenchymal transition'. This stage is complete by 24 hours in wounds healing by primary intention.

Wound retraction -Myofibroblasts are the pioneer mediators of this step which begins 7 days after the inciting stimulus to the tissue. The intercellular space is reduced by the actin- myosin interactions. Wound contraction occurs at a rate of 0.75mm/day. [24,31]

4) Phases of Remodelling

The last phase of wound healing aims at organization of the wound at the cellular level. This is achieved by maintaining a delicate balance between production and destruction of extracellular matrix proteins and formation of normal epithelium. Maturation of the scar tissue is further supported by replacement of the collagen type 1 with collagen type 3. Under normal circumstances, the wound area achieves a tissue strength of 50 % of its original by 3 months and 80 % of its initial capacity in the long run. [24,31]

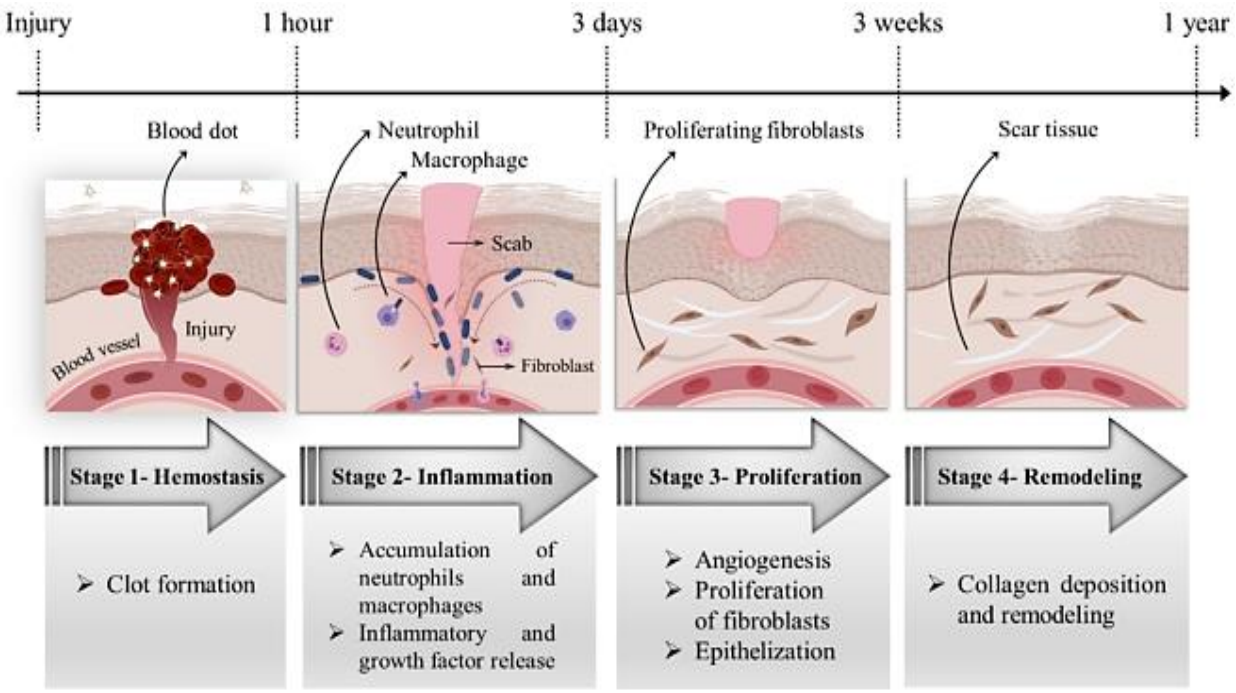


Figure 13. Stages of Wound healing

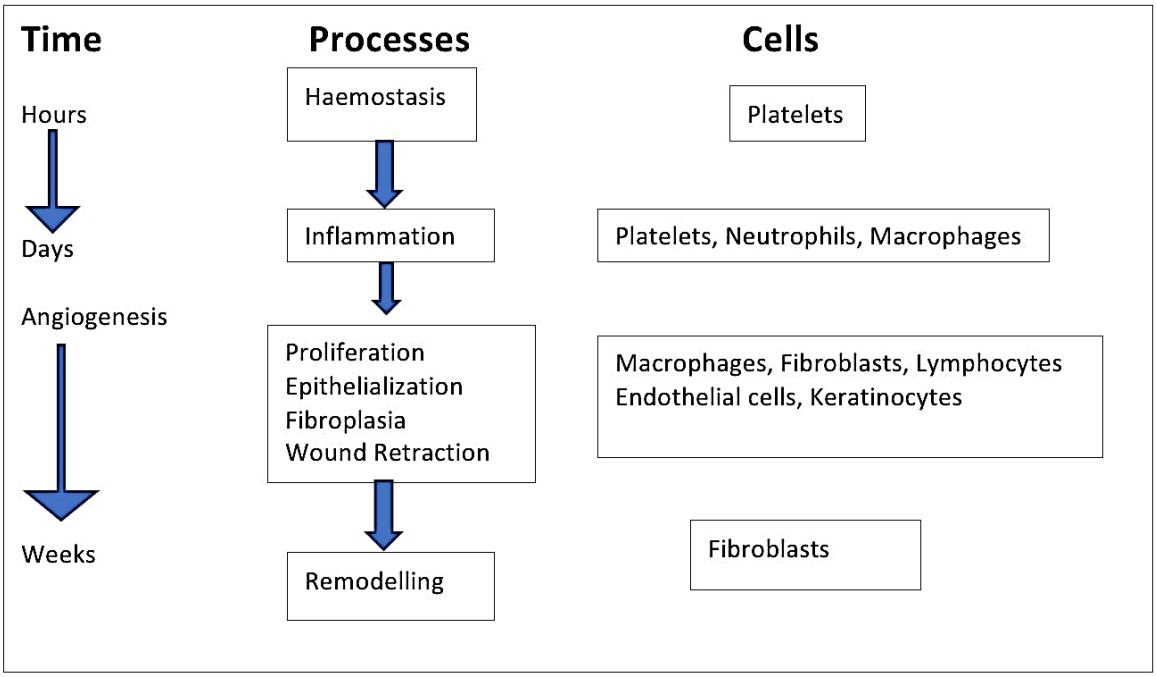


Figure 14. Physiology of wound healing

Factors affecting wound healing

The proliferative phase of wound healing in diabetics is hampered when growth factors like Transforming Growth Factor (TGF) and Insulin-like Growth Factor -1 (IGF-1) are absent and suboptimal functioning of enzymes is involved. Consequently, this prevents the proliferation of the cells and neovascularization in the tissue.

Matrix metalloproteinases (MMPs) are enzymes that maintain an optimal balance between production and degradation of extracellular matrix.

Diabetic wounds manifest increased levels of MMPs which results in unwanted degradation of extracellular matrix rich in tissue proteins favouring wound healing.

Additionally, defective migration of endothelial progenitor cells to the wound site occurs due to reduced Nitric oxide (NO).

The cumulative effect of all these factors results in delayed and impaired wound healing. [32,33]

ETIOPATHOLOGY OF DIABETIC FOOT ULCER

The crux of diabetic foot pathology is formed by hyperglycaemic state of diabetes. The mechanism behind diabetic foot ulcer formation comprises of interplay between neuropathy, vasculopathy and infection. (Figure 15)

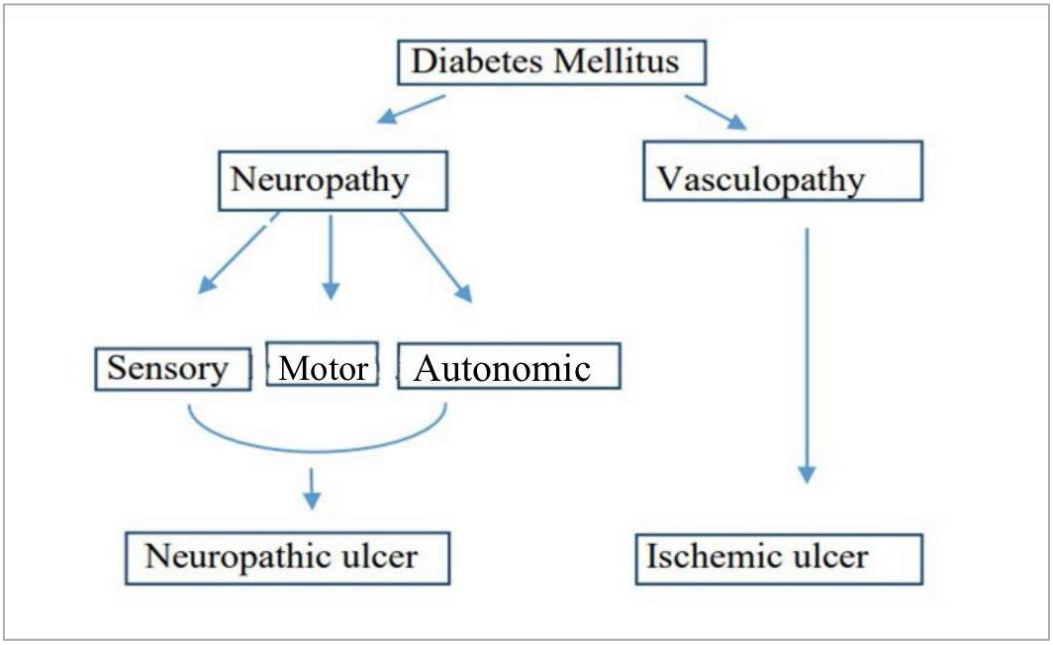


Figure 15. Pathophysiology of diabetic foot ulcer

RISK FACTORS:[26]

1) Peripheral neuropathy,
2) Peripheral arterial disease,
3) Poor sugar control,
4) Poor footwear,
5) Underlying infection and
6) Duration of diabetes are recognised risk factors for foot.

NEUROPATHY:

Chronic hyperglycemia leads to oxidative stress to neurons. Metabolic derangements such as nonenzymatic glycation and polyol pathway hyperactivity causes production of free radicals. This has a direct toxic effect on neurons along with reduction in nitric oxide production. The decrease in nitric oxide subsequently leads to endothelial dysfunction and thus reduced blood flow to the nerves. The sensori-motor neuropathy is typically symmetrical and is initiated from the distal extremities with an insidious progression centrally.

Sensor*y*-The loss of protective sensation of pain in the diabetic foot makes it more susceptible to trauma and consequently ulcer formation.

Motor- The nerve supply to intrinsic foot muscles is hampered due to destruction of the motor fibres. This leads to an imbalance between the flexion and extension of the foot due to atrophy of the intrinsic muscles. Hyperextension of the metatarso- phalangeal joint with flexion of the proximal or distal interphalangeal joints leads to claw toe and hammer toe deformities, respectively. The resultant foot deformities expose bony prominences which act as pressure points. This makes the foot a vulnerable target for skin erosion and ulcer formation.

Autonomi*c*- There is loss of sympathetic tone which causes increased arteriovenous shunting and inefficient nutrient flow. The functional impairment of sweat and sebaceous glands makes the foot dry and at a risk for skin breach. This predisposes the foot to ulcer formation and increases the risk for superadded infection.

Charcot Arthropathy is an amalgamation of motor, sensory and autonomic neuropathies in diabetics results. Decreased sensation along with muscle atrophy and joint laxity causes structural and functional deterioration of the foot. Autonomic neuropathy leads to impaired vascularity to the smooth muscle and the bones, leading to inflammation and bone resorption. The ultimate result is the damage to the arches of the foot which leads to 'rocker bottom' appearance of the foot. [22],[25],[34],[35]

MICROVASCULAR & MACROVASCULAR ANGIOPATHY:

The persistent hyperglycaemic state has a longstanding effect on the vasculature, ultimately progressing to peripheral arterial disease. The major hallmarks of vasculopathy are endothelial cell dysfunction and smooth cell abnormalities. There is increased release of thromboxane A2 which causes vasoconstriction and accelerated platelet aggregation resulting in plasma hypercoagulability. All these factors cumulatively cause lower limb ischemia in diabetics putting the foot in jeopardy for ulceration.

The diabetic vasculopathy has a specific binary manifestation- A nonocclusive microcirculatory impairment in the blood vessels of retina, peripheral nerves and kidney and a macro-circulatory disablement signified by atherosclerosis of blood vessels of the cardiac and peripheral vascular system.

Microvascular- Thickening of the capillary basement membrane hampers the leukocyte migration and creates a functional microcirculatory ischemia of the tissues after injury. This is further accentuated by the loss of neurogenic vasodilatory response to injury, making the foot more vulnerable to infection.

Macrovascular- Peripheral arterial disease is the hallmark of this complication. The lower extremity arterial disease presents primarily due to an accelerated atherosclerosis of tibial arteries. This finally results in critical limb ischemia and potential limb loss. [36,37,38]

INFECTIONS:

The entry of microorganisms through the sites of ulceration leads to the proliferation of microbes which ultimately causes an inflammatory reaction and advent of infection in the diabetic foot. The onset of infection in the foot can have disastrous consequences due to the presence of inter-communicating compartments. This along with the absence of pain sensation, which causes the patient to continue ambulation, allows rapid spread of the infection into deep seated soft tissues and even bone leading to osteomyelitis. Structures like plantar aponeurosis, fascia and muscle tendons do not possess the ability to resist infection. The combination of hyperglycemia, neuropathy and vasculopathy further reduces the body's immunity facilitating progressive spread of infection. One of the significant immune system changes observed in diabetics is increased T lymphocyte apoptosis which further delays healing. [34,35]

FOOT BIOMECHANICS

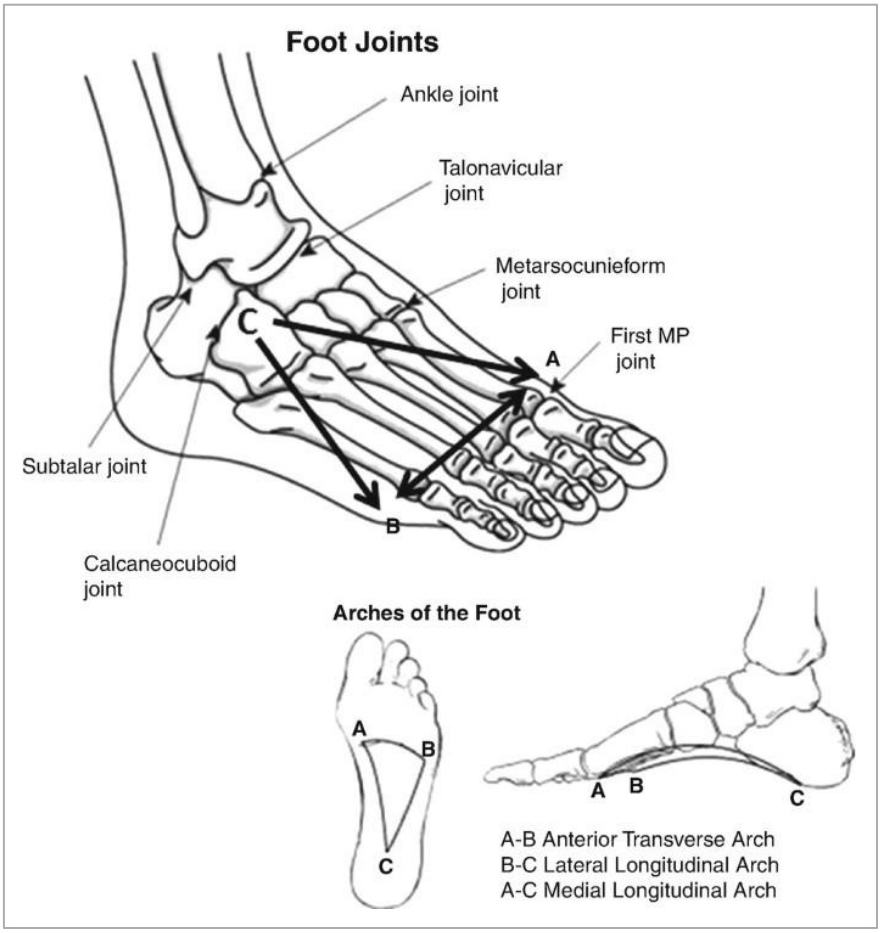


Figure 16. Biomechanics of the Diabetic Foot

The foot is exposed to an interplay of forces and their effects exerted on the foot structures. This forms the basis of foot biomechanics (Figure 16) [40]. In a diabetic foot appearing normal from the exterior, abnormal biomechanics is often the etiological factor behind abundant callus, foot deformities and foot ulcers. These ulcers show poor healing and tend to recur.

The basis of deranged biomechanics in a diabetic foot is formed by presence of peripheral neuropathy and elevated plantar pressure especially over sites of bony prominences. Due to loss of sensations over areas with lack of subcutaneous tissue and fat, the underlying tissue is exposed to damage and leads to callus formation. Once haemorrhage sets

in the callus, the site acts as a precursor to an ulcer. Additionally, trauma along with peripheral vascular disease act as significant factors causing tissue breakdown. [41,42]

The usual sites of ulcer in a diabetic foot are the plantar aspect of forefoot, midfoot and toes followed by the dorsum of heel and toe. Besides callus formation, the other intrinsic factors which increase plantar pressure are tissue quality, motor neuropathy leading to atrophy of foot muscles, and presence of foot deformities. Deformities such as clawing of toes, hammer toes and Charcot's arthropathy expose the heads of metatarsals, tips of toes and the midfoot, respectively to ulcer formation. Tissue breakdown is further accentuated by the absence of subcutaneous fat in these regions when the foot is deformed. [42]

Restricted joint movement at the metatarso-phalangeal, particularly that of the first toe, along with sub-talar joints, cause elevated plantar pressure. This is due to non-enzymatic glycosylation leading to stiffening of collagen at the joint capsules. The most pronounced extrinsic factors rising the plantar pressure are ill-fitting footwear and barefoot walking. [41,42]

There are three mechanisms which can give rise to elevated pressure in a diabetic foot predisposing it to ulcer formation.

1. Increased duration of pressures- A low pressure applied for a lengthy time duration leading to ischemia and consequent tissue breakdown. Usually noticed due to incorrect footwear or placement of the heel over aver a flat surface for long.
2. Increased magnitude of pressures- A large magnitude of force is applied over a relatively small area of skin such as trauma due to a sharp nail or glass piece in a diabetic patient with peripheral neuropathy. A 'foot slap' can cause the same nature of trauma. In this case, weak dorsiflexor muscles cause a decreased slowing down of the forefoot after the foot touches the ground.
3. Increased number of pressures- Failure of the tissue to maintain integrity because of recurrent loading as seen in a neuropathic diabetic foot. The foot is

subjected to repeated injury due to loss of sensations. This is also referred to as 'mechanical fatigue'. Kosiak et al in his study on ischemic ulcers, noted a reverse relationship between force and time. With a rise in force, there is a fall in the time period or frequency of force(s) essential to cause tissue damage. [36]

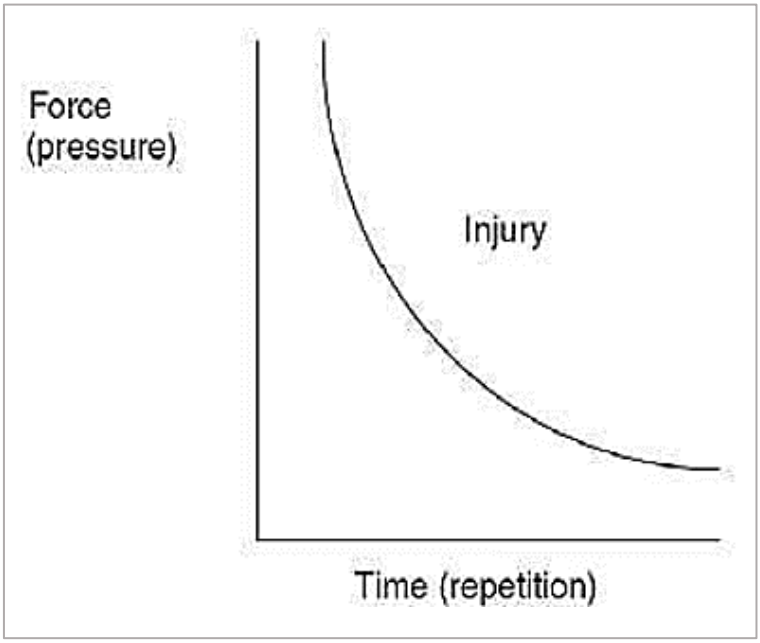


Figure 17. Relationship between Force and Time

The patient should undergo foot biomechanical assessment which comprises of testing for range of motion of joint, manual muscle strength testing and static and dynamic gait analysis. The treatment may include a limb salvage procedure followed by usage of off-loading devices such as prosthetics, custom accommodative and/ or functional orthotics, bracing and custom moulded shoes. Occasionally limb salvage surgery has to be followed with elective balancing procedures. The latter includes tendon transfer and lengthening, bony reconstruction and fusion procedures.[43]

CLASSIFICATIONS

1. The major classification is as follows (Table 2) [37,38]

    1. The Neuropathic foot – Neuropathy is predominant in this condition.

    2. The Ischemic foot- Vasculopathy is predominant.

    3. The Neuroischemic foot – Vasculopathy is predominant although neuropathy plays a major contributory role.

Feature	**Neuropathic ulcer**	**Ischemic ulcer**	**Neuro-ischemic ulcer**
Sensation	sensory loss	pain	degree of sensory loss
Callus/necrosis	callus present and often thick	necrosis common	minimal callus; prone to necrosis
Wound bed	pink and granulating surrounded by callus	pale and sloughy with poor granulation	poor granulation
Foot temperature and pulses	warm with bounding pulses	cool with absent pulses	cool with absent pulses
Other	dry skin and fissuring	delayed healing	high risk of infection
Typical location	weight-bearing areas of the foot, such as metatarsal heads, the heel and over the dorsum of clawed toes	tips of toes, nail edges and between the toes and lateral borders of the foot	margins of the foot and toes

Table 2. Types of Diabetic foot ulcer

2. The Wagner classification (Table 3) (Figure 18) [44]

Grade	Description
Grade 0	Inta, symptoms like pain in the foot (neuropathy)
Grade 1	A superficial ulcer that involves the entire thickness of the skin but not the underlying tissues
Grade 2	A deep ulcer that penetrates down to the muscle and Ligaments but does not affect the bones
Grade 3	A deep ulcer that involves inflammation of the bone, Abscess formation
Grade 4	Partial foot or localized gangrene
Grade 5	Severe gangrene that extends to the whole foot

Table 3. The Wagner classification

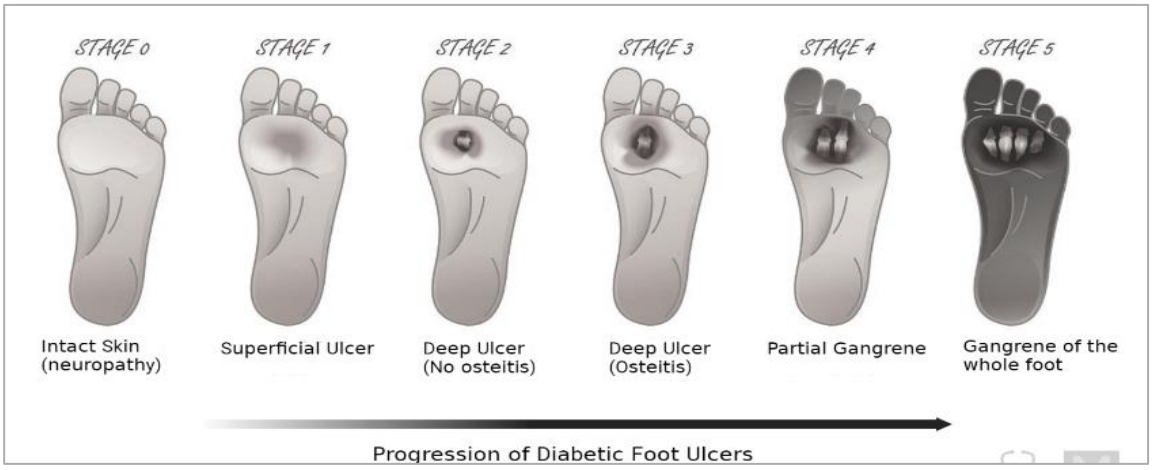


Figure 18. The Wagner classification

3. The most widespread used and accepted classification is the University of Texas Wound Classification System (Table 4) [44]

University of Texas Diabetic Wound Classification System				
Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre or post ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Would penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemi

Table 4. University of Texas Wound Classification System

4. The PEDIS Classification (Table 5) [44]

	Grade	Symptoms
Perfusion	**P1**	No symptoms/signs of PAD
	P2	Symptoms/signs of PAD, but not of CLI
	P3	CLI
Extend/size	**E**	Wound size (measured in square centimetres)
Depth/tissue lost	**D1**	Superficial full thickness ulcer, not penetrating any structure deeper than the dermis
	D2	Deep ulcer, penetrating below the dermis to subcutaneous structures, involving fascia, muscle, or tendon
	D3	All subsequent layers of the foot involved, including bone and/or joint (exposed bone, probing to bone)
Infection	**I1**	No symptoms or signs of infection
	I2	Infection involving the skin and the subcutaneous tissue only (without involvement of deeper tissues and without systemic signs); at least 2 of the following items are present: - local swelling or induration, - erythema > 0.5 to 2 cm surrounding the ulcer - local tenderness or pain - local warmth - purulent discharge
	I3	Erythema > 2 cm plus one of the items described above or infection involving structures deeper than skin and subcutaneous tissues (abscess, osteomyelitis, septic arthritis, fasciitis) without systemic inflammatory response signs
	I4	Any foot infection with the following signs of a SIRS manifested by two or more of the following conditions: - Temperature >38 or <36 Celsius - Heart rate > 90 beats/min - Respiratory rate > 20 breaths/min - PaCO2 <32 mm Hg - White blood cell count >12,000 or <4,000/cu mm - 10% immature (band) forms
Sensation	**S1**	No loss of protective sensation
	S2	Loss of protective sensation with absent pressure sensation on 2 of 3 sites on the plantar side of the foot or absent vibration sensation or vibration threshold >25 V on the hallux

Table 5. The PEDIS Classification

ASSESSMENT

This begins with a thorough history of the patient enquiring about any past history of ulcers, amputation, trauma, history of intermittent claudication and rest pain, loss of sensations to lower extremity. The general physical examination of the patient should look for any signs of anaemia, sepsis with or without fever.

Local examination should reflect the presence of any active infection in the form of ulcer, wet or dry gangrene of the lower limb. Other lesions such as skin cracks and fissures, presence of fungal infection, macerated skin especially in web spaces and calluses should be looked for.

Presence of deformities such as the claw toes, hammer toes, hallux limitus, hallux rigidus and pes cavus determine the chronicity of the diabetic infection in the foot. There is possibility of high arched foot with visible muscle wasting on the plantar and dorsal aspect of the foot.

On palpation, the temperature denotes the underlying pathology with a cold foot signifying peripheral ischemia and a warm foot pointing towards active infection of the limb.

According to 'The International Working Group on the Diabetic Foot' and the 'Infectious Disease Society of America', there is a validated clinical criterion for recognizing and classifying diabetic foot infection depending on its severity (Table 6) [37]

Clinical criteria	Grade/severity
No clinical signs of infection	Grade 1/uninfected
Superficial tissue lesion with at least two of the following signs: — Local warmth — Erythema >0.5–2cm around the ulcer — Local tenderness/pain — Local swelling/induration — Purulent discharge Other causes of inflammation of the skin must be excluded	Grade 2/mild
Erythema >2cm and one of the findings above or: — Infection involving structures beneath the skin/ subcutaneous tissues (eg deep abscess, lymphangitis, osteomyelitis, septic arthritis or fascitis) — No systemic inflammatory response (see Grade 4)	Grade 3/moderate
Presence of systemic signs with at least two of the following: — Temperature >39°C or <36°C — Pulse >90bpm — Respiratory rate >20/min — $PaCO_2$ <32mmHg — White cell count 12,000mm^3 or <4,000mm^3 — 10% immature leukocytes	Grade 4/severe

Table 6: Classification of Diabetic foot infection

Examination for Peripheral neuropathy

One of the simple and effective methods used for testing the peripheral neuropathy involves using a 10g (Semmes-Weinstein) monofilament. A 10 g monofilament, when placed over the sole and bent, exerts a buckling force of 10g. (Figure 21) The inability to sense this pressure is termed as sensory absence. Despite its affordability and portability, this test can have a variable accuracy in testing for neuropathy. The other commonly used simple method is using a standard 128 Hz tuning fork to test for vibration. (Figure 19) In order to increase the accuracy in diagnosis, this test can be combined with other modalities like neurothesiometer and biothesiometer. (Figure 20) [42,45].

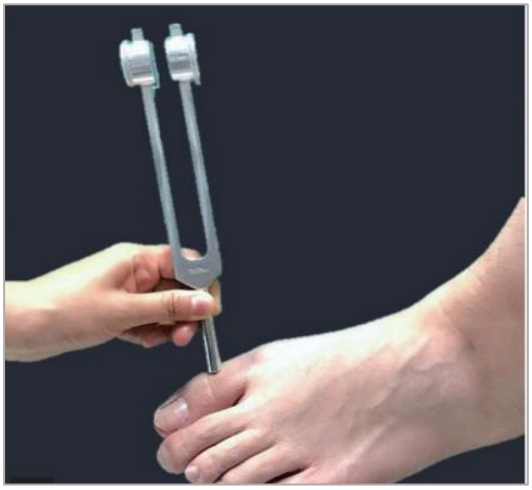


Figure 19: Tuning Fork test

Figure 20. Biothesiometer

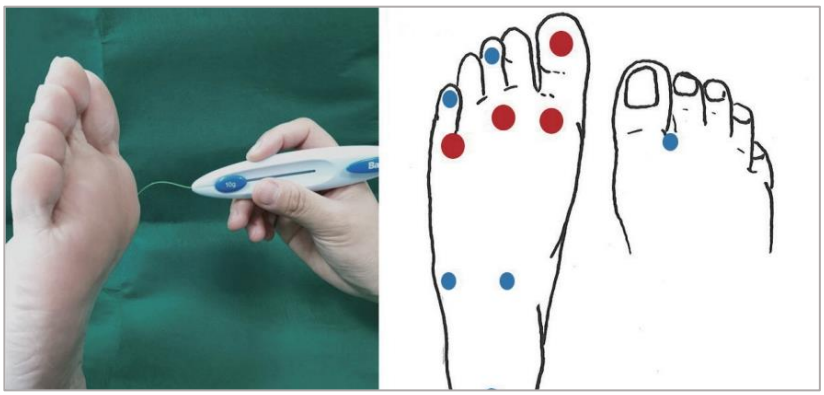


Figure 21. Monofilament test

Examination for Peripheral arterial disease

Peripheral arterial disease is present in approximately 40% of patients with diabetic foot ulcers. Along with palpation of the lower limb peripheral arteries, the ankle brachial pressure index (ABPI) can be a reliable measure to quantify the extent of peripheral arterial disease.

It is the ratio of the maximum ankle systolic blood pressure to the arm systolic blood pressure quantified using a doppler. Normally the ABPI ranges between 0.9-1.3.

The limitations of this technique are user dependency, availability of equipment, lack of training. There is a possibility of a false high value owing to diabetics having calcified arteries with poor compressibility.

The severity of the vasculopathy is estimated as per the following table (Figure 7) [46]

ABPI	Interpretation
>1.3	Consider presence of calcification
1.0–1.3	Likely normal
0.9–1.0	Possible mild disease, borderline PAD
0.5–0.9	Claudication
0.3–0.5	Severe occlusive disease
<0.3	Critical limb ischaemia

PAD: peripheral arterial disease.

Table 7. Estimation of Severity of the vasculopathy

Those with ABPI more than 1.3 due to noncompressible vessels can be subjected to alternative tests such measurement of systolic pressures in toes, pulse volume assessment, duplex ultrasound or transcutaneous oxygen quantification. Derangement in these tests prove the presence of peripheral arterial disease. [37,45,47]

INVESTIGATIONS:

1) Complete hemogram- haemoglobin and total leucocyte count to rule out anaemia and infection respectively.

2) Renal function test- to rule out diabetes induced nephropathy.

3) Xray of foot (Anteroposterior and lateral view)- to rule out osteomyelitis, foot deformities, Charcot's arthropathy, etc.

4) Wound swab culture and sensitivity- to look for infective microorganisms and specific antibiotic treatment.

5) Fasting blood sugar level and HbA1C- to know extent of glycemic control.

6) Urine ketone bodies- to rule out diabetic ketoacidosis.

7) Doppler study of lower limb- to look for diabetic vasculopathy changes.

TREATMENT:

The principle aim of diabetic foot ulcer management is wound closure. The target is to treat the diabetic foot ulcer at an early stage to facilitate its faster healing.

Managing diabetic foot complications aims to maintain the patient at the lowest possible stage. It is crucial to intervene promptly at each stage to halt progression. Immediate treatment is imperative for foot ulcers at stages 3, 4, or 5. Effective management necessitates a collaborative effort involving various specialists such as podiatrists, physicians, nurses, orthotists, radiologists, and surgeons.

The introduction of 'diabetic foot clinic' has been pioneer in setting new benchmarks in this arena. [47,48]

The key components of diabetic foot ulcer wound management are:

A. Treat the underlying cause

B. Local ulcer care

C. Pressure offloading

A. TREAT THE UNDERLYING CAUSE

It is crucial to identify the underlying causative factor of the diabetic foot ulcer. If detected during foot assessment, it should be treated along with the local wound care for a holistic approach to wound management.

Treatment of peripheral ischemia: Those having critical limb ischemia and superadded ulcers need treatment with medical therapy besides being considered for revascularization procedures. This not only accelerates the wound healing process but also delays a possible future amputation for the patient.

Achieving optimal diabetic control: It is necessary to aim for a tight glycemic control with proper tackling of risk factors like raised blood pressure, hyperlipidaemia and smoking. Optimal blood glucose aids wound healing, prevents adverse effects on immune system and inhibits infection. Nutritional deficiencies should be diagnosed if any and addressed accordingly. [47,49]

Identification of physical cause of trauma: It is important to do the patient's foot and footwear examination. The footwear reflects whether it is a proper fit and type, and helps to rule out the presence of pebbles, sharp objects etc. which might traumatize the foot.

B. LOCAL ULCER CARE

A balanced debridement, frequent inspection, avoidance of infection and excessive moisture to prevent maceration are crucial. It includes four components which tackle the various pathophysiological factors leading to a chronic diabetic foot ulcer. The framework for optimal local ulcer treatment is:

1. *Debridement of tissue*
2. *Local ulcer care with infection control*
3. *Moisture care*
4. *Advancement of epithelial edge*

1. DEBRIDEMENT OF TISSUE

The process of debridement is executed in all wounds, especially in those which are chronic in nature. It involves eliminating necrotic and nonviable tissue, and consequently formation of granulation tissue.[49] The frequency and extent of debridement required depends on the rate of healing of the ulcer.

The necessity of repeated wound debridement in certain ulcers is in order to maintain its wound bed. At every dressing, the need for debridement is assessed. Not opting to debride a wound and choosing the wrong method of doing it can both delay ulcer healing and lead to hazardous consequences. When undertaken in the operation theatre, this procedure is followed by aggressive cleansing of the deep-seated cavities in and around the wound.

The various modalities of ulcer debridement are as follows:

i) **Surgical**

Although there is no proven best method of debriding an ulcer, surgical debridement is considered as a gold standard technique in practice. Regular, sharp debridement with scissors and scalpel and /or forceps have the benefits of removal of slough, hyperkeratotic and necrotic tissue, and callus till viable bleeding tissue is visualized. It helps to drain pus or any other discharge, reduces pressure over the ulcer and allows clear inspection of the underlying floor and base of the ulcer. Surgical debridement helps to optimize efficacy of topical preparations on the ulcer which in turn promotes faster healing, e.g. CaS-HA (Figure 22) [50].

In patients with compromised peripheral vascular status needing revascularization, sharp debridement is not advocated. This is due to the risk of injury to the tissues with poor blood supply. A selective 'toothpick' approach rather than a more aggressive technique is considered more suitable in such patients.

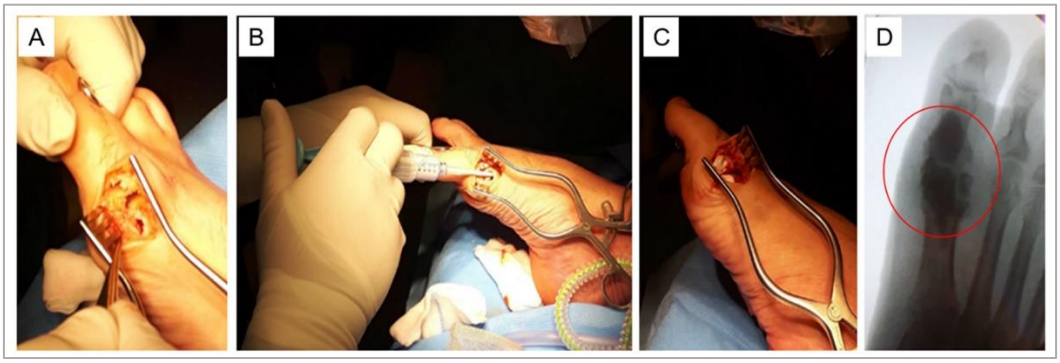


Figure 22. Surgical treatment with gentamicin-loaded calcium sulphate-hydroxyapatite (CaS-HA) bio-composite. (A) Surgical excision. (B) The dead space is irrigated. (C) The dead space is filled with gentamicin-loaded CaS-HA bio-composite. (D) Dorsal-plantar x-ray.

ii) **Enzymatic:**

This method involves using enzymatic agents such as papain, collagenase, dextran, streptokinase and streptodornase. Removal of nonviable tissue is undertaken, and healthy tissue is left behind. Ischemic ulcers are best suited for this debridement technique. The disadvantage of this modality is its high cost.

iii) **Biological**

Sterile maggots can ingest microbes and nonviable tissue without affecting viable tissue. These have also been efficacious in treatment of ulcers infected with Methicillin resistant Staphylococcus aureus. The other alternative are larvae of greenbottle fly, which can remove the slimy layer and exclude microbes in wound. These are especially found to be efficacious in diabetic foot ulcers.

The other benefits of these biological agents include regulation of proteases, degradation of the extracellular matrix, promotion of fibroblast migration and potential improvement of skin perfusion. Another discovery is Lucilia sericata

larvae are a source growth factor. Biological debridement is not that efficacious in treatment of neuropathic ulcers as the larvae cannot remove callus. (Figure 23) [51]

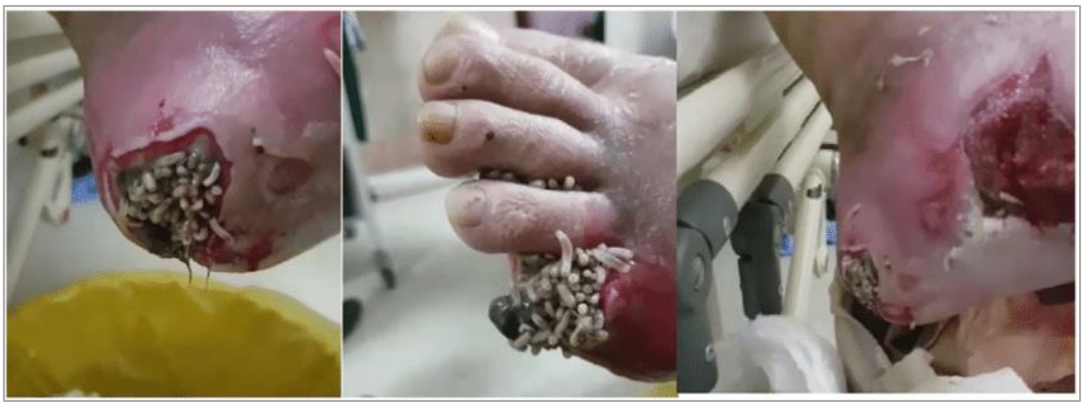


Figure 23. Maggots of Lucilia sericata in diabetic foot ulcer

iv) **Hydro-surgical**

In this modality, saline or sterile water is targeted at a high speed towards the ulcer in a coordinated manner. This form of mechanical debridement allows accurate identification and elimination of necrotic tissue from ulcer.

v) **Autolytic**

Moisture laden dressing makes the dead and necrotic soft and excludes them from the floor of the ulcer by naturally produced enzymes. This is due to the stimulation of the neutrophils and macrophages of the host immune system. Some of the useful dressings in this regard are hydrocolloids and hydrogels. However, the presence of moisture predisposes to maceration and should be avoided as much as possible. This method of debridement is contraindicated in patients with peripheral ischemia with or without the presence of dry gangrene.

2. LOCAL ULCER CARE WITH INFECTION CONTROL

Infected diabetic foot ulcers are critical due to their association with increased morbidity and mortality and require aggressive management. All infected ulcers necessitate antibiotic therapy [37]. Topical antimicrobial formulations provide high local concentrations over the wound bioburden without penetrating intact skin or deeper tissues [52].

Topical antibiotic therapy benefits patients with vasculopathy, aiding those with poor peripheral vascular supply [52]. Initial treatment involves broad-spectrum antibiotics targeting Staphylococcus aureus and beta-haemolytic Streptococcus, adjusted based on culture sensitivity and clinical response [37,53]. Surgical intervention and antibiotics are essential for abscesses, necrotizing fasciitis, and gangrene [37,53]

Biofilms complicate chronic wound infections, resisting antimicrobial penetration due to protective polymeric substances. Treatment includes wound bed preparation, debridement, and antimicrobial dressings [52]

Antimicrobial therapy includes disinfectants (e.g., alcohol, glutaraldehyde), antiseptics (e.g., iodine, chlorhexidine, silver), and antibiotics [54,55]. Systemic antibiotics like cephalosporins are initially broad-spectrum, later tailored based on culture results [54,55]

Topical antimicrobial agents are crucial in diabetic foot infections, especially with rising antimicrobial resistance [52]. They provide localized antimicrobial action but have limitations such as poor penetration in deep tissues and risks of systemic absorption and irritant dermatitis [55]

Managing diabetic foot ulcers involves a multifaceted approach with appropriate antibiotic therapy, biofilm management, and targeted use of topical antimicrobial agents [54].

TYPES	ACTIONS	INDICATIONS	PRECAUTIONS AND CONTRAINDICATIONS
ALGINATES	-Promotes autolytic debridement -Absorbs fluid -Moisture control	Moderate to high exuding wounds	Dry and necrotic wounds
FOAMS	-Absorbs fluid -Moisture control	Moderate to high exuding wounds	-Dry and necrotic wounds -wounds with minimal exudate
HONEY	Rehydrate wound bed Autolytic debridement Antimicrobial action	-Moderate exuding wounds -Critically colonised wounds	-May cause drawing pain due to osmotic effect -Known sensitivity
HYDROCOLLOIDS	-Absorb fluid -Promote autolytic debridement	-Moderate exuding wounds -Combined use with silver for antimicrobial activity	-dry/necrotic wounds -high exuding wounds -May encourage overgrannlation and maceration
HYDROGELS	-Rehydrate wound bed -Moisture control –Promote autolytic debridement -Cooling	-Dry/low to moderate exuding wounds -Combined use with silver for antimicrobial activity	-highly exuding wounds -where anaerobic infection is suspected -May cause maceration
IODINE	Antimicrobial action	-Critically colonised wounds or clinical signs of infection -Low to high exuding wounds	-Dry necrotic tissue -Known sensitivity to iodine -short-term use recommended (risk of systemic absorption)
Low-adherent wound contact layer (silicone)	-Protect new tissue growth -Atraumatic to periwound skin	-Low to high exuding wounds -Use as contact layer on superficial low exuding wounds	-May dry out if applied for long -Known sensitivity to silicone
SILVER	Antimicrobial action	-Critically colonised wounds	-Some may cause discolouration -Known sensitivity
POLYURETHRANE FILM	-Moisture control -Transparent (allow visualisation of wound)	-Primary dressing over superficial low exuding wounds	-moderate to high exuding wounds

Table 8. Types of ulcer dressings [37]

TYPE OF WOUND TISSUE	THERAPEUTIC GOAL	ROLE OF DRESSING	WOUND BED PREPARATION	PRIMARY DRESSING	SECONDARY DRESSING
Necrotic, black, dry	To remove devitalised tissue	-Hydration of wound bed -Promote autolytic debridement	Surgical or mechanical debridement	Hydrogel Honey	Polyurethane film dressing
Yellow with slough and low exudate	-To remove slough -provide clean wound bed for granulation tissue	-Rehydrate wound bed -Promote autolytic debridement	-Surgical or mechanical debridement -antiseptic wound cleansing	Hydrogel Honey	Polyurethane film dressing Low adherent (silicone) dressing
Yellow with slough, moderate to high exudate	-To remove slough -provide clean wound bed for granulation tissue -Exudate management	-Absorb excess fluid and maceration -Promote autolytic debridement	-Surgical or mechanical debridement -antiseptic wound cleansing	Absorbent dressing (alginate/foam)	polyurethane film dressing
Granulating, with exudate	-Promote granulation -Provide healthy wound bed for epithelialisation	-Maintain moisture balance -Protect new tissue growth	Wound cleansing	-Hydrogel -Absorbent dressing (alginate/foam) -Low adherent (silicone) dressing	-Pad and/or bandage -Avoid occlusive bandages
Epithelialising red with low exudate	Promote epithelialisation and wound maturation (contraction)	Protect new tissue growth		-Hydrocolloid -Polyurethane film dressing Low adherent (silicone) dressing	-Pad and/or bandage -Avoid occlusive bandages
Infected Low to high exudate	-Reduce bacterial load -Exudate management	-Antimicrobial action -Moist wound healing	Antiseptic wound cleansing	Antimicrobial dressing	-Pad and/or bandage -Avoid occlusive bandages

Table 9. Guide for Wound Management [37]

Dressing application and ulcer monitoring

Regular examination and assessment of the ulcer and the dressing is crucial for desired results. Ideally for infected ulcers, daily inspection of wound with change of dressing is advised. Dressing type may require change with improvement in condition of ulcer.

Prior to the application of the dressing, ulcers should be cleansed with ideal choice of antiseptic solution depending on the healing stage of the ulcer. This helps to eliminate devitalized tissue, remove the biofilm and decrease the discharge from the ulcer thus, preparing the wound bed for healing. [37,52,53] The measurement of the ulcer is undertaken by methods such as:

i) Grid tracing- Using a transparent sheet and graph paper.

ii) Digital planimetry- Software such as 'Tissue Analytics' and 'Wound Matrix'.

3. MOISTURE CARE

Moisture management is critical for healing diabetic foot ulcers. Maintaining an optimal moisture balance supports granulation tissue formation and epithelialization. Dressings like hydrocolloids, foams, alginates, and hydrogels are used based on exudate levels. Regular assessment ensures appropriate dressing selection and frequency of changes to promote effective wound healing [37,47,53]

Role Of Saline Dressing

Normal saline (0.9% sodium chloride solution) is commonly used in the treatment of diabetic foot ulcers due to its similarity to normal extracellular fluid. It serves as an effective wound cleansing agent, facilitating removal of necrotic debris and dead tissue. Saline-soaked gauze dressings, which provide a moist environment without causing trauma, are inexpensive, simple to use, and hypoallergenic [56]. However, normal saline does not possess proven antimicrobial properties [56].

4. ADVANCEMENT OF EPITHELIAL EDGE

Debridement of ulcer edges eliminates the physical restrictions to epithelial growth on ulcer floor. The line demarcating viable from necrotic tissue might become a source of infection and therefore the devitalized tissue needs to be debrided and eliminated. [37,47,55]

Adjuvant therapies

For ulcers which do not heal despite all conventional measures, adjunctive treatment modalities may be considered. These include:

1. **Negative pressure wound therapy (Vacuum-Assisted Closure Therapy**)

   Vacuum-assisted closure (VAC) therapy, also known as negative pressure therapy or sub-atmospheric therapy, involves applying pressure levels below atmospheric pressure to wounds. This non-invasive method reduces wound discharge and oedema while enhancing local angiogenesis. A recent advancement includes negative pressure wound therapy with instillation using antiseptic agents like Poly hexamethylene Biguanide. Benefits include improved blood supply via arteriole dilation, reduced oedema by removing excess fluid, decreased bacterial colonization by extracting bacteria, and promotion of granulation tissue formation for effective wound healing. (Figure 24)

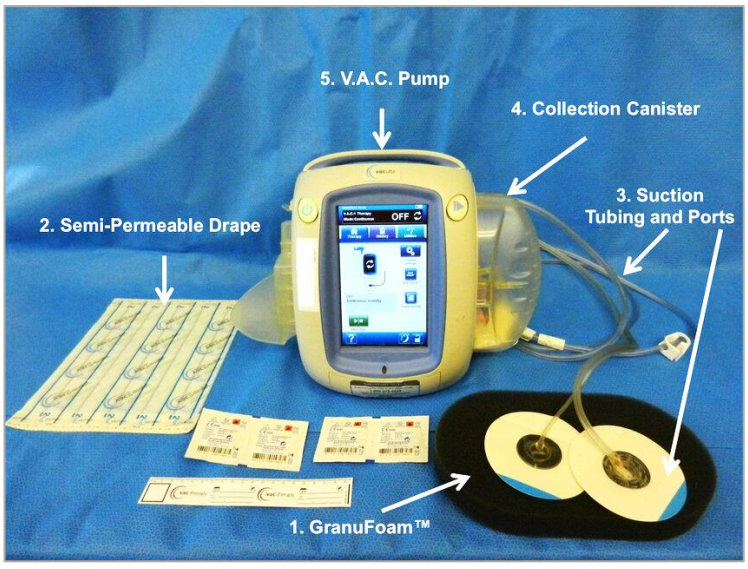


Figure 24. Vacuum-assisted closure therapy device.

2. **Hyperbaric oxygen therapy-** Exposure to high concentration oxygen at a high pressure can cause proliferation of keratinocytes and fibroblasts and improve the capacity of white blood cells to destroy bacteria. Oxygen acts as a key agent in healing (increased ATP production) and controlling microorganism proliferation (increased production of reactive oxygen species) and penetrates the wounds locally as well systemically via the lungs. The equipment required is elaborate and expensive, and thus not available in most hospitals. (Figure 25)

Figure 25. Hyperbaric Oxygen Therapy (HBOT) chamber.

3. **Ultrasonic stimulation-** Vibration of inflammatory wound tissue has been noticed to improve healing.
4. **Laser therapy-** This has the potential to form new blood vessels locally, inhibit inflammation and promote extracellular matrix synthesis.

5. **Electrical stimulation therapy**- It promotes fibroblast activity, local angiogenesis, and antibacterial effects to enhance ulcer healing. Despite higher costs compared to standard treatments, it is preferred for its potential to accelerate healing, reduce amputations, and improve overall functional quality of life. [49,53]

C. PRESSURE OFFLOADING

Offloading plays a crucial role in diabetic foot ulcer management by reducing vertical plantar pressure and horizontal shear stress, which are major contributors to ulcer onset and delayed healing [47]. Effective offloading prevents tissue damage and ulcer recurrence in patients with peripheral neuropathy [47]

The Total Contact Cast (TCC) is considered ideal for offloading ulcers on the forefoot or midfoot, accelerating healing by up to six weeks [47]. However, it has drawbacks such as skin irritation, hindered daily inspection of the wound, and potential disruption of quality of life. TCCs are contraindicated in neuropathy and vasculopathy due to risks of new ulceration and infection [47].

Alternative offloading options include removable devices like Scotch cast boots and removable cast walkers, preferred for infected or ischemic ulcers to maintain user-friendliness and allow wound inspection [47].Devices like the Instant Total Contact Cast combine efficacy with ease of application similar to removable cast walkers [47]. In cases where above-ankle devices are unsuitable, shoes and custom insoles can effectively offload forefoot ulcers by reducing pressure by up to 50%. (Figure 26) (Table 10). [37, 47, 49]

Figure 26. Various offloading devices and footwear

TYPE	KEY POINTS
REMOVABLE CAST WALKERS	- Similar pressure decrease to TCCs - More acceptable, easy to remove - Can be used on infected and ischemic wounds - Reduced healing rate compared with TCCs
SCOTCHCAST BOOTS	- Lighter, padded cast covering foot to ankle - Can be made nonremovable
HEALING SANDALS	-Designed to limit dorsiflexion of metatarsophalangeal joints - Light weight, stable, reusable Can increase risk of falling in patients with poor balance
CRUTCHES,WALKERS, WHEELCHAIRS	-Provides complete offloading of foot -Patients need good upper strength

Table 10: Offloading Devices

TOPICAL OXYGEN WOUND THERAPY

Oxygen plays a crucial role in various biological functions and is vital for the healing of wounds. Chronic wounds, often hypoxic, lack sufficient oxygen levels required to support enzymatic processes crucial for tissue repair. Supplementing oxygen can enhance these enzyme functions by increasing oxygen levels within the wound. Despite extensive research of topical oxygen therapy (at normal atmospheric pressure), effectiveness in healing chronic diabetic foot ulcers (DFU) remains inconclusive based on comparative clinical studies.

For over five decades, topical oxygen wound therapy (TOWT) has been utilized in clinical settings, showing promising results in both pre-clinical and clinical trials, indicating improved healing rates compared to standard treatments. However, TOT has been discredited in the past due to a lack of theoretical or clinical evidence supporting its efficacy as a wound healing approach.

Oxygen and Wound Healing

- Oxygen is essential for the healing of wounds, playing a critical role in various stages of the body's response to injury. (Table 11)

- Chronic wounds often lack sufficient oxygen supply, leading to low partial pressure levels that hinder crucial processes.

- In cases of chronic hypoxia, angiogenesis and the production of reactive oxygen species (ROS) are compromised, impacting growth factor activation and bacterial elimination.

- Acting as a key substrate, oxygen regulates the pace of numerous biochemical reactions vital for energy generation and cellular metabolism.

- Oxygen-dependent mechanisms involved in wound recovery encompass ATP synthesis powered by mitochondria and ROS production via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.

- The initial eradication of bacterial pathogens relies significantly on ROS-mediated phagocytosis and bacterial destruction by platelets and neutrophils.

- Collagen formation, deposition, and bonding necessitate molecular oxygen for proline and lysine hydroxylation to occur effectively.

- Elevating supplemental oxygen levels above the standard tissue threshold of 100 mmHg is recommended to enhance all essential biological processes required for effective healing.

Oxygen-Dependent Product	Enzyme or Substrate	Function	Cytokine, Cell Mediators; or Cellular/Tissue Effect
ATP	ATP synthase, Cytochrome C, Electronic Transport Chain	Chemical Energy for metabolism	
Reactive Oxygen Species (ROS) "respiratory burst" (Superoxide, Hydrogen peroxide (H_2O_2))	NADPH oxidase	Cellular Signaling/transduction Bacterial defenses Angiogenesis	Cell division and migration. Upregulation of Growth Factors (VEGF, PDGF, etc.) (leukocyte migration and phagocytosis, bacteriostatic H_2O_2) VEGF, PDGF, NO, etc.
Collagen synthesis	Prolyl hydroxylase, lysyl hydroxylase	Collagen deposition and crosslinking	Fibroblasts
Nitric oxide (NO)	Nitric oxide synthase	Vasodilatation, angiogenesis	Endothelium

NADPH: nicotinamide adenine dinucleotide phosphate; VEGF: vascular endothelial growth factor; PDGF: platelet derived growth factor.

Table 11. Role of Oxygen in Wound Healing

Topical Oxygen Devices Overview

- Topical oxygen therapy (TOT) is the application of oxygen directly to injured tissue using continuous diffusion or pressurized systems.
- There are three physical delivery systems for TOT: Continuous oxygen delivery, low constant pressure in a contained chamber (GRW Medical), and cyclically pressurized and humidified in a contained chamber (TWO2®). (Table 12)
- Continuous oxygen delivery devices use non-pressurized pure oxygen to diffuse through wound dressings, ensuring a constant flow of oxygen around the clock. These portable devices, powered by batteries, establish an oxygen gradient between the dressing and wound bed, aiding in oxygen diffusion. Dressings are changed weekly, and the generators are replaced after 1 to 2 weeks of continuous operation. Lightweight and convenient, these devices can be carried in a pouch, allowing unrestricted movement. Recent randomized controlled trials have demonstrated their user-friendliness and positive impact on wound healing.
- Devices providing lower constant pressure supply 100% oxygen for 90 minutes over four consecutive days each week while maintaining pressure within the chamber at up to 22 mmHg (1.03 atm). Despite being less commonly utilized, these devices have exhibited promising clinical efficacy in recent years. However, most studies have been either case series or uncontrolled trials with discussions on a poorly conducted RCT involving a similar device. A recent retrospective analysis of non-healing wounds from the manufacturer's database indicated that more than 50% of wounds less than one year old achieved healing.
- The TWO2 system is a medical device that utilizes cyclically pressurized pure oxygen in a disposable extremity chamber linked to a fixed oxygen concentrator. This

elevated pressure differential aids in the deeper penetration of oxygen molecules into wound tissue, thereby enhancing various molecular and enzymatic processes. By applying cyclical pressure ranging from 8 mmHg to 38 mmHg, it induces sequential non-contact compression on the limb, decreasing peripheral oedema and promoting perfusion at the wound site. Clinical trials have shown its effectiveness in treating both Venous Leg Ulcers (VLUs) and Diabetic Foot Ulcers (DFUs). Additionally, humidity can be incorporated as necessary.

Continuous Diffusion (CDO)	22 mmHg Constant Pressure	10mb to 50 mb Cyclical Pressure
		
Variable Healing in UT-1A wounds shown in 3 RCTs to date	One database retrospective review and no recent controlled studies	Recent Sham controlled RCT in DFU Shows 4x healing rate vs. SOC/sham
Several case series	Mostly low level case series	Multiple controlled studies in DFU and VLU showing efficacy
Low continuous flow of O_2 (3–15 mL/h)	Low O_2 flow and low constant pressure	High O_2 flow rate and deeper O_2 penetration into wound bed Higher diffusion gradient
Sealed, Disposable Dressing Low O_2 PP Diffusion Gradient	Does not significantly reduce edema	Cyclical pressure reduces edema and stimulates angiogenesis
No compression or humidification Can macerate wound	Minimal compression and no humidification	Cyclical non-contact compression with humidification

Table 12. Types of topical oxygen devices

RECENT STUDIES RELATED TO THE CURRENT RESEARCH

Leslie et al. (1988) [57] studied 28 diabetic foot ulcer patients, with 12 receiving topical hyperbaric oxygen (THO) therapy and 16 as controls. Despite similar clinical parameters and microbial profiles, THO did not significantly accelerate wound healing compared to controls. Both groups showed reductions in ulcer size, but without statistical significance in ulcer area changes between them. The study concluded THO did not expedite healing, suggesting no advantage over standard care.

According to **Kessler et al. (2003) [58] ,** hyperbaric oxygen therapy facilitates wound healing by enhancing neovascularization, recruiting stem cells, producing growth factors, and facilitating cell migration in their randomised control study on non-ischemic diabetic foot ulcers.

The impact of topical oxygen on pigs was investigated by **Fries et al. (2005)[59].** In as little as 4 minutes, Fries et al. observed a rise in pO2 from less than 10 to 40 mmHg following the application of topical oxygen at a rate of 3–6 L/min using a plastic device. Lastly, Fries et al. were able to demonstrate through histology that lesions treated with oxygen exhibited symptoms of enhanced angiogenesis and tissue oxygenation in pigs.

In their prospective study on diabetic foot ulcers, **Blackman et al. (2010**) [60] contrasted the healing rates of chronic diabetic foot ulcers treated with topical oxygen and advanced moist wound therapy. Topical wound oxygen devices were implemented. The humidified oxygen was administered to an extremity chamber in a cyclical manner by a topical wound oxygen device. The chamber was pressurised to 50 mb during the cycle. Five days per week, sixty-minute treatments were administered. They discovered that the percentage of diabetic foot ulcers that had fully healed was substantially higher in patients who received topical wound oxygen than in those who received advanced moist wound

therapy. They determined that topical oxygen wound therapy is a straightforward, non-invasive procedure that can facilitate wound healing and does not have any adverse effects.

In a similar way, **Tawfick et al. (2009)** [61] discovered that topical oxygen therapy was advantageous in terms of a shortened healing time and an improvement in the quality of life when comparing conventional compression dressings and topical oxygen on refractory venous ulcers. They employed a topical oxygen device for 180 minutes twice daily at a pressure of 50 mb. The oxygen flow rate was maintained at 10 litres per minute.

Numerous authors have investigated the cost of topical oxygen therapy in comparison to hyperbaric oxygen therapy, like by **Agarwal V et al. (2015) [62].** The cost of topical oxygen therapy is approximately 42,000 INR per week, while the cost of hyperbaric oxygen therapy is between 4,50,000 and 50,00,000 INR per week, contingent upon the number of sessions attended.

Driver et al. (2017) [[63] conducted a multicentric randomized study from 2009 to 2012 assessing the efficacy of Total Contact Oxygen Therapy (TCOT) on diabetic foot ulcers (DFUs). Participants (N = 122) with nonhealing DFUs were randomized to receive TCOT or a sham device alongside moist wound therapy (MWT). TCOT involved continuous delivery of oxygen to the wound site using a 15-day device. Results showed a higher healing rate in the TCOT group (54% vs. control 49%) and a shorter median time to complete closure (TCOT: 63 days vs. control: 77 days).

Niederauer MQ et al. (2017) [64] conducted a prospective, randomised, double-blind, multicentre trial to evaluate the efficacy of continuous diffusion of oxygen (CDO) therapy in the treatment of chronic diabetic foot ulcers (DFUs). In the study, 100 subjects, aged 58.3 ± 12.1 years, were randomised to receive either active continuous diffusion of oxygen (CDO) therapy using an active CDO device or an otherwise fully operational sham device that

provided moist wound therapy (MWT) without delivering oxygen. 79% of the subjects were male. The patients were monitored until closure or 12 weeks, whichever occurred first. The results indicated that the treatment arms did not exhibit any significant differences in the descriptive characteristics that were assessed. Nevertheless, the active arm exhibited a substantially higher percentage of individuals who were cured than the sham, particularly in the case of more chronic lesions. Compared to the sham, patients who were randomised to the active device experienced quicker closure rates. The study determined that CDO therapy results in faster closure time and higher closure rates than standard therapy.

Niederauer MQ et al. (2018) [65] conducted a study to ascertain whether continuous diffusion of oxygen (CDO) therapy enhances the healing process in diabetic foot ulcers (DFU) patients. 146 patients were enlisted in a randomised, double-blind, placebo-controlled study. In comparison to the placebo, CDO therapy resulted in a higher proportion of healed DFUs (195%) and a reduced time to 50% DFU closure (32.4% versus 16.7%). In larger wounds (273%), more chronic wounds (334%), and weight-bearing wounds (465%), the relative performance of active CDO over placebo increased. The study determined that CDO results in a greater number of healed DFUs and a shorter time to closure in individuals with DFUs than the placebo. The relative performance did not exhibit a significant difference with respect to wound size; however, it demonstrated superior performance in weight-bearing wounds and more chronic wounds.

Frykberg et al. (2019) [66] conducted a randomized trial assessing multimodality cyclical pressure Topical Wound Oxygen (TWO2) therapy versus placebo in refractory diabetic foot ulcers (DFUs). The study found significantly higher rates of ulcer healing with TWO2 therapy at 12 weeks (41.7% vs. 13.5% closure rate) and continued benefit at 12 months (56% vs. 27% closure rate).

Nataraj et al. (2019) [67] conducted a systematic review on topical oxygen therapy for diabetic foot ulcers, analysing five studies. They found that low-grade ulcers (grade 1) tended to completely heal, while higher-grade ulcers (grades 2, 3, and above) showed significant healing with reductions in size and tissue depth, supporting the efficacy of topical oxygen therapy in chronic DFUs.

Frykberg et al. (2021) [68] highlighted the therapeutic role of oxygen in healing chronic, hypoxic lesions like diabetic foot ulcers. They reviewed the history and efficacy of topical oxygen therapy (TOT), advocating for its recognition as a validated adjunctive therapy based on clinical evidence demonstrating superior healing rates compared to conventional treatments.

The study conducted by **Serena T et al. (2021)** [69] investigated the influence of topical oxygen therapy (TOT) on the recovery rates of diabetic foot ulcers (DFUs) that are difficult to repair. The multicentre, open-label, community-based trial evaluated the efficacy of standard care (SOC) with or without TOT in patients with DFUs or minor amputation incisions over a 12-week period. The primary endpoints were the number of patients who achieved complete wound closure and the percentage change in ulcer size. The secondary endpoints were pain levels and adverse events. The study discovered that the addition of TOT to SOC substantially reduced lesion area, with a mean reduction of 70% in the SOC group and 70% in the SOC plus TOT group. There were no discernible variations in adverse events or pain levels.

Sethi et al. (2022) [70] conducted a systematic review of seven studies on total contact cast (TOT) as adjuvant therapy for superficial, well-vascularized diabetic foot ulcers (DFUs). They found that TOT significantly enhanced complete wound healing compared to standard care (SC), although no benefit was observed in terms of reducing amputations. Two studies reported a reduction in time to healing, particularly for larger DFUs. However, most studies

had moderate or high risk of bias, limiting definitive conclusions on cost-effectiveness. Despite these limitations, TOT was deemed safe and associated with higher rates of complete wound healing in this patient population.

Andrew et al. (2022) [71] provided a comprehensive review of evidence-based therapies for diabetic foot ulcers (DFUs), including sucrose octasulfate dressings, autologous leukocyte, platelet, and fibrin multilayered patches, topical oxygen therapies, and negative pressure wound therapy. They also discussed novel therapies tailored for neuropathic and neuro-ischemic lesions, as well as the emerging role of wearable technologies in preventing DFU recurrence. The review highlighted current treatment options and emphasized areas needing further research.

Carter et al. (2023) [72] conducted a systematic review and meta-analysis of four randomized controlled trials (RCTs) evaluating topical oxygen therapy (TOT) as an adjunctive treatment for Wagner 1 and 2 diabetic foot ulcers. Using the GRADE (Grading, of Recommendations, Development, and Evaluation) methodology, they assessed patient characteristics, outcomes, risk of bias, and evidence quality. Despite moderate risk of bias across all domains, the meta-analysis indicated that TOT is a viable treatment option for chronic Wagner 1 or 2 DFUs without infection or ischemia, with moderate evidence supporting its efficacy.

Thus, all studies have used various modalities of oxygen delivery to the diabetic foot ulcers for healing. After reviewing various studies and their results, it is clear that most studies show faster healing rates with or without additional benefits. However, not one effective standardised treatment has been yet decided. We can surmise the fact that Topical Oxygen Wound therapy has yet not been extensively researched and routinely used for diabetic foot ulcer management, leaving ample opportunity for us to fill this lacuna.

METHODOLOGY

The present study is conducted in KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, and KLES Dr. Prabhakar Kore Hospital and Medical Research Centre from January 2023 to December 2023.

1. Source of Data:

Data was sourced from patients with diabetic ulcers admitted in general surgery wards at KAHER'S Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi, and KLES Dr. Prabhakar Kore Hospital and Medical Research Centre.

2. Study Design:

The study design was a Randomized Control Study using SPSS program.

3. Study Period:

The study was conducted for 1 year, from January 2023 to December 2023.

4. Sample Size:

A total sample size of 60 was used.

The minimum sample size formula based on two proportions is $n = \frac{(z_\alpha + z_\beta)^2 \bar{p}(1-\bar{p})}{d^2}$

where p_1 and p_2 are the proportions of the two groups.

$p = \frac{p_1 + p_2}{2}$ and $d = p_1 - p_2$

z_α is linked with the level of significance and z_β is linked with the power of the test. For 5% level of the significance $z_\alpha = 1.96$ and $z_\beta = 0.84$ for 80% power of the test.

The parameter considered in the calculation is the rate of healing.

By taking proportion, p_1 = 80% and p_2 = 40% the sample size obtained is 24.

To get confirmative results, the sample size will be raised to 30.

There would be two groups with size of 30 each.

5. Study Participants

i) Inclusion Criteria:

a) Patients in the age group of >18 years

b) Patients with a diabetic lower limb ulcer

c) Wegner grade I & II ulcers

d) Patients who gave their consent

ii) Exclusion Criteria:

a) Patients suffering from cardiovascular disease or on anticoagulant therapy.

b) Patients having a wound with exposure of bone.

c) Patients with any immunosuppressive disease or on immunosuppressant therapy

d) Patients with Ischemic limb, varicose veins, PVD, Osteomyelitis, Gangrene

e) Patients with ulcers of a malignant nature

f) Patients that failed to follow up.

6. Sampling Technique:

Computer generated randomization program was used to assign interventions to patients in either group A (TOWT with conventional dressing) or group B (only conventional dressing).

7. Sampling Size:

A total of 60 patients were taken, 30 each in test and control groups.

8. Study Protocol:

Ethical clearance was given by the Ethical research committee of JNMC, Belagavi. Data collection instrument was used for data collection. All patients satisfying inclusion criteria were considered as subjects for the study. The patients were then included in the study after taking written and informed consent.

Selected patients were randomized into two groups namely, the control group (n=30) and test group(n=30) based on the computerized randomization chart. (Figure 27)

Demographic data of the patients was noted in a predesigned proforma. A Detailed history of the patient was taken. A thorough clinical examination was done.

Test for vascularity was done by palpating peripheral pulses, and color doppler was done where indicated. Patients with Peripheral Vascular Disease (PVD) were excluded from the study. Test for peripheral neuropathy was done by Semmes-Weinstein monofilament test and categorized accordingly.

Blood investigations were done as listed below. Wound culture and sensitivity were done on Day 0 and 14.

X-ray foot was done. Patients with Osteomyelitis were excluded from the study.

All patients were started on broad spectrum Intravenous antibiotics at admission – Cefotaxime 1gm BD and Metronidazole 100mg TID. The antibiotics were changed as per culture and sensitivity reports on Day 2.

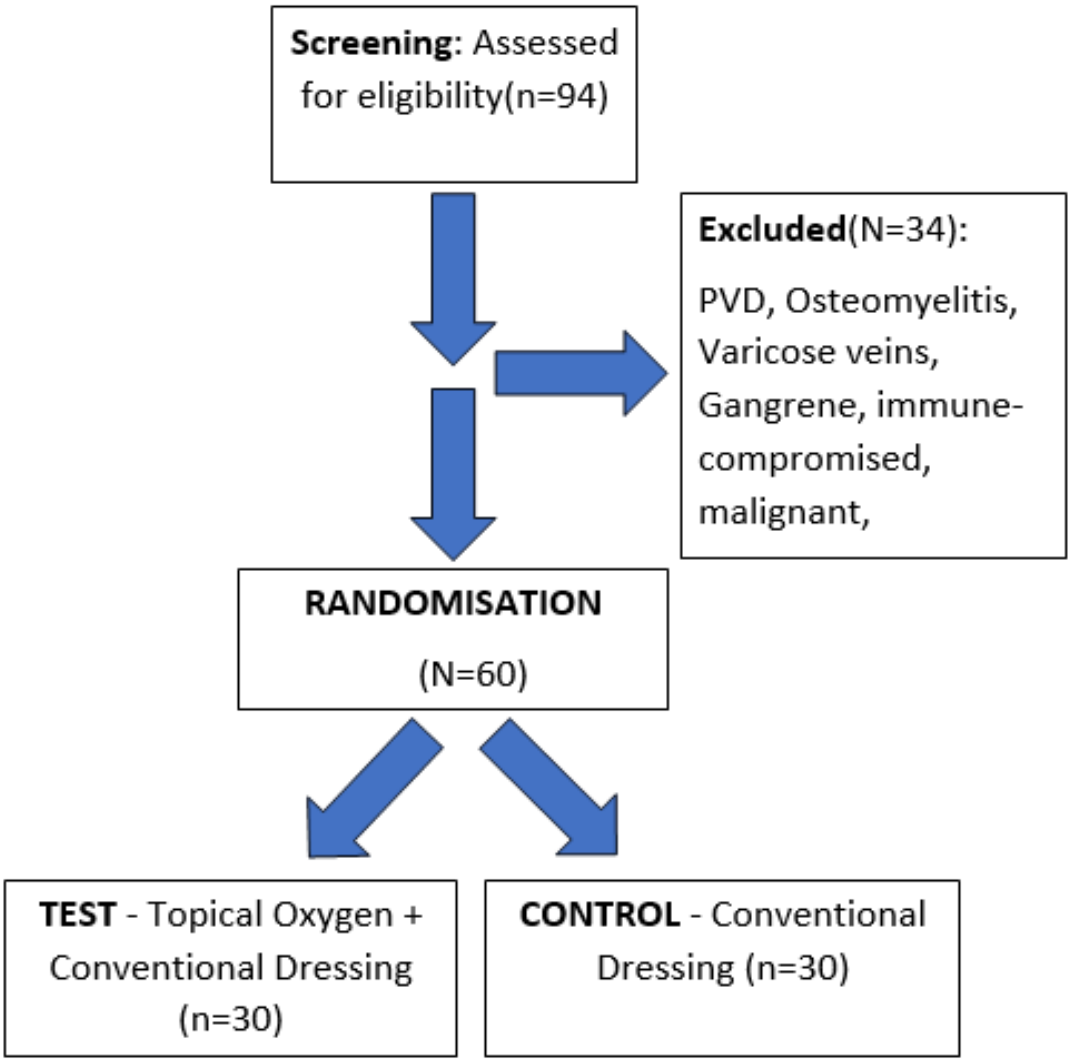


Figure 27. Flowchart showing Study Population Selection and Distribution.

9. Investigations:

- CBC, LFT, MR, PT INR, APTT

- Fasting blood sugar, HbA1c

- UKB, as and where indicated

- Wound C/S of the wound on Day 0 & 14.

- Lower Limb X-ray, as and wherever indicated

- Colour Doppler of the lower limb, as and wherever indicated

GROUP A- TEST GROUP

In this group of 30 patients, dressing was done after giving Topical Oxygen Wound Therapy (TOWT) + Conventional Dressing.

The ulcer was cleaned using conventional povidone-iodine 10% w/v solution and normal saline dressing methods, after which the leg and foot were put in a **sterile polyethylene transparent bag**, made using C-Arm covers. (Image 1)

Image 1. Sterile Polyethylene Cover (C-ARM COVER).

Oxygen was delivered via tubes readily available in the wards (**O2 mask tube with Suction catheters/Foley's catheter**), and oxygen was delivered via **wall-mounted Oxygen Flow meters** in the wards. (Image 2)

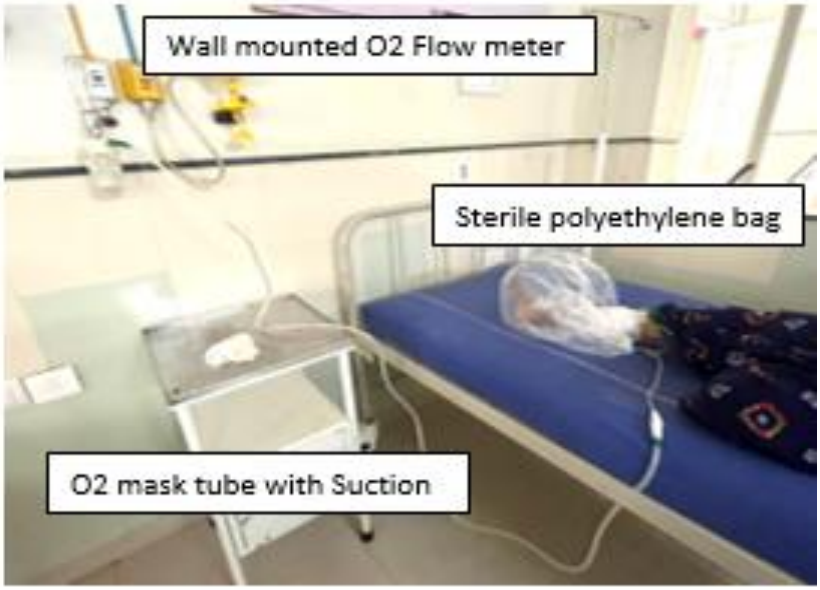


Image 2. Topical Wound Oxygen Therapy Setup.

An increase in pressure of **30mmHg** was recorded via an **Aneroid Barometer** in the bags and maintained using the O2 flow as required (usually about **10 L/m**). (Image 3)

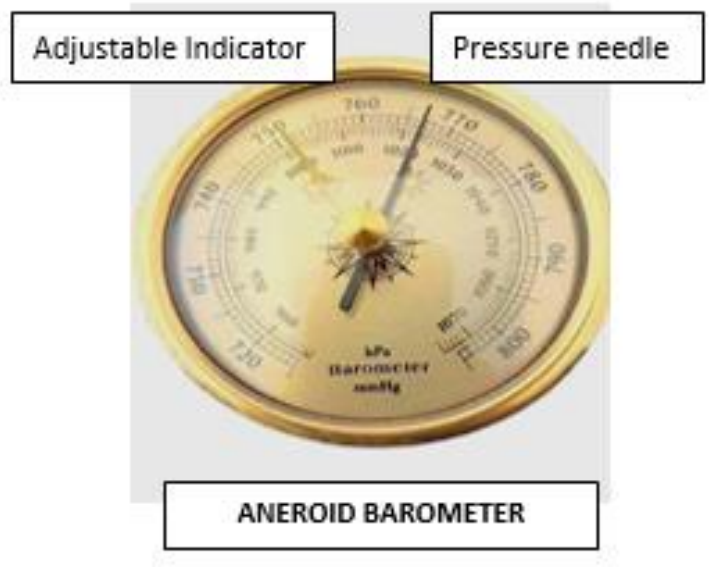


Image 3. Aneroid Barometer.

The ulcer was given **Topical Oxygen Wound Therapy (TOWT)** for **60 minutes** daily for **14 days**. (Image 4)

Image 4. Topical Oxygen Wound Therapy being given in Surgery ward.

GROUP B- CONTROL GROUP

In this group of 30 patients, standard treatment that is conventional **povidone-iodine 10% w/v solution** and **normal saline** dressings were done daily for 14 days. (Image 5)

Image 5. Povidone-Iodine Solution (10%). Normal Saline (0.9%).

Pressure offloading was executed for patients with ulcers on sole of foot.

10. Calculation of wound area:

The dimensions of the ulcer i.e. length, width and area were measured by outlining the ulcer over a sterile transparent film placed over it. This was followed by placing the film over graph paper and counting the number of squares also referred to as 'grid tracing'. The length of the smallest square is 1mm.

The ulcer dimensions are measured on day 0(x) = initial wound area, and day 14(y) = final wound area.

The reduction in area and percentage reduction in area are calculated as follows:

Ulcer area on Day Zero (D0) = x

Ulcer area on Day Fourteen (D14) = y

Reduction in Ulcer area = x-y

Percentage (%) Reduction in Ulcer area = ((x-y) / x) * 100

Assessment of antibacterial property of topical oxygen wound therapy with convention dressings as compared to conventional dressing was done by sending a wound swab for culture and sensitivity test on day 0 and day 14 of the dressing.

The culture and sensitivity test reports, both of day 0 and day 14, for all patients were obtained and documented. The patient was therefore followed up for a period of 15 days with dressings changed every day.

All the data collected from the patients was then tabulated in a Microsoft excel spreadsheet. The data was statistically analysed.

11. Data Collection Procedure:

- 60 patients with chronic diabetic lower limb ulcers - 30 in the testing group and 30 in the control group

- Testing group received Topical Oxygen Wound Therapy (TOWT) + Conventional dressings daily for 14 days.

- Control group received Conventional dressings daily for 14 days.

Patients at the end of the study with smaller ulcers were allowed to heal with secondary intention and larger ones were taken up for Split thickness skin grafting.

12. Statistical Analysis:

The present study is done in KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, and the findings are tabulated as below.

During the study year from January 2023 to December 2023, 60 patients with diabetic foot ulcers are randomized into the study (Topical Oxygen Wound Therapy (TOWT) + Conventional Dressing) and control (Conventional Dressing) groups. These groups were studied for the effect of Topical Oxygen Wound Therapy (TOWT) + Conventional Dressing versus Conventional dressings decrease in size of ulcer.

A total of 60 patients met the selection criteria. Categorical data was denoted as rate and percentage. The expression of continuous data was in the form of mean +/- standard deviation or SD. A comparison of categorical results was carried out using Chi-square test and of continuous results by dependent t-test and independent t-test.

A probability value (p-value) of less than or equal to 0.05 was considered as statistically significant.

RESULTS

The present study is conducted in KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, from February 2022 to February 2023,

In total, 60 patients with diabetic foot ulcers are randomized into test (Topical Oxygen + Conventional Dressing) and control (Conventional dressings) groups. These groups were studied for the effect of Topical Oxygen + Conventional Dressings versus Conventional dressings alone on reduction in size of the ulcer.

Data collected was included into spreadsheets of Microsoft excel. The data was analyzed, and the results obtained were tabulated as represented below.

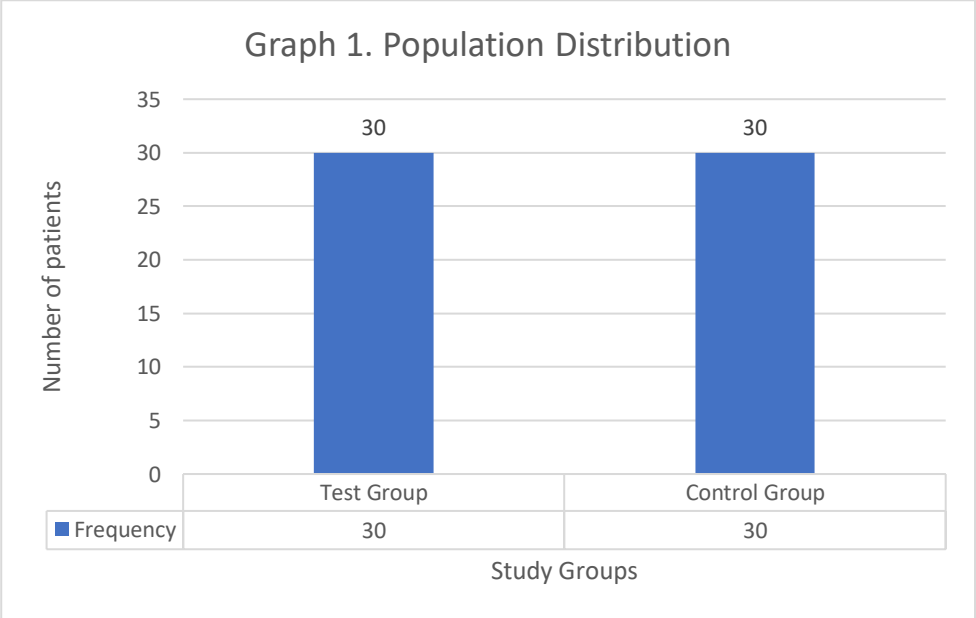
'P' value less than 0.05 considered significant statistically.

1. DEMOGRAPHIC DETAILS

a) POPULATION DISTRIBUTION

Table 13. Descriptive analysis of group in the study population (N=60)

Group	Frequency	Percentages
Test Group	30	50.00%
Control Group	30	50.00%
TOTAL	60	100.00%



Among the study population 30(50%) participants were in group A and the remaining 30(50%) participants were in group B.

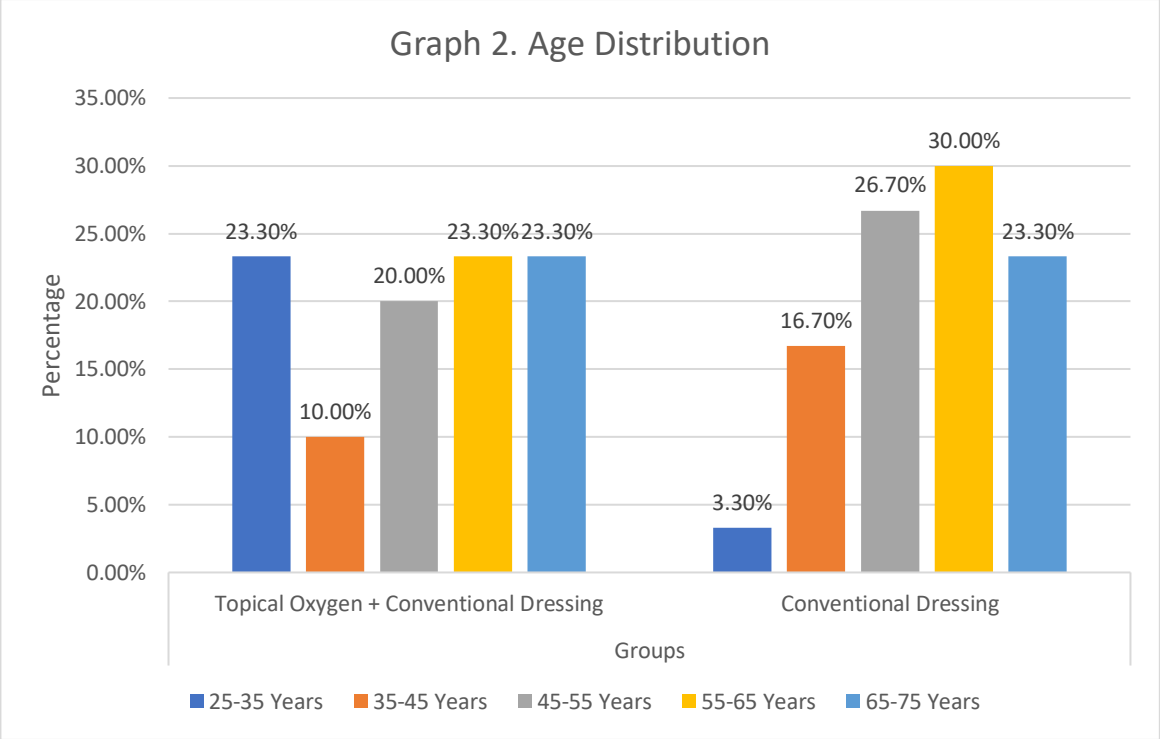
Test Group - population where **Topical Oxygen + Conventional Dressing** is done.

Control Group - population where only **Conventional Dressing** is done.

b) AGE

Table 14. The distribution of Age Groups among Study Groups

Age Groups		Groups		Total
		Test Group	Control Group	
25-35 Years	Number(N)	7	1	8
	Percentage (%)	23.3%	3.3%	13.3%
35-45 Years	N	3	5	8
	%	10.0%	16.7%	13.3%
45-55 Years	N	6	8	14
	%	20.0%	26.7%	23.3%
55-65 Years	N	7	9	16
	%	23.3%	30.0%	26.7%
65-75 Years	N	7	7	14
	%	23.3%	23.3%	23.3%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	5.536	4	0.237	Non-Sig

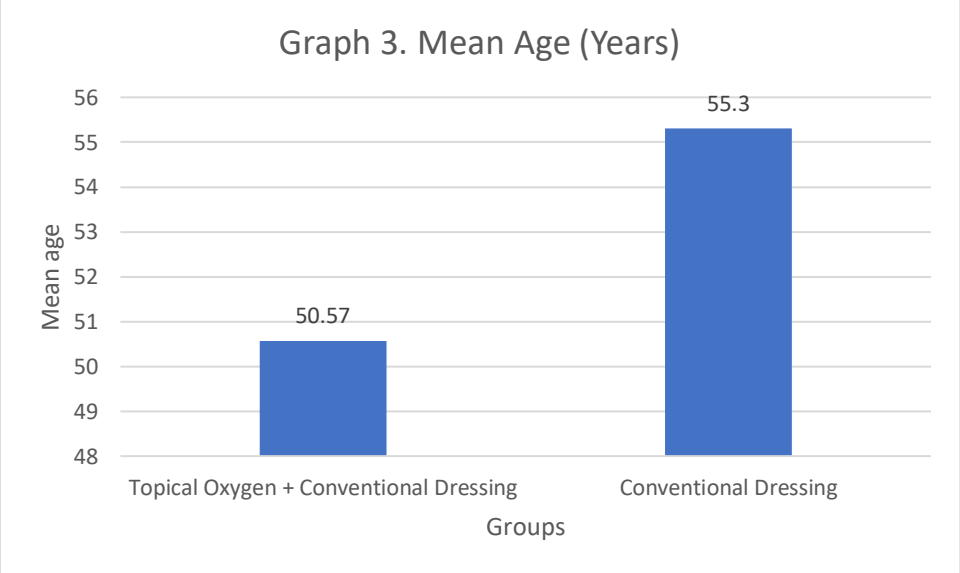


The majority of the patients in Topical Oxygen + Conventional Dressing Group are from 25-30 years, 55-65 years & 65-75 years age groups (23.3% each). The majority of the patients in Conventional Dressing Group are from 55-65 years age group (30.0%).

As per chi-square test, the distribution between Study Groups and Age Groups was found to be **not significant** (P>0.05).

Table 15. Comparison of Mean Age Between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
Age (years)	**Test Group**	30	50.57	14.644	-1.332	0.188	Not Sig
	Control Group	30	55.30	12.820			



The mean age of 50.57 years was observed for the Topical Oxygen + Conventional Dressing Group.

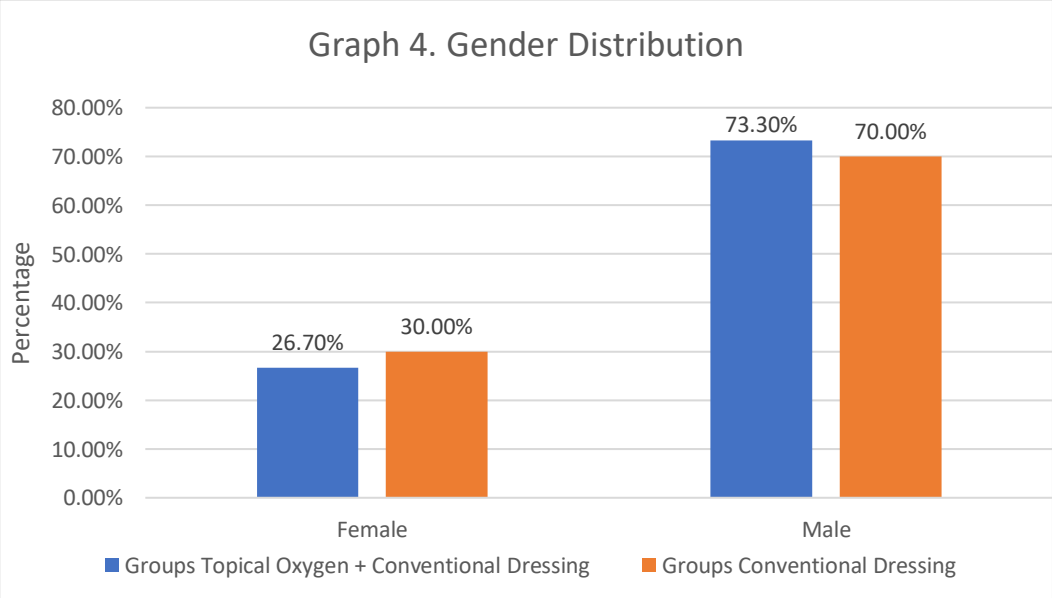
The mean age of 55.30 years was observed for the Conventional Dressing Group.

Student T-Test showed non-significant for both Groups with respect to mean age of patients. (P>0.05).

c) GENDER

Table 16. The distribution of Gender Groups among Study Groups

GENDER		Groups		Total
		Test Group	Control Group	
Female	Number(N)	8	9	17
	Percentage (%)	26.7%	30.0%	28.3%
Male	N	22	21	43
	%	73.3%	70.0%	71.7%
	N (%)	30 (100%)	30 (100%)	60(100%)
Pearson Chi-Square	Value	Df	P Value	Result
	0.082	1	0.774	Non-Sig



Most Topical Oxygen + Conventional Dressing Group patients were Males (73.3%).

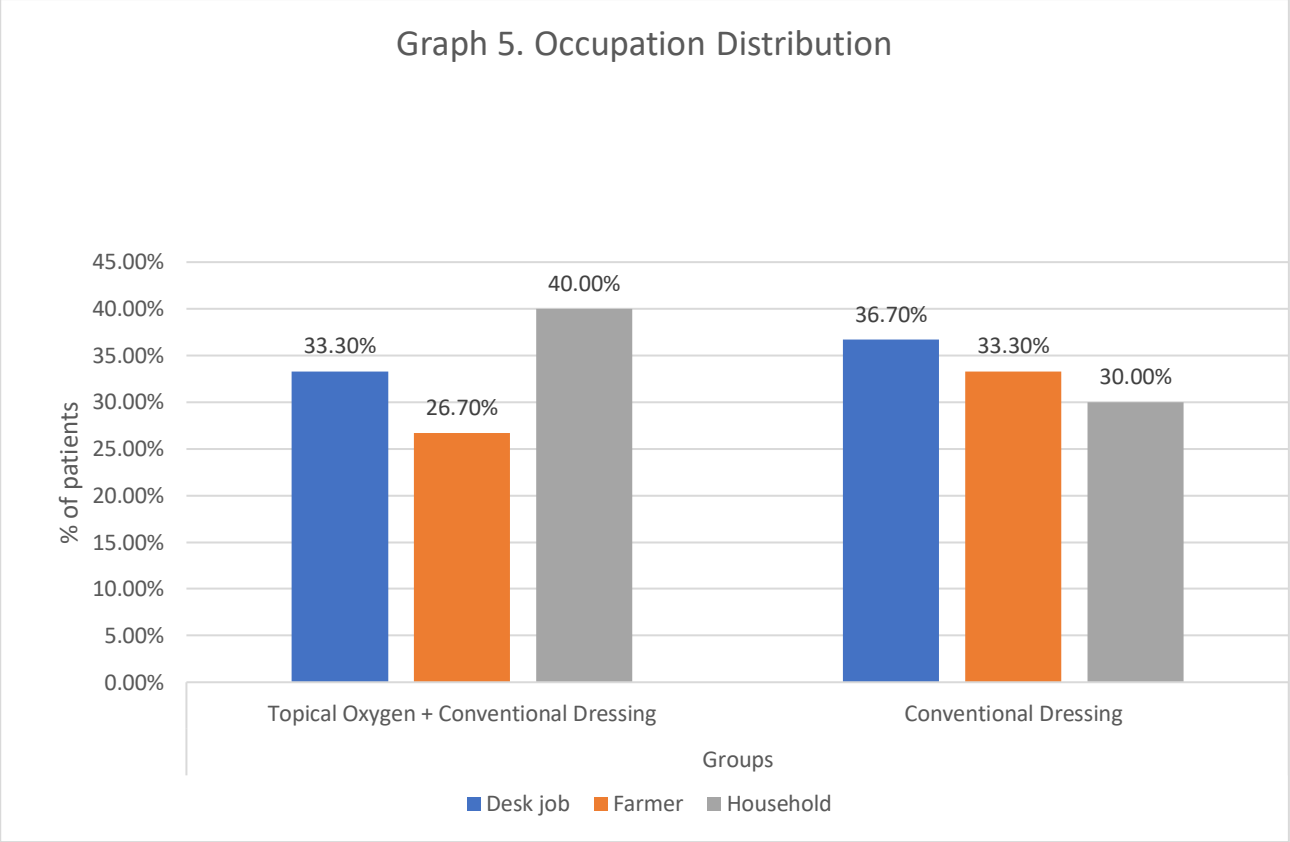
Most Conventional Dressing Group patients were Males (70.0%).

As per chi-square test, the distribution between Study Groups and Gender was found to be not significant (P>0.05)

d) OCCUPATION

Table 17. The distribution of Occupation among Study Groups

OCCUPATION		Groups		Total
		Test Group	Control Group	
Desk job	Number(N)	10	11	21
	Percentage (%)	33.3%	36.7%	35.0%
Farmer	N	8	10	18
	%	26.7%	33.3%	30.0%
Household	N	12	9	21
	%	40.0%	30.0%	35.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	0.698	2	0.705	Non-Sig



The Topical Oxygen + Conventional Dressing Group's patient's occupations were mostly Household (40.0%), followed by Desk Jobs (33.3%).

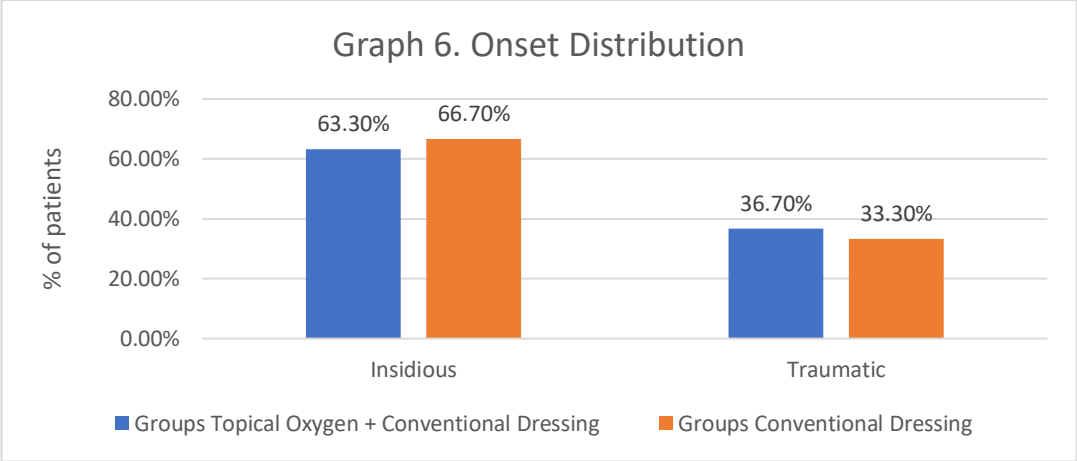
The Conventional Dressing Group Group's patient's occupations were mostly Desk Job (36.7%), followed by Farmer (33.3%) and Household (30.0%).

A chi-square test for the between Study Groups and Occupations was found to be not significant (P>0.05).

2. ONSET

Table 18. The distribution of onset among Study Groups

ONSET		Groups		Total
		Test Group	Control Group	
Insidious	Number(N)	19	20	39
	Percentage (%)	63.3%	66.7%	65.0%
Traumatic	N	11	10	21
	%	36.7%	33.3%	35.0%
	N (%)	30 (100%)	30 (100%)	60 (100%)
Pearson Chi-Square	Value	Df	P Value	Result
	0.073	1	0.787	Non-Sig



The ONSET for the Topical Oxygen + Conventional Dressing Group was Insidious in 63.3% patients. The ONSET for the Conventional Dressing Group was Insidious in 66.7% patients.

A chi-square test for the distribution between Study Groups and ONSET was found to be not significant (P>0.05).

3. DURATION OF ULCER:

Table 19. The distribution of Duration of Ulcer (Weeks) among Study Groups

Groups	Weeks<= 6.00	Weeks > 6.00	Percentage Weeks <=6.00 (%)	Percentage Weeks >6.00 (%)	Total
Test Group	22	8	73.33	26.67	30
Control Group	17	13	56.67	43.33	30

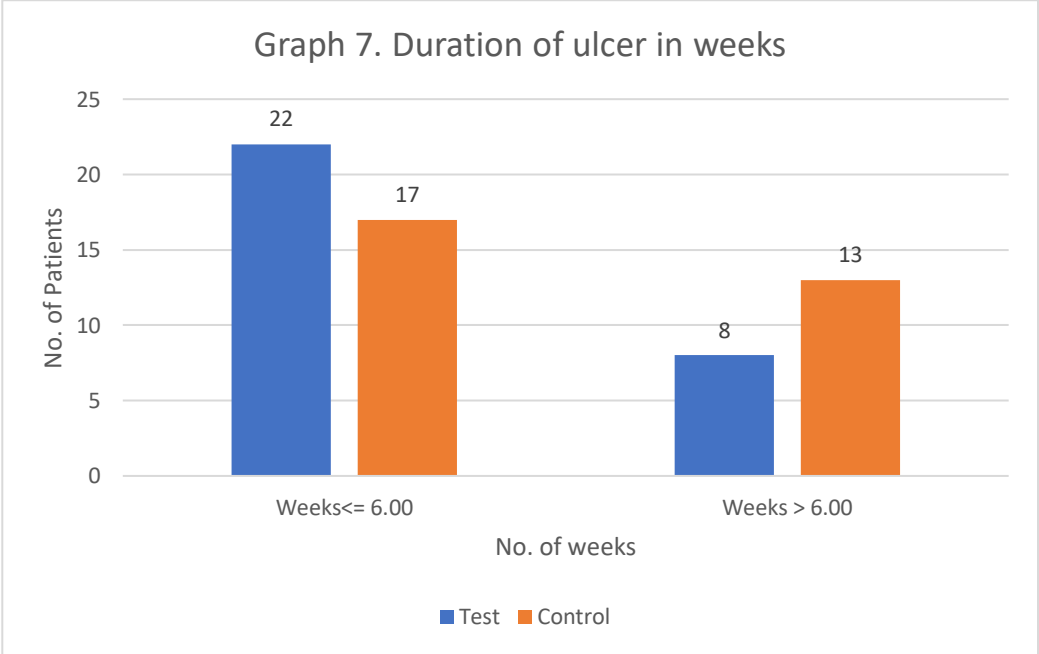
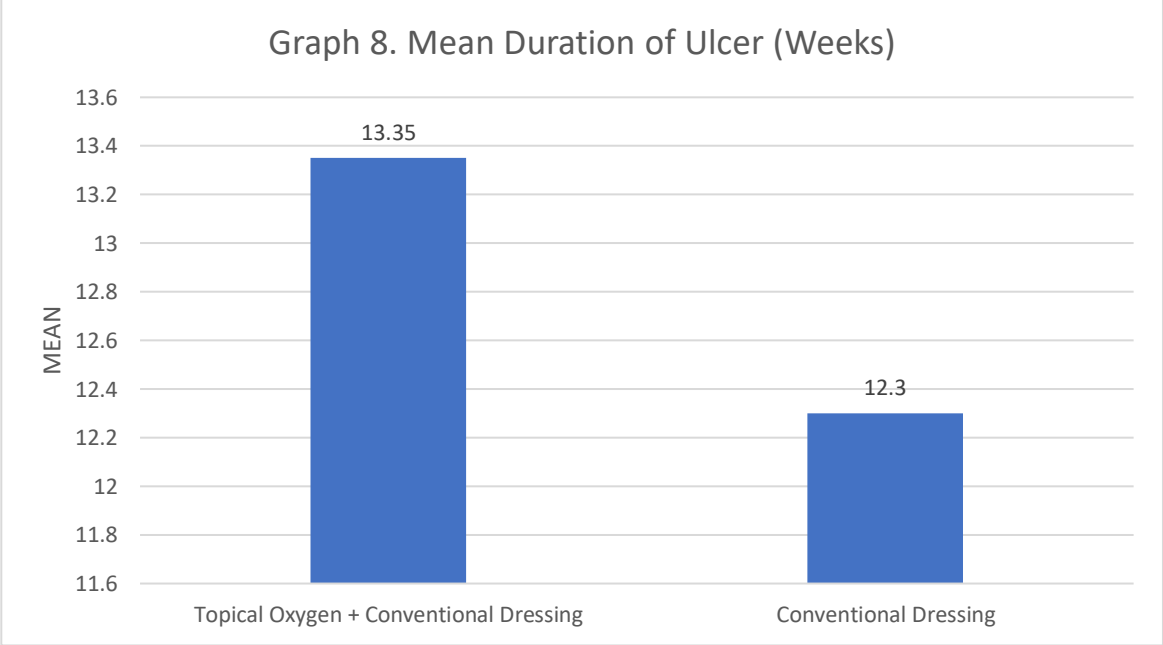


Table 20. Comparison of mean Duration of Ulcer (Weeks) Between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
Duration Of Ulcer (Weeks)	**Test Group**	30	13.35	11.407	0.302	0.764	Not Sig
	Control Group	30	12.30	15.381			



Most ulcers in both groups were of duration <=6 weeks, 73.33% in the Topical Oxygen + Conventional Dressing Group and 56.67% in the Conventional Dressing Group.

The mean duration of ulcer for the Topical Oxygen + Conventional Dressing Group was 13.35 weeks. The mean duration of ulcer for the Conventional Dressing Group was 12.30 weeks. Student T-Test between Study groups and mean duration of ulcer was non-significant (P>0.05).

4. DURATION OF DIABETES MELLITUS

Table 21. The distribution of Duration of Diabetes (Years) among Study Groups

Category	Test Group	Percentage	Control Group	Percentage
1 to 5	8	26.67%	17	56.67%
6 to 10	13	43.33%	3	10.00%
11 to 15	2	6.67%	7	23.33%
More than 15	7	23.33%	2	6.67%
Total	30	100.00%	30	100.00%

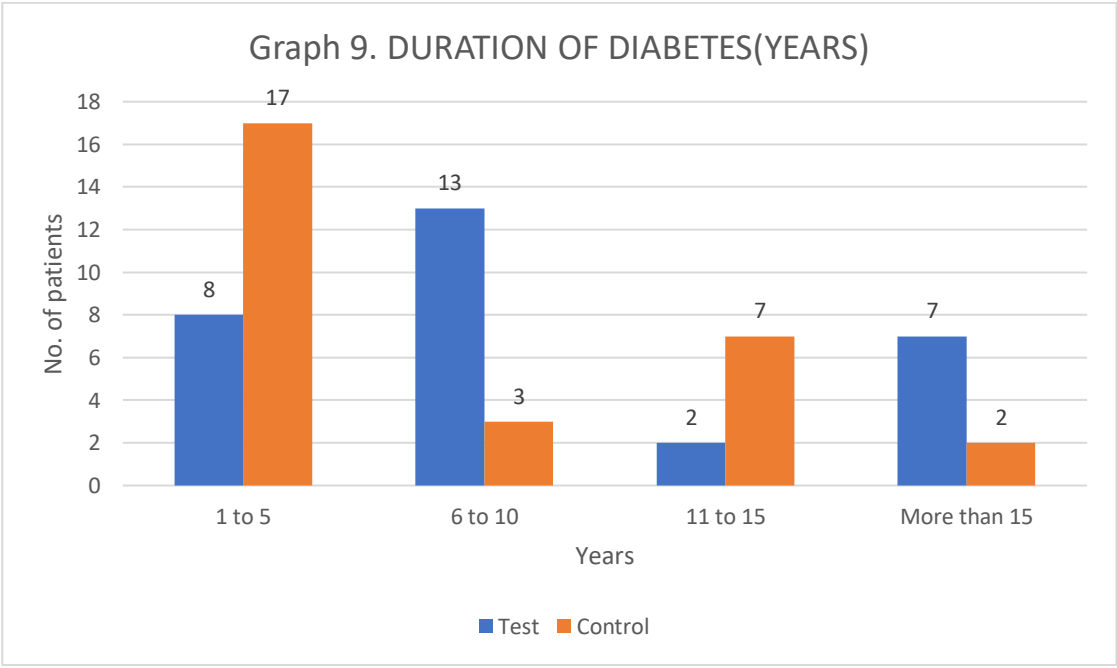
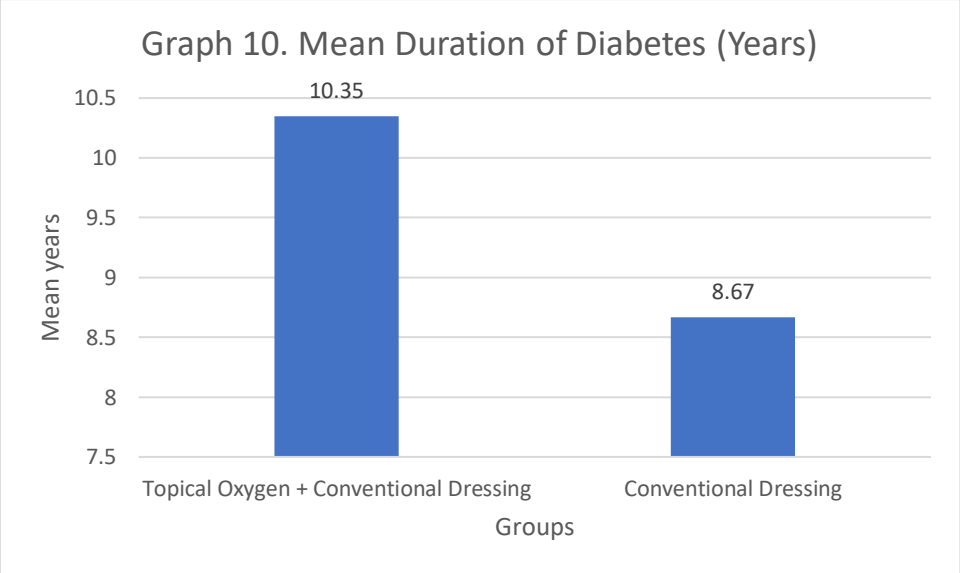


Table 22. Comparison of mean Duration of Diabetes (Years) among Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
Diabetes Duration (Years)	**Test Group**	30	10.35	7.378	0.890	0.377	Not Sig
	Control Group	30	8.67	7.270			



Most patients in the Test group had diabetes for 6-10 years (43.44%) while the Control group had for 1-5 years (56.67%).

The mean duration of Diabetes for the Topical Oxygen + Conventional Dressing Group was 10.35 years.

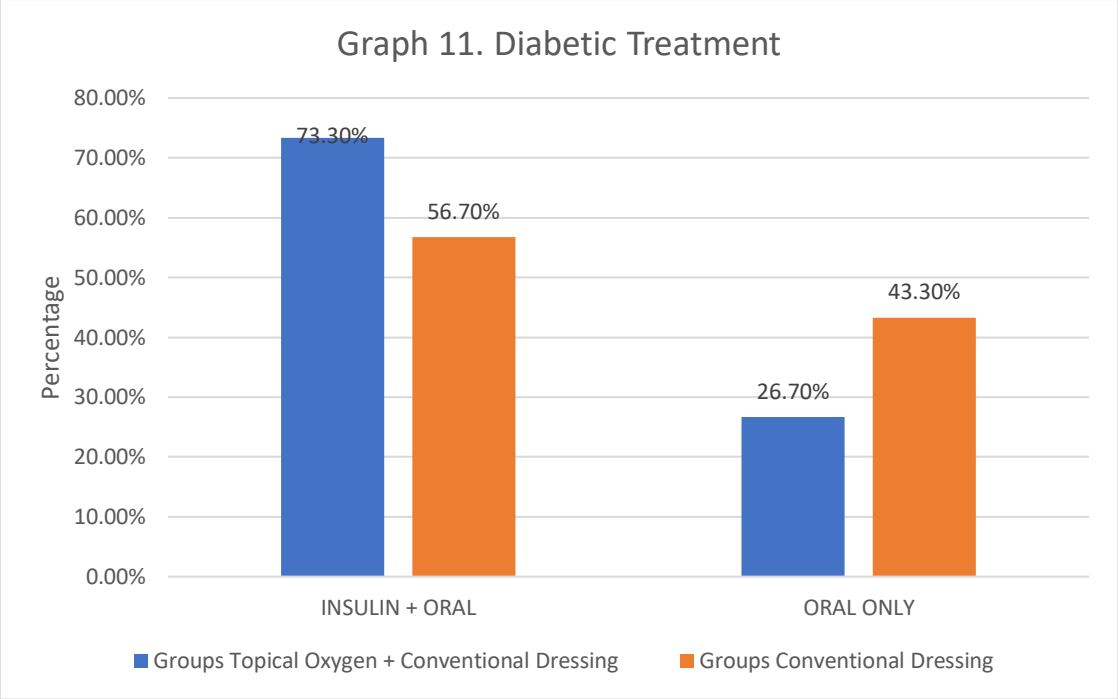
The mean duration of Diabetes for the Conventional Dressing Group was 8.67 years.

Student T-Test of the two Study groups and duration of the ulcers was non-significant (P>0.05).

5. TREATMENT OF DIABETES MELLITUS

Table 23. The distribution of Treatment of Diabetes Mellitus among Study Groups

DIABETIC TREATMENT		Groups		Total
		Test Group	Control Group	
INSULIN + ORAL	Number(N)	22	17	39
	Percentage (%)	73.3%	56.7%	65.0%
ORAL ONLY	N	8	13	21
	%	26.7%	43.3%	35.0%
	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	1.832	1	0.176	Non-Sig



The Topical Oxygen + Conventional Dressing Group's most patients were on INSULIN + ORAL therapy (73.3%) for Diabetes, followed by Oral Hypoglycaemic Agents (OHAs) only (26.70%).

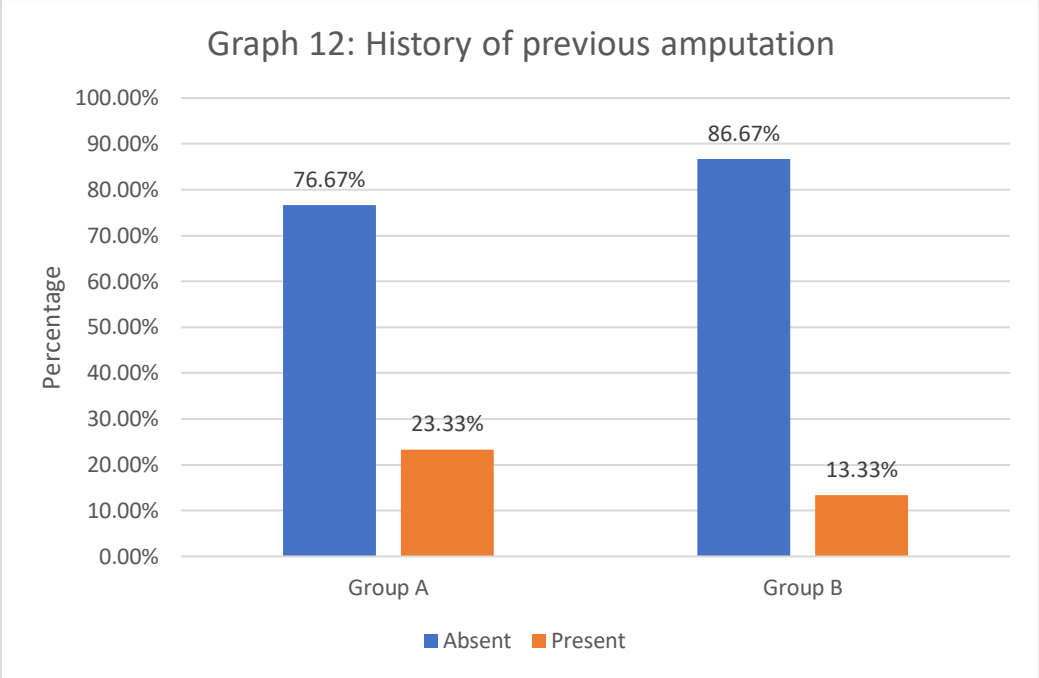
The Conventional Dressing Group's most patients were also on INSULIN + ORAL therapy (56.7%) for Diabetes, followed by OHAs only (43.3%).

Chi-square test for the distribution between Study Groups and Treatment of Diabetes Mellitus was found to be not significant (P>0.05).

6. HISTORY OF PREVIOUS AMPUTATIONS

Table 24. The distribution of History of Previous Amputation among Study Groups

HISTORY OF PREVIOUS AMPUTATION		**Groups**		**Total**
		Test Group	**Control Group**	
Absent	Number (N)	23	26	49
	Percentage (%)	76.67%	86.67%	81.66%
Present	N	7	4	11
	%	23.33%	13.33%	18.33%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	1.522	1	0.217	Non-significant



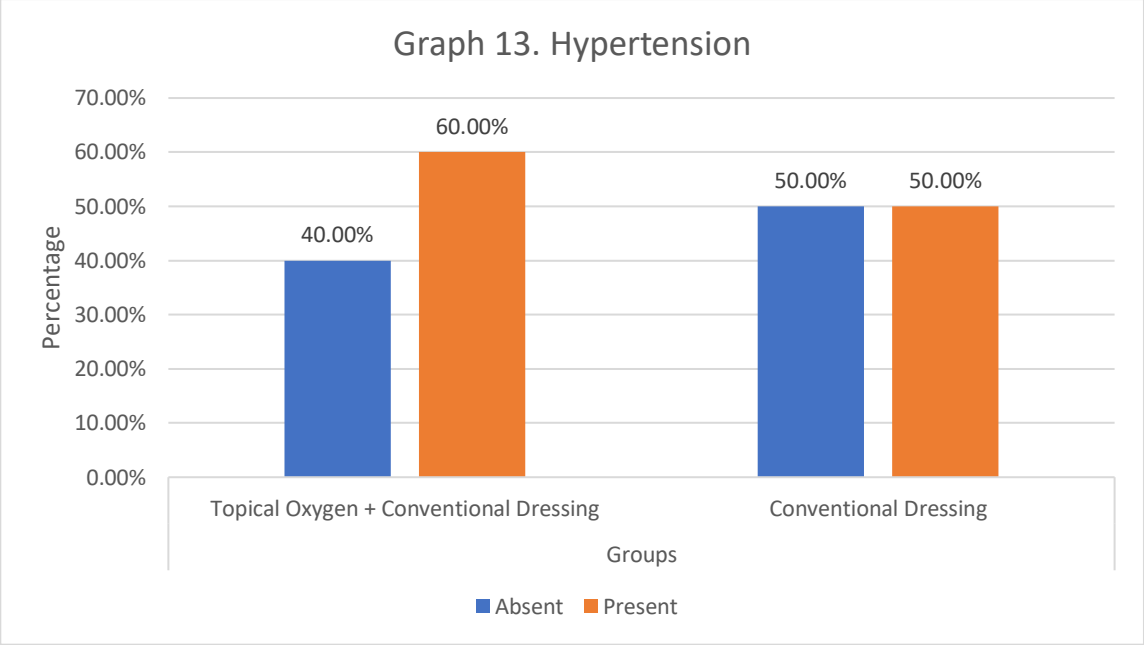
For both Study groups, most patients had no previous Amputation history (76.67% in Test Group and 86.67% in Control Group).

A chi-square test for the distribution between Study Groups and History of previous Amputation was non-significant (P>0.05).

7. HYPERTENSION

Table 25. The Distribution of Hypertension among Study Groups

HYPERTENSION		Groups		Total
		Test Group	Control Group	
Absent	Number(N)	12	15	27
	Percentage (%)	40.0%	50.0%	45.0%
Present	N	18	15	33
	%	60.0%	50.0%	55.0%
	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	.606	1	0.436	Non-Sig



Most patients in the Topical Oxygen + Conventional Dressing Group had Hypertension (60.0%).

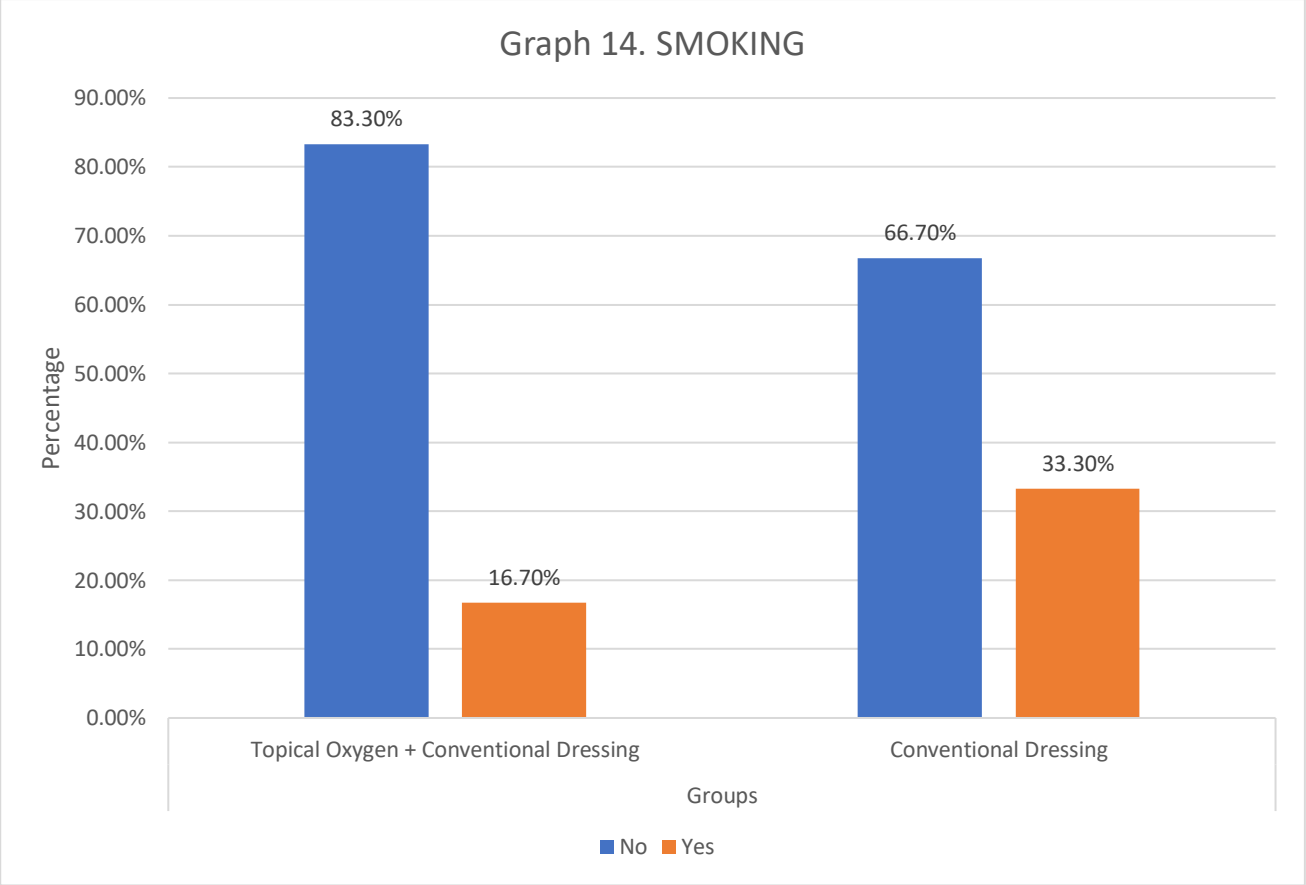
Half of the patients of the Conventional Dressing Group had Hypertension (50.0%).

Chi-square test for the distribution between Study Groups and Hypertension was found to be not significant (P>0.05).

8. HISTORY OF SMOKING

Table 26. The distribution of History of Smoking among Study Groups

History of SMOKING consumption		**Groups**		**Total**
		Test Group	**Control Group**	
No	Number(N)	25	20	45
	Percentage (%)	83.3%	66.7%	75.0%
Yes	N	5	10	15
	%	16.7%	33.3%	25.0%
	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	2.222	1	0.136	Non-Sig



Most patients in the Topical Oxygen + Conventional Dressing Group were non-smokers (83.30%).

Most patients in the Conventional Dressing Group were also non-smokers (66.7%).

chi-square test for the distribution between Study Groups and the history of Tobacco consumption was found to be not significant (P>0.05).

9. BASAL METABOLIC RATE (BMI)

Table 27. Distribution of Patients as per Basal Metabolic Rate (BMI) (Kg/M2) Between Two Study Groups

Category	Test Group	Percentage	Control Group	Percentage
Underweight	-	-	1	3.33%
Normal weight	8	26.70%	10	33.33%
Overweight	19	63.30%	15	50.00%
Obesity	3	10.00%	4	13.33%
Total	30	100.00%	30	100.00%

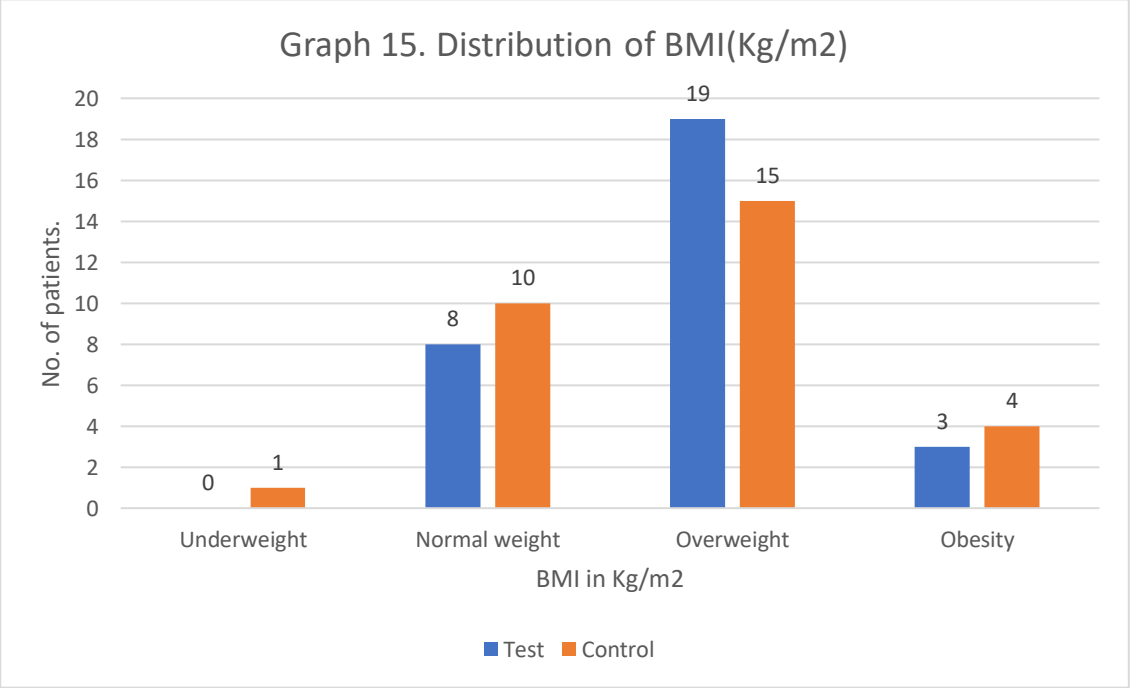
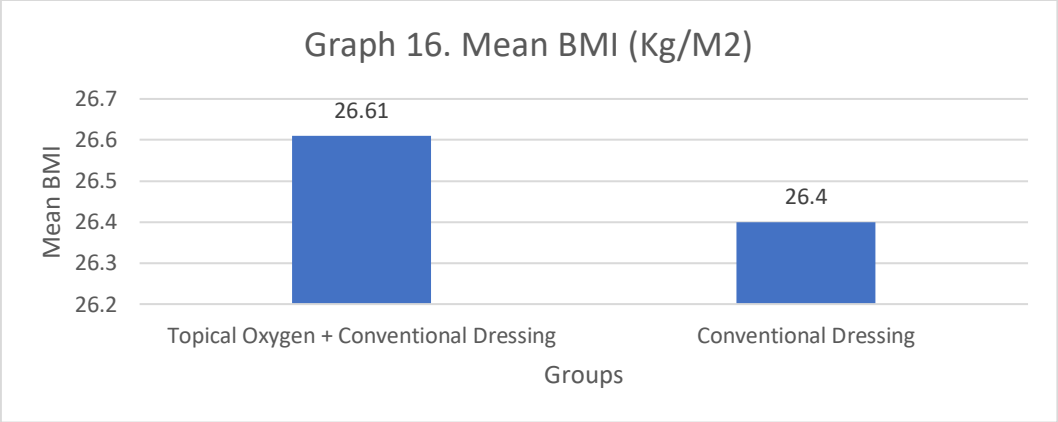


Table 28. Comparison of mean Basal Metabolic Rate (BMI) (Kg/M2) among Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
BMI (Kg/M2)	**Test Group**	30	26.61	2.897	0.233	0.817	Not Sig
	Control Group	30	26.40	3.810			



Most patients in both groups were Overweight, 63.3% in Test Group and 50.0% in Control Group.

The mean Basal Metabolic Rate (BMI) for the Topical Oxygen + Conventional Dressing Group was 26.61 Kg/M2.

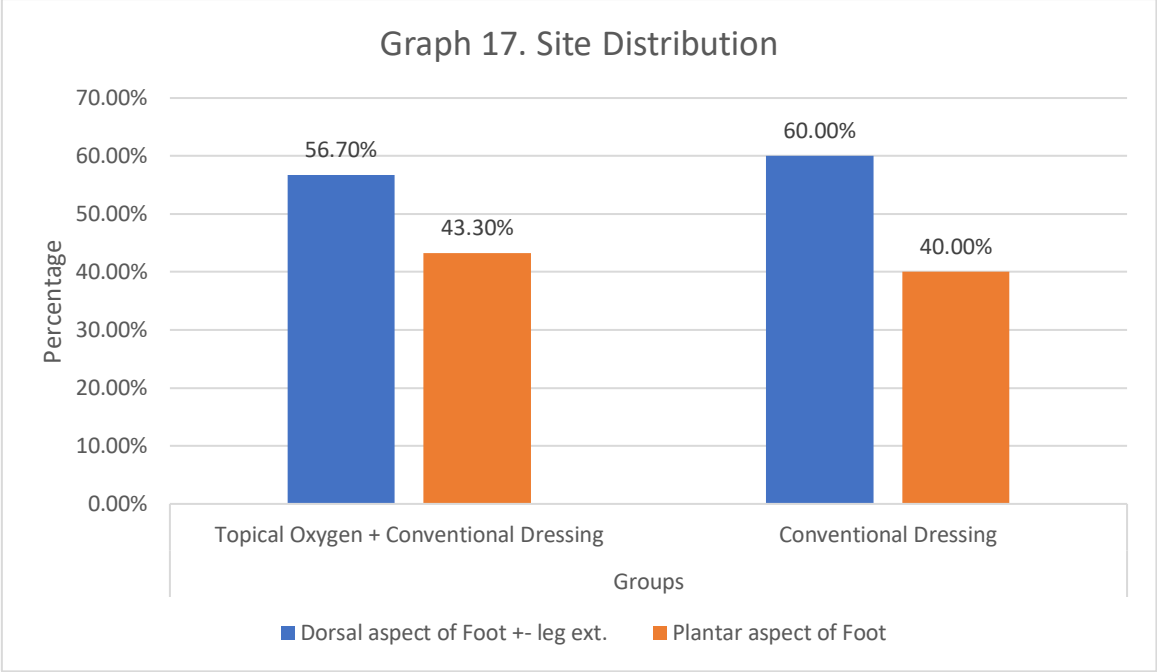
The mean BMI for the Conventional Dressing Group was 26.40 Kg/M2.

Student T-Test of the two Study groups and BMI was non-significant (P>0.05).

10. SITE

Table 29. The distribution between Study Groups and Site

SITE		Groups		Total
		Test Group	Control Group	
Dorsal aspect of Foot +- leg ext.	Number(N)	17	18	35
	Percentage (%)	56.7%	60.0%	58.3%
Plantar aspect of Foot	N	13	12	25
	%	43.3%	40.0%	41.7%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	0.069	1	0.793	Non-Sig



The Topical Oxygen + Conventional Dressing Group's most patients had ulcers over the Dorsal aspect of Foot +- leg extension (56.7%), followed by the Plantar aspect of foot (43.3%).

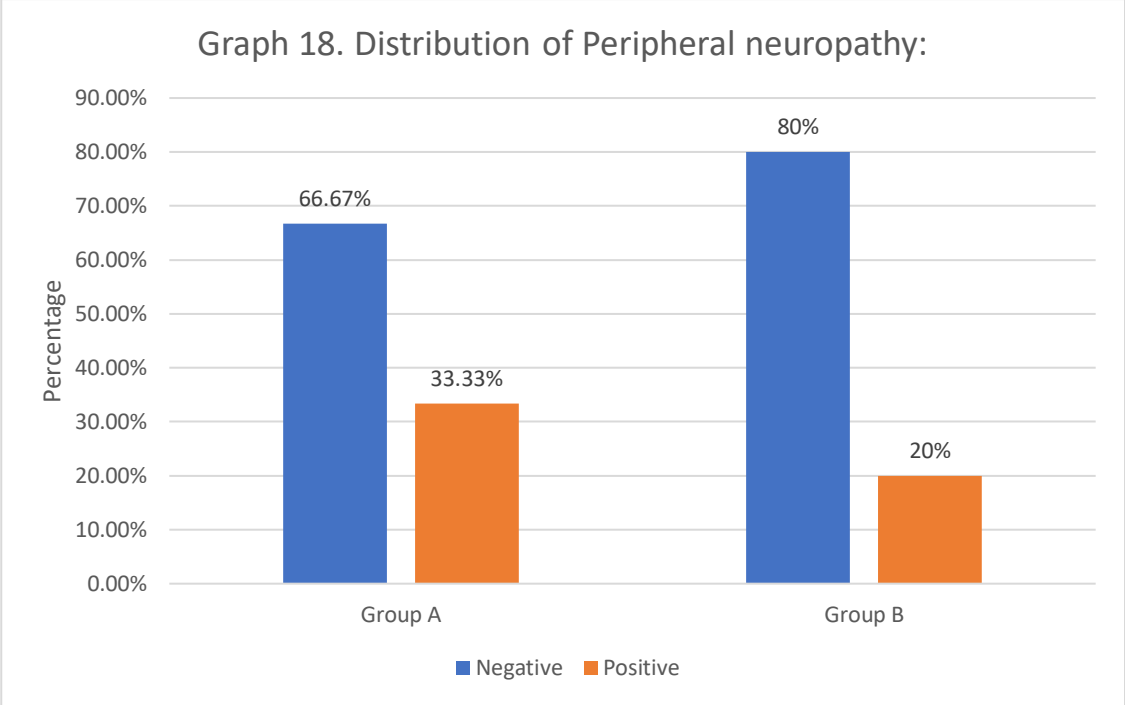
The Conventional Dressing Group's most patients also had ulcers over the Dorsal aspect of Foot +- leg extension (60%), followed by the Plantar aspect of foot (40%).

Chi square test for the distribution between Study Groups and SITE was found to be not significant (P>0.05).

11. PERIPHERAL NEUROPATHY STATUS

Table 30. The distribution of Peripheral Neuropathy among Study Groups

PERIPHERAL NEUROPATHY		**Groups**		**Total**
		Test Group	**Control Group**	
Negative	Number(N)	20	24	44
	Percentage (%)	66.67%	80%	73.33%
Positive	N	10	6	16
	%	33.33%	20%	26.66%
TOTAL	N	30	30	60
	%	100.0%	100.0%	100.0%
Pearson Chi-Square	Value	Df	P Value	Result
	1.36	1	0.244	Non sig.



For both the Study groups most, patients had no peripheral neuropathy, 66.67% in Test group and 80.0% in Control Group.

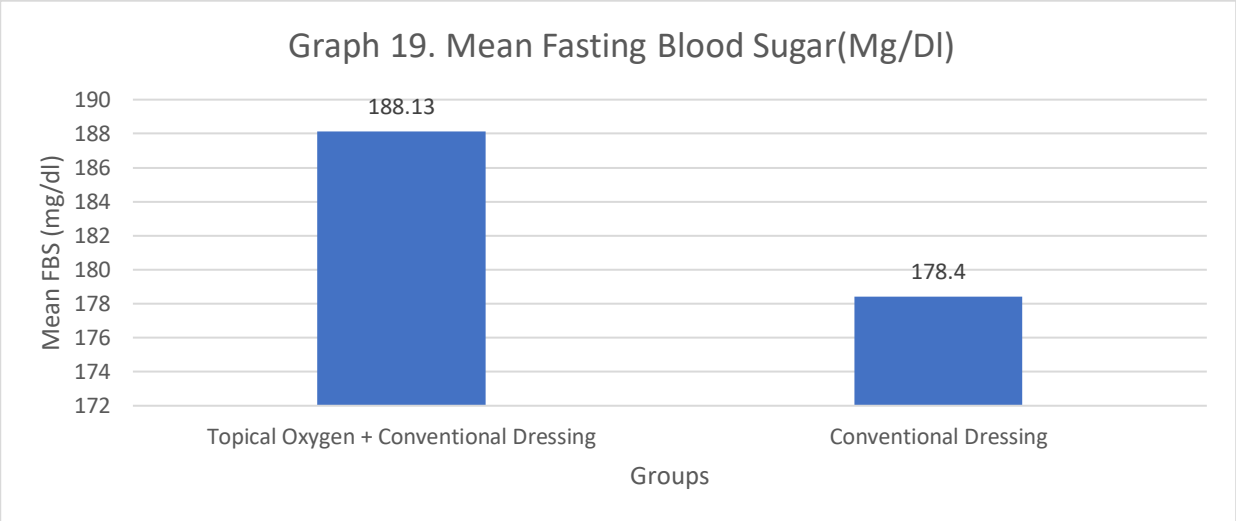
A chi-square test for the distribution between Study Groups and Peripheral Neuropathy was found to be not significant (P>0.05).

12. INVESTIGATIONS

i) FASTING BLOOD SUGAR (FBS)

Table 31. Comparison of Fasting Blood Sugar (Mg/Dl) among Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
FASTING BLOOD SUGER (Mg/Dl)	**Test Group**	30	188.1	71.80	0.585	0.561	Not Sig
	Control Group	30	178.4	56.15			



The mean FBS of 188.13 Mg/Dl was for the Topical Oxygen + Conventional Dressing Group and 178.40 Mg/Dl for the Conventional Dressing Group.

Student T-Test of the two Study groups and the Fasting Blood Sugar (FBS) was non-significant (P>0.05).

ii) GLYCATED HEMOGLOBIN (HbA1c)

Table 32. Distribution of Patients as per Glycated Haemoglobin (HbA1c) Between Two Study Groups

Category	Test Group	Percentage	Control Group	Percentage
Less than 6.5 (controlled)	13	43.30%	9	30%
More than 6.5 (uncontrolled)	17	56.70%	21	70%
Total	30	100%	30	100%

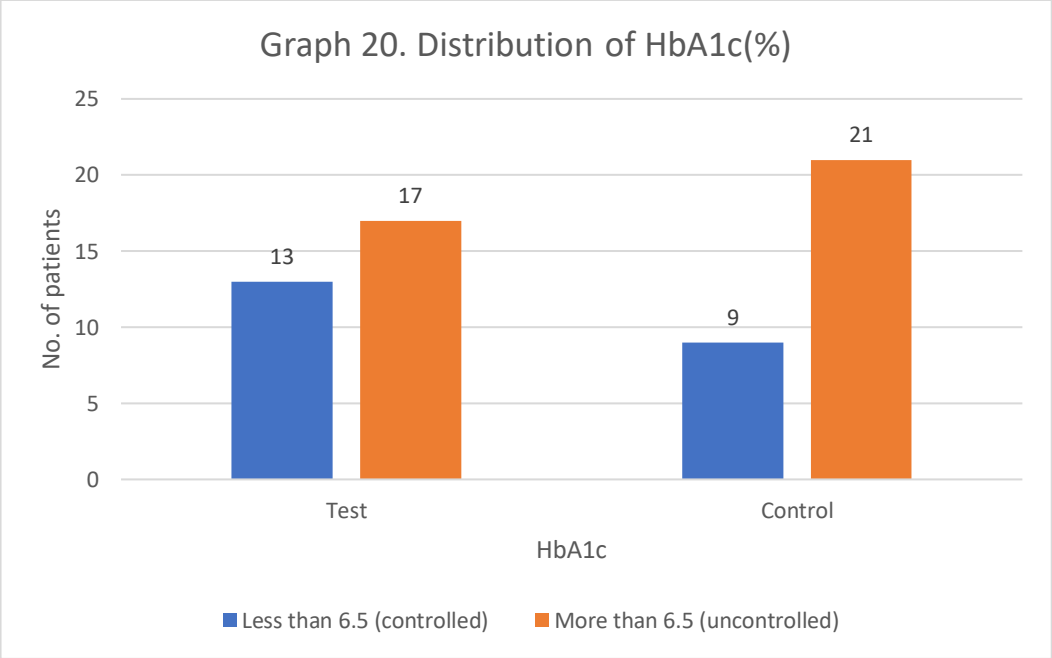
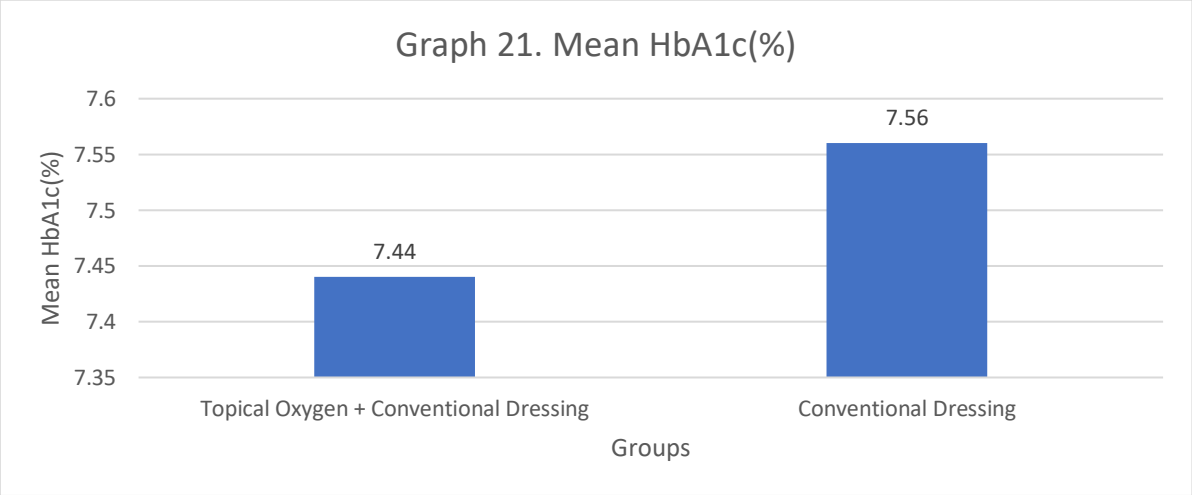


Table 33. Comparison of Mean HbA1c (Glycated Haemoglobin) Between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
HbA1c (%)	**Test Group**	30	7.44	1.877	-0.251	0.803	Not Sig
	Control Group	30	7.56	1.832			



Most patients in either group had uncontrolled diabetes (>6% HbA1c), 56.70% in Test Group and 70.0% in Control Group.

The mean HbA1c for the Topical Oxygen + Conventional Dressing Group was 7.44%.

The mean HbA1c for the Conventional Dressing Group was 7.56%.

Student T-Test of the two Study groups and HbA1c was non-significant (P>0.05).

iii) CULTURE & SENSITIVITY

Table 34. Distribution of Culture reports and Study groups on Day 0 & 14

Organisms	Test Group		Control Group		Total
	Day 0	Day 14	Day 0	Day 14	
Acinetobacter	3 (10%)	0	2 (6.67%)	0	5
Klebsiella pneumoniae	3 (10%)	0	0	0	3
Staphylococcus aureus	2 (6.67%)	0	2 (6.67%)	0	4
Candida sp.	1 (3.33%)	0	0	0	1
Streptococcus agalactiae	0	1 (3.33%)	0	1 (3.33%)	2
Escherichia coli	3 (10%)	4 (13.33%)	4 (13.33%)	3 (10%)	14
MRSA	5 (16.67%)	4 (13.33%)	4 (13.33%)	3 (10%)	16
Pseudomonas aeruginosa	5 (16.67%)	0	3 (10%)	2 (6.67%)	10
Proteus mirabilis	0	0	2 (6.67%)	1 (3.33%)	3
Enterococcus faecalis	0	0	1 (3.33%)	0	1
Total Positive	22(73.3%)	9(30%)	18(60%)	12(40%)	61
Negative	8 (26.67%)	21 (70%)	12 (40%)	18 (60%)	59
Total	**30 (100%)**	**30 (100%)**	**30 (100%)**	**30 (100%)**	**120**

Most common infection was MRSA (16.67%) on Day 0 of Test group. Most common infection was MRSA (13.3%) and E. coli (13.3%) on Day 0 of Control group.

The table shows Total positive culture & sensitivity tests of 22 patients in Test Group and 18 in Control Group on Day 0.

The table shows Total positive culture & sensitivity tests of 9 patients in Test Group and 12 in Control Group on Day 14.

Therefore, reduction in number of organisms isolated from each group after 14 days of their respective dressings are:

Test Group = 22 – 9 = 13

Control group = 18 – 12 = 6

Thus, the usage of the Topical Oxygen + Conventional Dressing in the test group witnessed a marginally more reduction in the bioburden as compared to the control group where Conventional dressing was used.

13. WOUND HEALING

The reduction in area and percentage reduction in area are calculated as follows:

Ulcer area on Day 0 = x

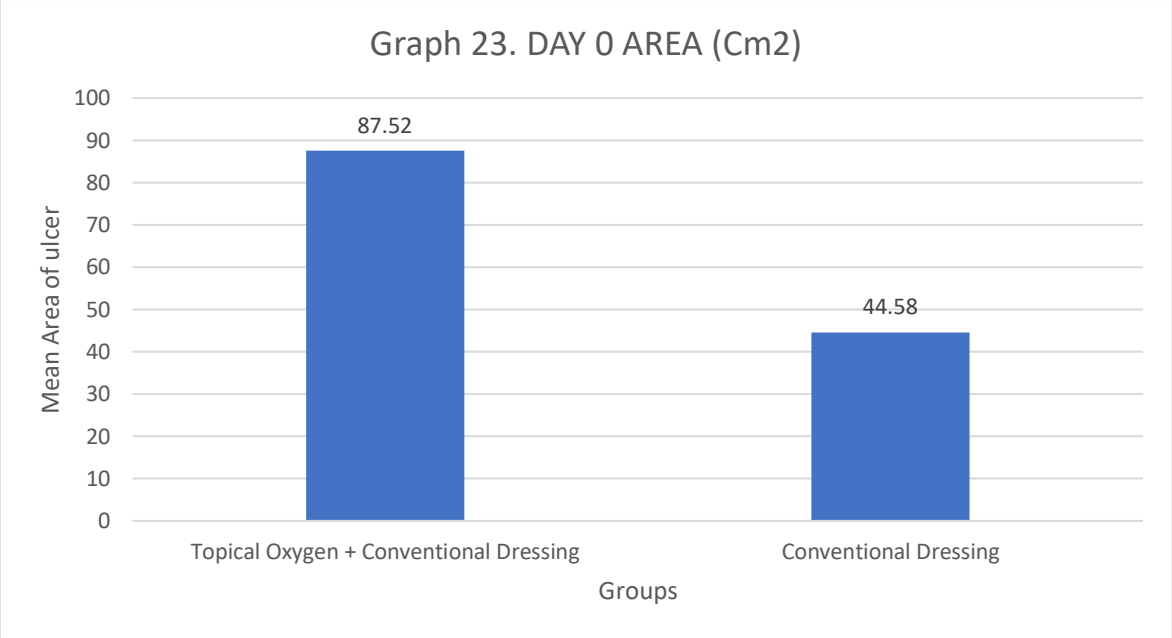
Ulcer area on Day 14 = y

Ulcer Area Reduction = x-y

Percentage of Reduction in Ulcer area (**Ulcer Contraction**) = $\frac{x-y}{x}x100$

Table 35. Comparison of DAY0 AREA (Cm2) between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
DAY 0 AREA (Cm2)	**Test Group**	30	87.52 Cm2	117.845	1.799	0.077	Not Sig
	Control Group	30	44.58 Cm2	56.531			



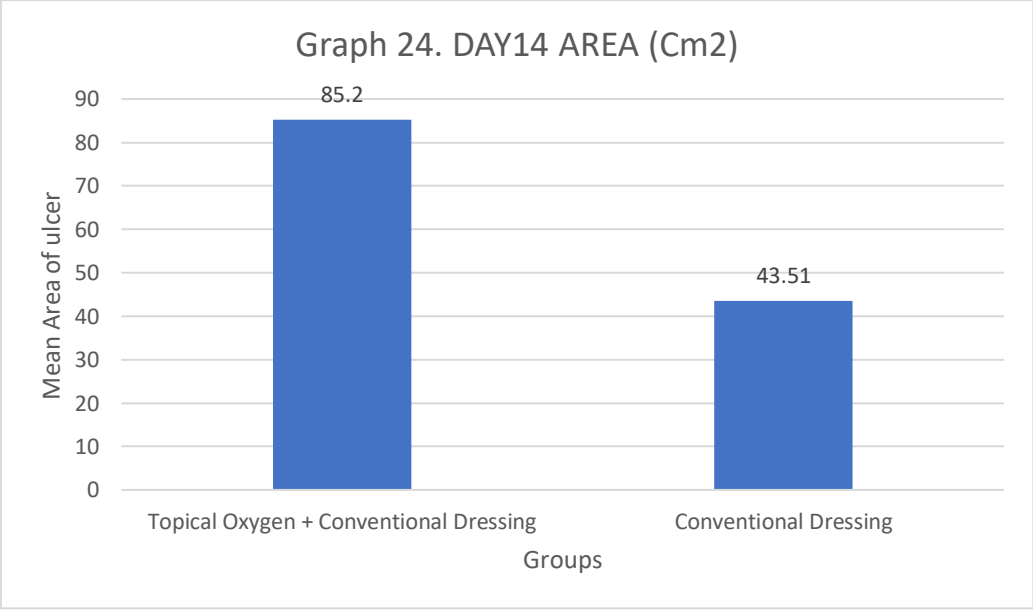
The mean area of 87.52 Cm2 was for Topical Oxygen + Conventional Dressing Group.

The mean area of 44.58 Cm2 was for Conventional Dressing Group.

Student T-Test of two Study groups and DAY0 AREA of the ulcer was not significant (P>0.05).

Table 36. Comparison of DAY14 AREA (Cm2) Between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
DAY 14 AREA (Cm2)	**Test Group**	30	85.20 Cm2	115.4	1.787	0.079	Not Sig
	Control Group	30	43.51 Cm2	54.8			



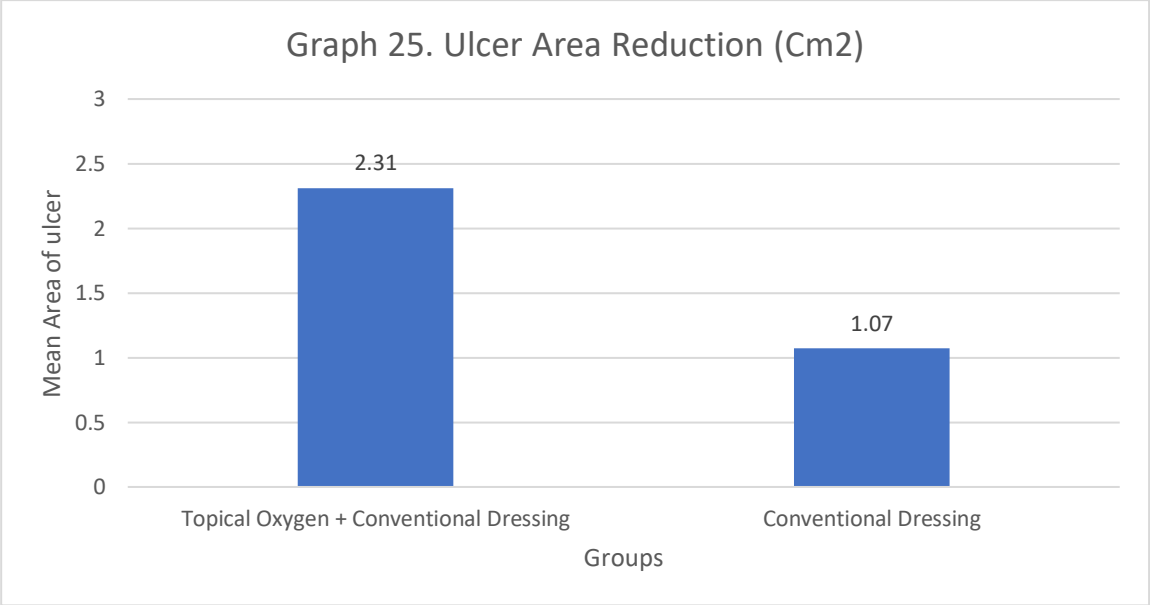
The mean area of ulcer was 85.20 Cm2 for Topical Oxygen + Conventional Dressing Group.

The mean area of ulcer was 43.51 Cm2 for Conventional Dressing Group.

Student T-Test of two Study groups and DAY14 AREA of the ulcers was not significant (P>0.05).

Table 37. Comparison of Ulcer Reduction (Cm2) Between Two Study Groups

Parameter	Groups	Number(N)	Mean	Std. Dev	T Test	P Value	Result
Ulcer Area Reduction (Cm2)	**Test Group**	30	2.31 Cm2	2.517	2.163	0.035	Sig
	Control Group	30	1.07 Cm2	1.896			



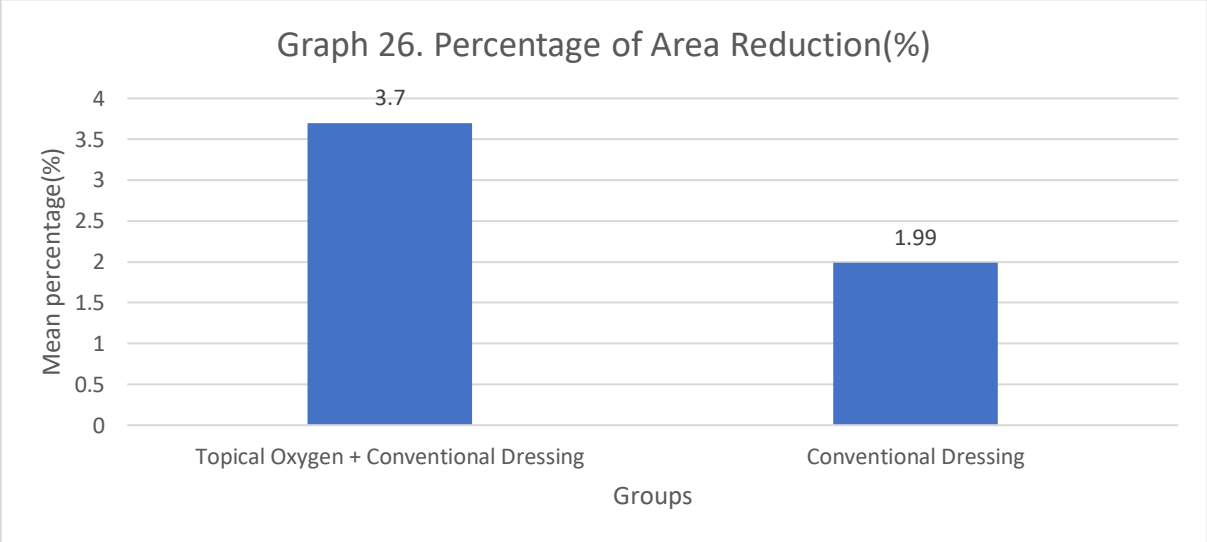
Ulcer Area Reduction (Cm2) = DAY14 AREA - DAY0 AREA

The mean Ulcer Area Reduction was 2.31 Cm2 for the Topical Oxygen + Conventional Dressing Group. The mean Ulcer Area Reduction was 1.07 Cm2 for the Conventional Dressing Group.

Student T-Test of the two Study groups and Ulcer Area Reduction of the ulcers was **significant** (P>0.05).

Table 38. Comparison of Percentage of Area Reduction (%) Between Two Study Groups

Parameter	Groups	Number (N)	Mean	Std. Dev	T Test	P Value	Result
Percentage Of Area Reduction **(%)**	**Test Group**	30	3.70	2.409	3.270	0.002	Sig
	Control Group	30	1.99	1.545			



Percentage Of Area Reduction (%) = Ulcer Area Reduction (Cm2) x 100 / DAY0 AREA

The mean Percentage of Area Reduction of ulcers was 3.70 % for the Topical Oxygen + Conventional Dressing Group.

The mean Percentage of Area Reduction of ulcers was 1.99 % for the Conventional Dressing Group.

Student T-Test of the two Study groups and Percentage of Area Reduction of the ulcers was **significant** (P>0.05).

DISCUSSION

This randomised control study was conducted to focus on eliciting the wound healing dynamics with adjuvant Topical oxygen therapy on DFUs. It was executed under the department of general surgery at KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar. Belagavi, between January 2023 to December 2023.

A total of 60 patients who satisfied the selection criteria and were willing to participate, were taken as the study population. These patients were categorized into two groups of 30 each, where the Test group received treatment with topical oxygen therapy along with conventional dressing, and Control group received conventional dressing alone.

The mean age for the Topical Oxygen with Conventional therapy is 50.57 +- 14.644 years was comparable to the mean age of 55.30 +- 12.820 years for the Conventional Dressing Group. (P>0.05). This clearly signified the prevalence of majority of the diabetic foot ulcers in patients who were more than 50 years of age. This was in agreement with the study done by Niederauer et al that signified increasing age as a key risk factor for diabetic foot ulcer.[73]

The Test group comprised of 22(73.3%) patients who were males and 8 (26.7%) who were females with Male to female ratio of 2.75:1, whereas the Control group included 21 (7%) male patients and 9 (30%) female patients with Male to female ratio of 2.3:1. This emphasized the male predisposition for diabetic foot ulcers in this study. Blackman et al in his study also proved that men have a higher risk for foot ulceration. [74]

On the basis of the site of the ulcer, the control group had 18 (60%) patients with a dorsal ulcer and 12 (40%) with plantar ulcer. The test group had 17(56.7%) patients with ulcer on the dorsum and 13(43.3%) with that on the plantar aspect. Both the groups were comparable in terms of the site of ulcers. Frykberg et al.[68] and Serena et al[69] assessed the frequency of foot ulcers in diabetics and found most of the ulcers on the plantar aspect of the

patients. This was attributed to patients having peripheral neuropathy were at an increased risk of foot trauma and deformities like flat foot, Charcot's foot, etc.

Our study depicts the mean BMI in the control group as 26.61 kg/m2 and in the test group as 26.40 kg/m2, showing most patients to be overweight. There was a statistically non-significant difference between the two groups (P value 0.817). In a study done by Frykberg et al,[75] the mean BMI of the test and control group was 30.8 and 31.2 kg/m2 respectively. A high body mass index is therefore reflective of obesity, which in turn directly stimulates the development of diabetic foot ulcers.

In our study the distribution of the risk factors between the test and control group were as follows (mean)- duration of diabetes: 10.35 and 8.67 years, HbA1c: 7.44% and 7.56%, peripheral neuropathy: 33.33% and 20.00%, H/o previous amputations: 23.33% and 13.33%, and smokers: 16.7% and 33.3%, respectively. Thus, showing matching due to randomisation in both the groups. Niederauer et al in comparison had smoking history in 27% and 36% of patients, peripheral neuropathy in 43.8% and 36.6% of patients and a mean HbA1c of 8.4% and 8.3 %, in test and control group respectively.[73] The patients with these risk factors are at a higher predisposition of developing chronic diabetic foot ulcers.

For the duration of ulcers, the mean duration of ulcer (weeks) for test group was non significantly higher than the mean value for control group (13.35 +- 11.407 and 12.30 +- 15.381 weeks, respectively (P>0.05). Niederauer et al reported comparable findings (P>0.05).[73]

On analysing the change in size of the ulcer in respect to area of ulcer over 14 days, it was observed that the mean area of the ulcer in the control group on day 0 and day 14 was 44.58 cm^2 and 43.51 cm^2, respectively with the mean difference in ulcer size being 1.07 cm^2. The mean area of the ulcer in the test group on day 0 and day 14 was 87.52 cm^2 and 85.20 cm^2, respectively with the mean difference in ulcer size being 2.31 cm^2. This was a

statistically significant reduction in area of the ulcer in the test group when compared to the control group, indicating faster healing rates. (p value<0.035) This is in concordance with the study by Niederauer et al. [73] showing reduction of 1.34 and 0.94 cm^2 in test and control group respectively. Other studies have compared healing using days required for complete/50% epithelisation of the ulcer, attributed to longer study period and follow ups.

The mean percentage reduction in area of ulcer over 14 days in the control and test groups are 1.99% and 3.70%, respectively. This difference is statistically significant in the test group in comparison to the control group (p value = 0.002). This signified that the reduction in ulcer area over 14 days was more in the test group where topical oxygen was given along with conventional dressing. Serena et al. [69] presented similar results, indicating a significant reduction in Ulcer area in both groups: the conventional group showed an average reduction of 40%, while the conventional combined with topical oxygen wound therapy (TOWT) group demonstrated a mean reduction of 70% (p=0.005).

Culture and sensitivity showed in the test group, out of 30 samples, 22 samples tested positive at day 0 whereas at Day 14 only 9 patients tested positive. At Day 0, the most isolated pathogen were Methicillin resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa [5(16.67%) each], followed by Escherichia coli [3(10%)]. However, at Day 14, the isolated pathogen i.e., Escherichia coli [4(13.33%)], MRSA [4(13.33%)] and Streptococcus agalactiae [1(3.33%)] were observed. For the control group, 18 pathogens were isolated at Day 0 which reduced to 12 at Day 14 following conventional dressings, showing a majority of Escherichia coli and MRSA isolates. Thus, the test group witnessed a marginally more reduction in the bioburden as compared to the control group. In a meta-analysis conducted by Macdonald et al, most common pathogen isolated was Staphylococcus aureus followed by Pseudomonas and E. coli. However, the microbial nature of diabetic ulcers may vary depending upon geographic distribution. [76]

Table 39. Comparison of current study with other studies with respect to demography, risk factors, intervention and outcomes.

PARAMETERS	PRESENT STUDY		NIEDERAUER ET AL		BLACKMAN ET AL		FRYKBERG ET AL	
TIME OF STUDY	RCT		RCT		RCT		RCT	
NO OF PATIENTS	60		146		28		73	
INTERPRETATION	30 mmHg 10L/min O_2 1 hour daily for 14 days		Transcutaneous O_2 system with 3ml/hr, 24 hrs a day for 12 weeks		37.5 mmHg 1hr daily, 4 days a week, for 90 days		7.5-37.5 mmHg 10L/min for 90 min daily 5 days a week for 12 weeks	
STUDY GROUPS	Test (30)	Control (30)	Test (74)	Control (72)	Test (17)	Control (11)	Test (36)	Control (37)
AGE (years)	50.57	55.30	56.1	56.6	62.4	63.4	64.6	61.9
GENDER (M: F)	2.74	2.33	3.92	3.0	2.4	2.66	8.09	5.25
SMOKERS (%)	16.7	33.3	-	-	0	11.8	27	36
NEUROPATHY (%)	33.3	20	43.8	36.6	100	100	78	78
HbA1C (%)	7.44	7.56	8.4	8.3	-	-	-	-
ULCER DURATION (weeks)	13.35	12.30	18.8	20.5	42.7	22.4	4 weeks to 1 year	
INITIAL ULCER AREA (cm^2)	87.52	44.5	3.54	3.89	4.1	1.4	1.97	0.40
ULCER AREA REDUCTION (cm^2)	2.31 cm^2	1.07 cm^2	1.34 cm^2	0.94 cm^2	-	-	-	-
WOUND HEALING	3.70%	1.99%	18.4days	28.9days	56 days	93 days	15 ulcers	5 ulcers
	Ulcer area reduction (%) after 14 days		For 50% epithelization		For complete wound closure		closed at 12 weeks	

The patients receiving the oxygen topically did not experience any adverse effects during the course of application of the therapy and tolerated it well. Other studies like Blackman et al also show no adverse effects of giving topical oxygen therapy as adjuvant to conventional dressing in diabetic foot ulcers, deeming it a safe modality of treatment.[74]

Overall, the patients receiving Topical oxygen wound therapy showed superior outcomes in terms of reduction of percentage of ulcer area and bacterial colonisation compared to conventional dressings alone in a safe manner.

Limitations of the Study

This study had a small population of 60 patients with 30 each in test and control groups, who were followed for a short period of 15 days only. It was conducted at a single centre. The temperature and humidity of oxygen delivered were not standardised. These are the limitations of this study.

Future Scope of Study

There is no standard commercially available formulation of topical oxygen that can be used daily. With the increasing number of diabetic foot ulcers, this stresses the need of formulating an ideal device that can be applied for general clinical practice on a regular basis, easily and economically, in a surgery ward setting. It is advised to have a longer follow up of the patients, till attainment of complete healing of ulcer. There is a need of large-scale and multi-centric clinical studies which can warrant the efficacy and characteristics of topical oxygen wound therapy in diabetic foot ulcer healing.

CONCLUSION

The study has shown the wound healing dynamics in diabetic lower limb ulcers between the two study groups receiving topical oxygen wound therapy along with conventional dressings (Test group) and conventional dressings (Control group) alone.

We conclude that the application of topical oxygen wound therapy (TOWT) along with conventional dressings has significant decrease in ulcer area with respect to dressings with only conventional methods for diabetic foot ulcers. This signifies the superior healing rates when receiving TOWT as compared to conventional dressing groups.

During the course of this study, the application of this topical modality witnessed no adverse effects, which thus marks the safety of this method.

The topical oxygen wound therapy delivered to all patients was also economical as it used most materials readily available in surgery wards without requirement of special devices for delivery.

Regarding the anti-microbial activity, the test group showed more decrease in number of positive wound cultures over study period compared to the control group. This indicated the anti-microbial properties of topical oxygen wound therapy on DFUs.

Additional follow up studies would provide more insight into the impacts of Topical oxygen wound therapy with conventional dressings in the future.

SUMMARY

This study aimed to evaluate the efficacy of topical oxygen wound therapy (TOWT) as an adjunctive treatment for diabetic foot ulcer management through a randomized controlled study. The research sought to compare the healing rates of diabetic lower limb ulcers treated with TOWT alongside conventional dressing versus those treated with conventional dressing alone. Sixty patients who met the inclusion criteria and agreed to take part were included in the study. They were divided into two groups of 30 each. One group (Test group) was given topical oxygen wound therapy in addition to conventional dressing, while the other group (Control group) only received conventional dressing.

The mean age of patients in Test and Control groups were 50.57 and 55.30 years respectively, thus showing most patients being of elderly in the study. The study consisted of predominantly male patients, i.e. 71.7% of the total.

The patients in the study had ulcers mostly on dorsal aspect of foot with or without leg extension, 56.7% for test group and 60.0% for control group. The bulk of patients had insidious onset of ulcer in either group (65.0%). The test group had 13.35 weeks of mean duration of ulcer, while the control group had 12.30 weeks, showing chronic ulcers in most cases.

The mean duration of diabetes for the test and control group were 10.35 years and 8.67 years respectively. Patients in the study had mean HbA1c of 7.44% for the test group and 7.56% for the control group.

The patients in the study had various risk factors with distribution between test and control group as follows: Smokers – 16.7% and 33.3%, History of previous amputation – 23.33% and 13.33%, Peripheral neuropathy – 33.33% and 20.0%, and Hypertension – 60.0%

and 40.0% respectively. Therefore, most patients were non-smokers without history of previous amputation, and not having peripheral neuropathy.

The Study groups, as a result of randomisation, have been matched with respect to all initial parameters and, show no statistical difference in either group.

The difference in the mean area reduction of ulcers over 14 days in the test group was significantly greater as compared to control group, i.e. 2.31 cm^2 and 1.07 cm^2 respectively (p value = 0.035). Thus, the healing of ulcer in the test group was significantly higher in comparison to the control group.

The mean percentage reduction in area of ulcer in the test and control groups were 3.70% and 1.99% respectively showing a significant difference (p value = 0.002). This signified that the healing rates of ulcers was more in the group where topical oxygen wound therapy along with conventional dressings was given. The study results suggest that healing of diabetic foot ulcers treated with topical oxygen alongside conventional dressing occurred faster compared to those treated solely with conventional dressing.

In adjunct to this, topical oxygen wound therapy also showcased antimicrobial property by virtue of more negative bacterial colonisations in culture reports after 14 days of dressings in the test group. However, this was not statistically significant.

The study shows no adverse effects in the patients of either group after intervention. Therefore, there are no side effects of adjuvant TOWT as shown in our study.

The adjuvant topical oxygen wound therapy has considerable advantages over conventional dressings alone for management of DFUs. It has shown better results in healing of diabetic foot ulcers and anti-microbial action when compared to conventional dressings alone, in an economical, safe and comfortable way.

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KAHERs JNMC BELAGAVI

INFORMED CONSENT FORM

"EVALUATE THE ROLE OF TOPICAL OXYGEN THERAPY IN WOUND HEALING DYNAMICS OF DIABETIC LOWER LIMB ULCERS - A RANDOMISED CONTROLLED STUDY."

Name of Student/Principal Investigator: Reg. No. BH0121009

Name of Guide/Co Investigators:

Objective: To compare healing rates of diabetic ulcers treated with Topical Oxygen Therapy versus that with advanced moist dressing therapy

Introduction: Any treatment modality's main goal is to get the wound closed as soon as possible. Debridement, infection control, revascularization of ischemic tissues, and avoiding unwarranted pressure over the wound are all part of the standard treatment. Oxygen (O2) is essential to wound healing. Local tissue hypoxia caused by disrupted or compromised vasculature, is a key factor that limits wound healing. There is a paucity of research in area of topical oxygen therapy applying modalities. Therefore, a randomized controlled trial is needed to validate this novel modality of applying topical oxygen therapy.

Explanation of procedure: Wound that is to be dressed is prepared by opening the dressing and removing the superficial slough. Sterile disposable cover is used for covering the wound. For abdominal and pelvis wounds, two artificial holes are created at one end of the cover for the inclusion of the limb. Free end of the cover is secured with adhesive, and a hole is created for the insertion of the suction catheter. Oxygen cylinder is connected to the suction catheter, and oxygen is supplied at the rate of 10 L/min. The pressure is measured by the help of CVP manometer which is connected to one more hole. The pressure can be built till 30 m bars. This therapy is kept for 90 min and regular dressing is done after the procedure. The same cycle is repeated everyday till the wound is granulating.

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: As per literature review, there are no complications/risks associated with topical oxygen therapy being given to diabetic's lower limb ulcer patients.

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.

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

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:"_____" If you have any question or complaints with regard to your right as study participant you may contact Dr _____

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 "**EVALUATE THE ROLE OF TOPICAL OXYGEN THERAPY IN WOUND HEALING DYNAMICS OF DIABETIC LOWER LIMB ULCERS - A RANDOMISED CONTROLLED STUDY.**"

I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.

1. I understood that my participation in the study is voluntary and that I am free to withdraw any time, without giving any reason, without my medical care or legal rights being affected.
2. I understood that sponsor and others working on the sponsor's behalf, The Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and at any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this. However, I understood that my identity will not be revealed in any information released to third parties or published.
3. I agree to restrict the use of any data or results that arise from this study provided such as use for scientific purposes.
4. I agree to take part in the above study.

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:

[If patient has limited ability to read and write, an impartial witness should be present during the entire informed consent discussion and patient's legally acceptable representative should sign on the patient's behalf.] In these instances, the patient's thumb impression taken in place of signature.

Patient's legally acceptable representative name:

I, as the patient's legally acceptable representative was present during the consenting and understand the preceding information describing this study. All of the questions regarding the study and the patient's participation in it have been answered to my satisfaction. I state that all the aspects of the study were clearly presented during the consent procedure. The patient is willing to participate in this study and I sign below on his/her behalf testifying to this effect.

Name of Patient:

Name and Signature of Representative:

Impartial Witness Declaration

By signing the consent form I attest that the information was accurately explained to and apparently understood by the patient and the representative (if applicable) and that the informed consent was freely given by the patient.

Name of Impartial Witness: **Date:** **Signature:**

PROFORMA

SCREENING:

Screening No.

Enrolment No. /IP No.

Date of Screening

First Name

Middle Name

Last Name

Age (Years)

Address

H No.

Street

Taluka

District

Phone No.1

Phone No.2

Patient with diabetic leg ulcer:

- Yes
- No

Patient age above 18:

- Yes
- No

Applicant is willing to give consent

- Yes
- No

Patient has no associated illness or complications:

- Yes
- No

FINAL RESULT

- Ineligible ☐
- Eligible but refused ☐
- Eligible and participating ☐

PROFORMA

Name: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

DOA: ☐☐ ☐☐ ☐☐☐☐

Age: ☐☐ YEARS

Sex: ☐☐

Occupation: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Address:

H No. ☐☐☐☐☐

Street ☐☐☐☐☐☐☐☐☐

Taluka ☐☐☐☐☐☐☐☐☐

District ☐☐☐☐☐☐☐☐

Phone No.1 ☐☐☐☐☐☐☐☐☐☐

Phone No.2 ☐☐☐☐☐☐☐☐☐☐

CHIEF COMPLAINTS:

Leg ulcer– ☐

Pain – ☐

Duration- ☐☐ months

H/O PRESENT ILLNESS:

ULCER- ☐

LOCATION: 1. RIGHT LOWER LIMB ☐ 2. LEFT LOWER LIMB ☐

ONSET: 1. INSIDIOUS ☐ 2. SUDDEN ☐ 3. TRAUMATIC ☐

DURATION: ☐☐ DAYS

PROGRESSIVE ☐

DISCHARGE: 1. SEROUS ☐ 2. PURULENT ☐

FOUL SMELLING: ☐

C/O EPISODES OF FEVER-

C/O PAIN-

DURATION OF PAIN- DAYS

PAST HISTORY:

K/C/O T2DM SINCE: ☐☐ MONTHS

H/O any Chronic drug use- ☐

H/O HTN - ☐

H/O previous surgery – ☐

H/O PVD - ☐

H/O VARICOSE VEINS: ☐

H/O SIMILAR COMPLAINS IN THE PAST –IN SAME OR OPPOSITE LIMB- ☐

PERSONAL HISTORY:

Smoker - ☐

Alcoholic- ☐

GENERAL PHYSICAL EXAMINATION:

Nutritional status- 1. WELL, BUILT ☐ 2. POORLY BUILT ☐

Pallor - ☐

Icterus- ☐

Cyanosis/ clubbing/ oedema ☐

Generalized/ regional lymphadenopathy - ☐

Pulse rate- ☐☐☐ BPM

Blood pressure- ☐☐☐ / ☐☐☐ MMHG

LOCAL EXAMINATION:

SITE:

RIGHT LOWER LIMB ☐

LEFT LOWER LIMB ☐

SIZE: ☐☐ X ☐☐ CMS

FLOOR:

1.GRANULATING ☐ 2. SLOUGH ☐

BASE:

1.BONE ☐ 2. MUSCLE ☐

DISCHARGE:

1.SEROUS ☐ 2. PURULENT ☐

TENDERNESS- ☐

PERIPHERAL PULSES: ☐

SURROUNDING AREA:

- ERYTHEMA- ☐
- EDEMA- ☐
- EXAMINATION FOR PERIPHERAL NEUROPATHY- ☐
- VARICOSE VEINS- ☐

SYSTEMIC EXAMINATION

PER ABDOMEN- SOFT, NON-TENDER ☐

CARDIOVASCULAR SYSTEM – normal- ☐

RESPIRATORY SYSTEM – normal- ☐

CENTRAL NERVOUS SYSTEM –normal ☐

DIAGNOSIS:

INVESTIGATIONS:

ROUTINE ☐

FBS ☐ <110 MG/DL ☐ >110MG/DL ☐

HbA1c ☐ >6 % ☐ <6% ☐

UKB- ☐

Colour Doppler- ☐ VARICOSE VEINS ☐ DVT ☐ PVD ☐

Leg X-Ray - ☐ OSTEOMYLITIS ☐

WOUND CULTURE/SENSITIVITY TEST-
DAY 0 -

DAY 14 -

TREATMENT GIVEN:

1.TOPICAL OXYGEN THERAPY WITH CONVENTIONAL WOUND DRESSING ☐

2.CONVENTIONAL WOUND DRESSING ALONE ☐

IV/ORAL ANTIBIOTICS: ☐

DIABETIC MANAGEMENT: ☐

BLOOD SUGARS UNDER CONTROL: ☐

OBSERVATIONS:

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14
TOWT/ Conven -tional														

Wound area as on Day 0 - ☐☐ CM^2

Wound area as on Day 14 - ☐☐ CM^2

wound area reduction - ☐☐ CM^2

% wound area reduction- ☐☐ %

Floor of ulcer as on Day 0-

1. GRANULATING ☐

2. SLOUGH ☐

Floor of ulcer as on Day 14-

1. GRANULATING ☐

2. SLOUGH ☐

PHOTOGRAPHS

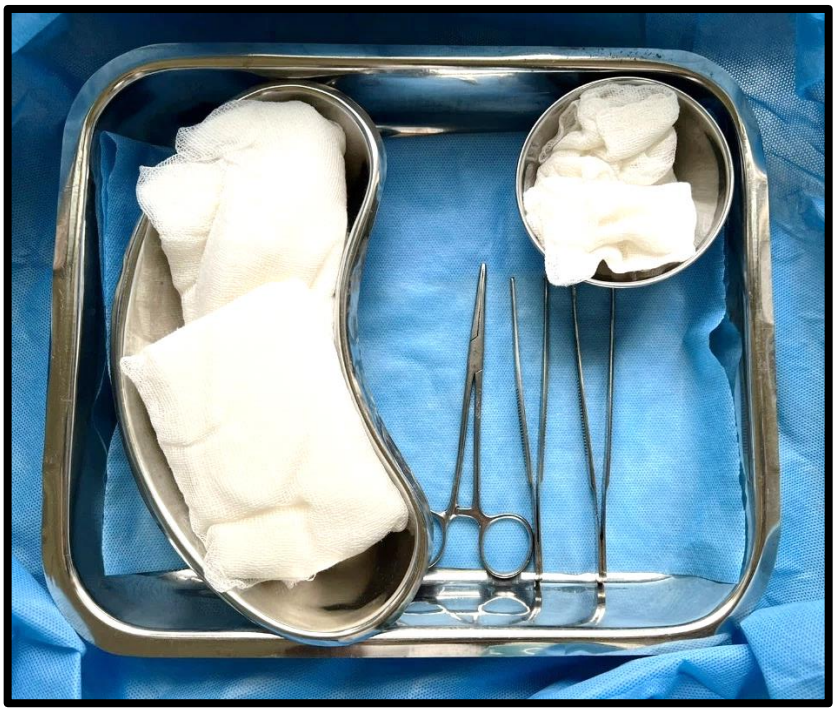

IMAGE 6. DRESSING MATERIAL

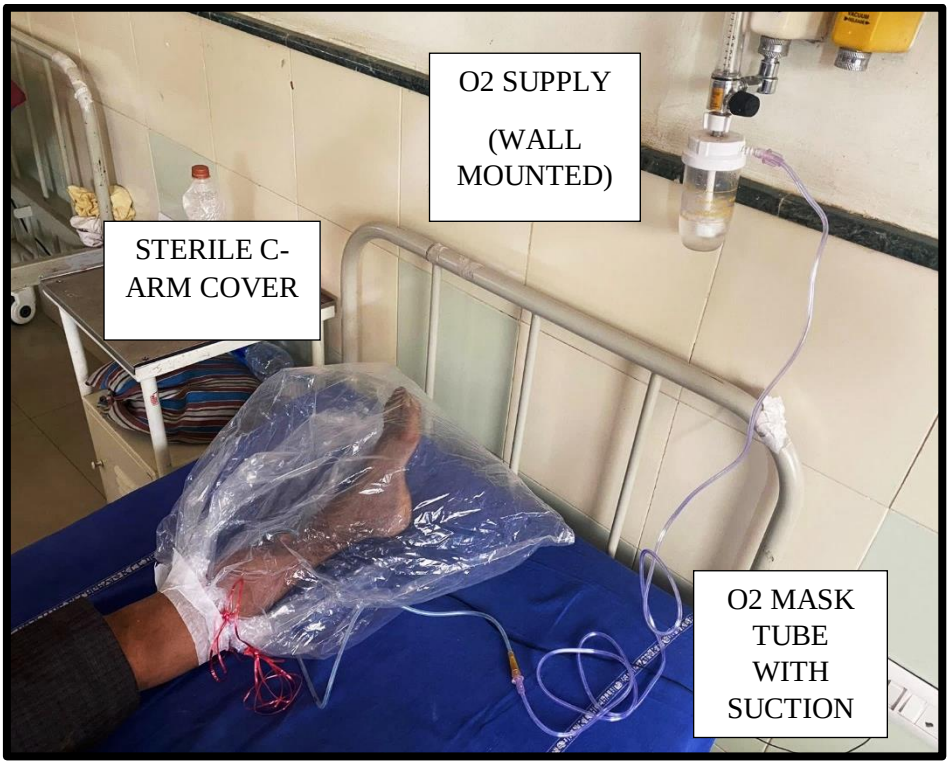

IMAGE 7. TOPICAL OXYGEN THERAPY SETUP

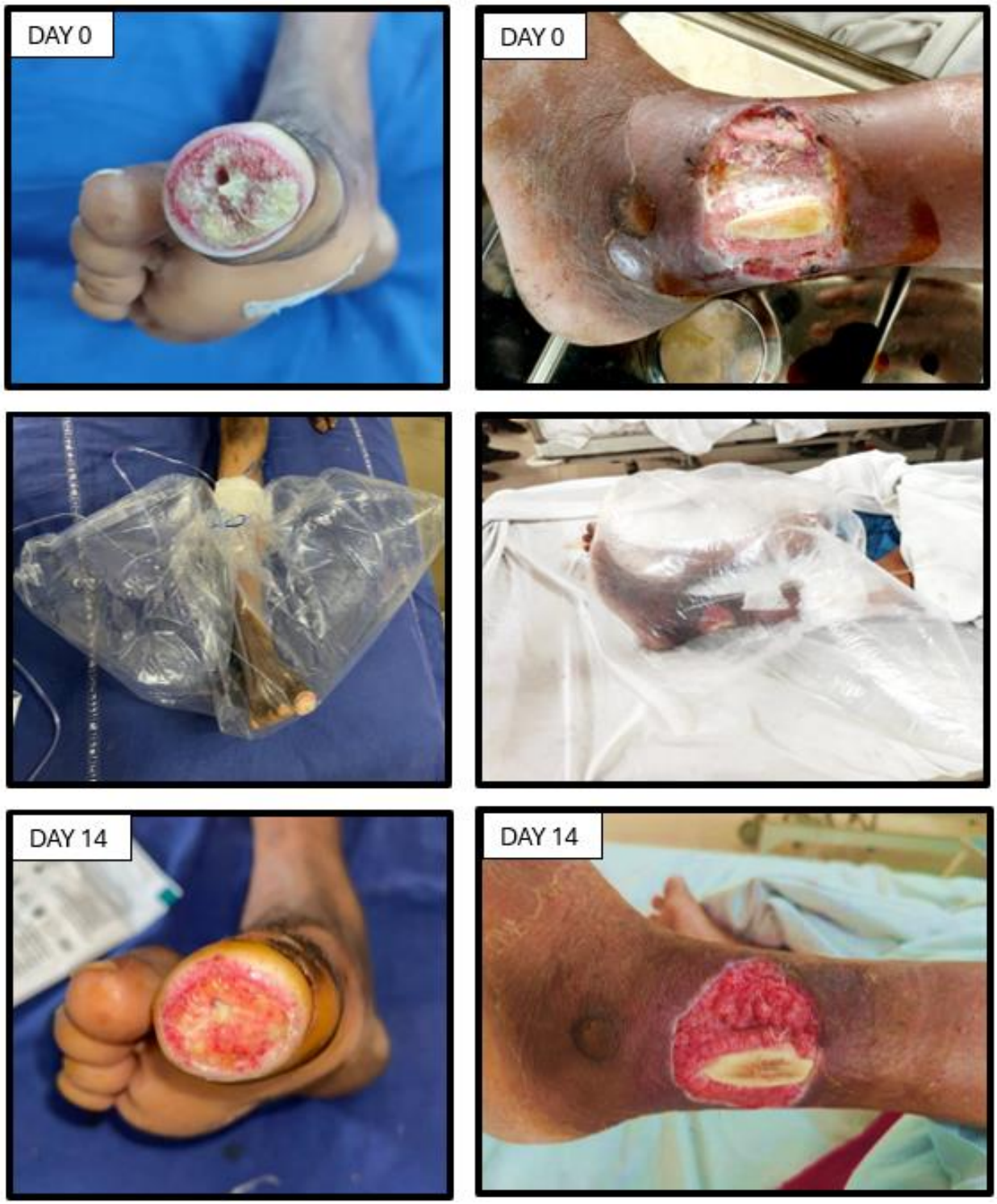

IMAGE 8. ULCER ON DAY-0 AND DAY-14 IN TEST GROUP.

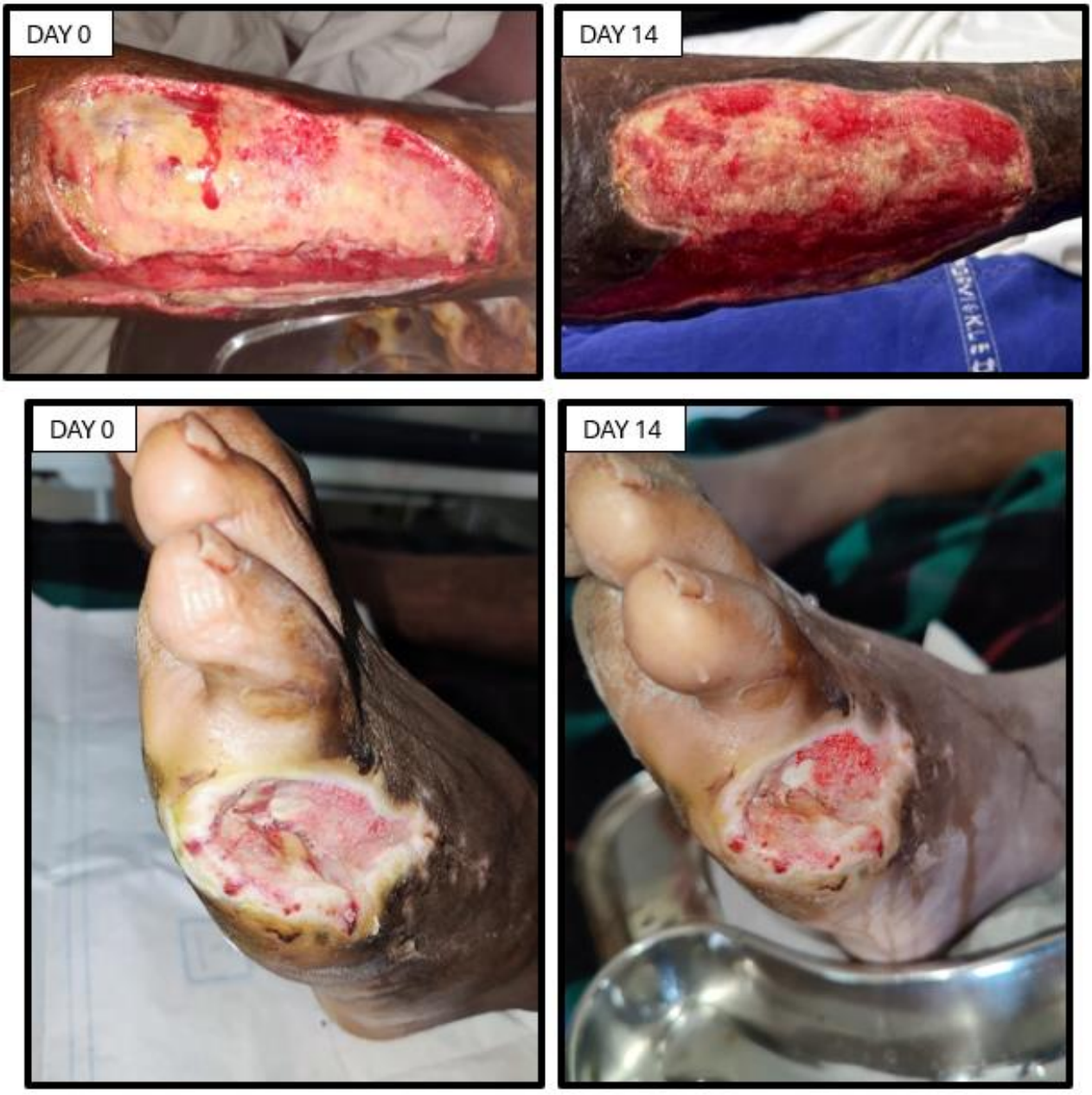

IMAGE 9. ULCER ON DAY-0 AND DAY-14 IN CONTROL GROUP.

KEY TO MASTER CHART

- ✓ Sl. No. – Serial number
- ✓ IP NO – In-patient number
- ✓ M- Male
- ✓ F- Female
- ✓ P – Present
- ✓ A – Absent
- ✓ R- Right sided
- ✓ L- Left sided.
- ✓ DF- Dorsal Foot
- ✓ PF- Plantar Foot
- ✓ DL- Dorsal Leg
- ✓ PL- Plantar Leg
- ✓ T- Traumatic
- ✓ I- Insidious
- ✓ HTN- Hypertension
- ✓ BMI- Basal Metabolic Index
- ✓ DM – Diabetes mellitus
- ✓ I- Insulin
- ✓ O- Oral Hypoglycaemics
- ✓ cm^2- Centimetre Square
- ✓ Kg/m^2- Kilogram Per Meter Square
- ✓ mg/dl- Milligram Per Decilitre
- ✓ FBS- Fasting Blood Sugar
- ✓ HbA1c- Glycated Haemoglobin
- ✓ C/S- Culture/Sensitivity
- ✓ D 0 – Day zero
- ✓ D 14 – Day fourteen

MASTERCHART - TEST GROUP - PAGE 1

S.NO	IP NO	AGE (in years)	SEX	OCCUPATION	DURATION OF ULCER IN WEEKS	SITE	ONSET	DIABETES DURATION (in years)	CURRENTLY USE TOBACCO	PERIPHERAL NEUROPATHY	HISTORY OF PREVIOUS AMPUTATION
1	10037948	51	M	Desk job	12	R DF	T	10	P	A	A
2	10038580	56	M	Farmer	0.5	R DF	I	2	A	A	P
3	10017354	32	F	Household	7	L DF+DL	T	3	A	A	A
4	10029187	32	F	Desk job	3	L DF+DL	I	3	A	A	A
5	1007724	44	F	Desk job	4	L DF+DL	T	6	A	A	A
6	10030746	68	M	Household	12	L PF	I	20	P	P	P
7	6132912	56	M	Desk job	20	R PF	I	5	A	A	A
8	10037503	26	M	Desk job	4	R PF	T	0.5	A	A	A
9	10050276	33	M	Farmer	32	R DF	I	3	P	A	A
10	10010169	72	F	Household	8	L PF	T	20	A	P	A
11	10026780	45	M	Farmer	14	L PF	I	10	P	A	P
12	10013343	48	M	Farmer	8	L PF	I	10	A	P	A
13	10053807	36	M	Desk job	48	R PF	I	20	P	A	A
14	10050276	33	M	Household	9	R DF	I	2	A	A	A
15	1100245	38	M	Desk job	8	L DF+DL	T	8	A	A	A
16	10016216	57	F	Household	16	R DF+DL+ PL	I	10	A	A	A
17	10025373	58	M	Farmer	8	L PF	T	20	A	P	P
18	1168420	54	M	Farmer	20	R DF+DL	T	5	A	A	A
19	10016155	74	M	Household	4	R DF	I	26	A	P	A
20	1208743	70	M	Household	28	R PF	T	10	A	P	A
21	10050956	56	M	Farmer	8	L PF	I	10	A	A	A
22	10053639	53	F	Household	12	L DF	I	17	A	P	A
23	10017354	32	F	Desk job	7	R DF	I	5	A	A	A
24	1132463	68	M	Household	24	L DF +DL	T	10	A	P	A
25	1100456	55	M	Household	4	R DF	I	20	A	A	A
26	1166919	55	F	Farmer	20	R PF	I	1	A	A	P
27	1199119	70	M	Household	4	R PF	I	20	A	P	A
28	1199119	70	M	Household	4	R DF	T	20	A	P	P
29	7033531	28	M	Desk job	12	R DF	I	10	A	A	A
30	1171139	47	M	Desk job	40	R PF	I	4	A	A	A

MASTERCHART - TEST GROUP - PAGE 2

S.NO	DM Treatment	HTN	BMI (Kg/m2)	FBS(mg/dl)	HbA1c %	DAY 0 C/S	DAY 14 C/S	D 0 AREA(cm2)	WAGNER GRADE	D 14 AREA (cm2)	WOUND REDUCTION (cm2)	PERCENTAGE OF AREA REDUCTION (%)
1	I + O	P	29.6	240	8.6	Negative	Negative	220.1	2	215.66	4.44	2.02
2	I + O	P	28.2	112	5.9	ACINETOBACTER	S.AGALACTIAE	83.75	2	81.95	1.80	2.15
3	I + O	A	26.5	148	6.4	K.PNEUMONIAE	E.COLI	142.56	2	138.41	4.15	2.91
4	I + O	A	23.8	202	7.6	Negative	Negative	231.5	2	225.15	6.35	2.74
5	I + O	A	28.6	208	8.8	STAPH.AUREUS	Negative	358.15	2	352.00	6.15	1.72
6	I + O	P	22.7	225	9.8	Negative	Negative	24.05	2	23.00	1.05	4.37
7	I + O	P	26.5	153	7.5	Negative	Negative	12.2	2	12.10	0.10	0.82
8	O	A	22.8	156	5.8	Negative	Negative	19.22	2	18.62	0.60	3.12
9	I + O	A	29.7	320	6.2	Negative	Negative	44.08	2	41.63	2.45	5.56
10	I + O	P	20.4	352	9.1	CANDIDA SP.	Negative	15.96	2	15.56	0.40	2.51
11	O	P	28.4	143	5.7	MRSA	MRSA	1.5	2	1.50	0.00	0.00
12	O	P	27.4	193	9.4	K.PNEUMONIAE	Negative	9.8	2	9.50	0.30	3.06
13	O	A	28.1	164	6.8	P.AERUGINOSA	Negative	40.8	2	38.50	2.30	5.64
14	I + O	A	26.5	114	5.8	Negative	Negative	71.3	2	67.45	3.85	5.40
15	I + O	P	30.4	176	7.4	Negative	Negative	292.5	2	285.65	6.85	2.34
16	I + O	P	27.4	294	13.8	Negative	Negative	428.75	2	419.30	9.45	2.20
17	I + O	A	26.8	94	6.1	MRSA	Negative	20.8	2	19.50	1.30	6.25
18	I + O	P	20.6	176	7.5	MRSA	E.COLI	282.75	2	276.20	6.55	2.32
19	I + O	P	31.2	230	5.8	P.AERUGINOSA	Negative	47.04	2	45.12	1.92	4.08
20	I + O	A	21.3	296	11.4	P.AERUGINOSA	Negative	41.36	2	40.06	1.30	3.14
21	O	A	27.4	99	5.7	MRSA	Negative	8.36	2	7.96	0.40	4.78
22	I + O	P	30.6	128	6.3	Negative	Negative	12.48	2	12.48	0.00	0.00
23	O	A	27.4	288	7.4	STAPH.AUREUS	Negative	1.68	2	1.48	0.20	11.90
24	I + O	P	24.5	144	6.4	P.AERUGINOSA	Negative	72.4	2	69.80	2.60	3.59
25	I + O	P	24.6	130	7.4	ACINETOBACTER	Negative	11.2	2	10.60	0.60	5.36
26	I + O	P	26.5	106	5.9	ACINETOBACTER	Negative	15.5	2	14.60	0.90	5.81
27	I + O	P	28.3	165	7.6	E.COLI	K.OXYTOCA	9.25	2	8.75	0.50	5.41
28	I + O	P	28.3	294	8.6	E.COLI	Negative	56.8	2	55.35	1.45	2.55
29	O	A	25.4	160	6.7	P.AERUGINOSA	Negative	42.9	2	42.00	0.90	2.10
30	O	P	28.3	134	5.8	K.PNEUMONIAE	Negative	6.72	2	6.22	0.50	7.44

MASTERCHART - CONTROL GROUP - PAGE 1

S.NO	IP NO	AGE (in years)	SEX	OCCUPATION	DURATION OF ULCER IN WEEKS	SITE	ONSET	DIABETES DURATION (in years)	CURRENTLY USE TOBACCO	PERIPHERAL NEUROPATHY	HISTORY OF PREVIOUS AMPUTATION
1	10038588	70	F	Household	8	R PF	I	24	A	P	A
2	10027855	46	M	Farmer	72	L DF + DL	T	2	A	A	A
3	10043943	62	M	Desk job	8	L DF + DL	T	1.5	P	A	A
4	6555216	50	M	Farmer	32	R DF	I	5	A	A	A
5	10035012	40	M	Farmer	1.5	R DF	T	7	P	A	A
6	10014152	23	M	Student	4	L DF + DL + PL	I	1.5	A	A	A
7	1157708	38	M	Desk job	16	L PF	I	5	P	A	A
8	1915996	64	M	Household	32	L PF	I	16	A	P	A
9	6473377	75	M	Household	40	R DF	T	11	A	P	P
10	6928984	70	F	Household	5	R PF	I	12	A	A	A
11	6990849	38	M	Farmer	0.5	L PF	I	2	P	A	A
12	6897024	66	M	Desk job	15.2	R PF	I	15	P	P	A
13	1158129	60	M	Desk job	24	L DF	I	1	P	A	A
14	1038888	70	F	Household	0.67	R PF	I	13	A	A	A
15	10042913	36	M	Desk job	0.67	R PF	I	2	A	A	A
16	10044291	52	F	Desk job	0.33	L PF	I	2	A	A	A
17	10043375	40	M	Farmer	8	L DF	T	1	P	A	A
18	10043528	72	F	Household	4	L DF	I	10	A	A	A
19	10045355	56	M	Desk job	16	R PF	I	4	A	A	P
20	10039373	62	M	Farmer	1	R DF	T	22	A	A	A
21	10050618	56	M	Farmer	4	L DF	T	10	A	A	A
22	1167694	54	M	Desk job	8	L DF	I	0.5	A	A	A
23	10053063	54	M	Desk job	4	M DF	I	1.5	A	A	A
24	10051933	73	F	Household	12	R PF	I	25	A	P	P
25	10039373	62	M	Household	8	R DF+ DL	I	14	P	A	A
26	10042023	50	M	Farmer	24	R PF	I	14	P	P	P
27	10050077	48	M	Farmer	4	R DF + DL	T	8	P	A	A
28	10052569	57	F	Desk job	4	R DF + DL	T	15	A	A	A
29	10043294	64	F	Household	8	R PF +DF + DL	T	10	A	P	A
30	10059117	51	F	Desk job	4	L DF	I	15	A	A	A

MASTERCHART - CONTROL GROUP - PAGE 2

S.NO	DM Treatment	HTN	BMI (Kg/m2)	FBS(mg/dl)	HbA1c %	DAY 0 C/S	DAY 14 C/S	D 0 AREA(cm2)	WAGNER GRADE	D 14 AREA (cm2)	WOUND REDUCTION (cm2)	PERCENTAGE OF AREA REDUCTION (%)
1	I + O	P	28.4	240	12.5	STAPH.AUREUS	S.AGALACTIAE	1.08	2	1.08	0.00	0.00
2	I + O	P	26.1	112	5.8	ACINETOBACTER	Negative	172.5	2	170.08	2.42	1.40
3	I + O	P	21.3	148	6.8	E.COLI	Negative	153.66	2	147.58	6.08	3.96
4	I + O	A	25.9	202	7.9	E.COLI	Negative	64.08	2	63.2	0.88	1.37
5	O	A	35.8	208	6.8	STAPH.AUREUS	E.COLI	52.7	2	51.86	0.84	1.59
6	I + O	A	23.5	129	5.8	P.AERUGINOSA	Negative	207.46	2	198.85	8.61	4.15
7	O	A	28.5	153	9.6	PROTEUS MIRABILIS	PROTEUS MIRABILIS	1.3	2	1.28	0.02	1.54
8	O	P	30.2	201	8.4	MRSA	Negative	10.2	2	10.15	0.05	0.49
9	I + O	P	26.8	320	11.5	E.COLI	Negative	68.2	2	67.93	0.27	0.40
10	I + O	P	22.9	191	7.6	Negative	Negative	12.1	2	12.1	0.00	0.00
11	O	A	24.6	143	7.8	COAG.NEG STAPH.	E.COLI	20.3	2	20.08	0.22	1.08
12	O	P	31.4	193	9.1	Negative	Negative	24.1	2	23.8	0.30	1.24
13	O	A	27.3	164	6.6	Negative	Negative	1.42	2	1.4	0.02	1.41
14	I + O	P	19.7	154	7.4	K.PNEUMONIAE	K.OXYTOCA	12.4	2	12.2	0.20	1.61
15	O	A	27.1	176	6.2	Negative	Negative	7.84	2	7.77	0.07	0.89
16	O	P	26.8	116	5.5	Negative	Negative	1	2	1	0.00	0.00
17	I + O	A	31.5	94	6.1	Negative	Negative	29.11	2	28.47	0.64	2.20
18	I + O	P	20.7	176	7.1	ACINETOBACTER	Negative	14.7	2	13.86	0.84	5.71
19	I + O	A	23.8	230	7.4	Negative	Negative	1.67	2	1.64	0.03	1.80
20	I + O	P	30.2	99	5.6	MORGANELLA	Negative	20.8	2	19.84	0.96	4.62
21	O	A	28.9	168	6.8	MRSA	Negative	32.4	2	31.79	0.61	1.88
22	I + O	A	29.2	128	5.8	STAPH.EPIDERMIDIS	Negative	20.4	2	19.6	0.80	3.92
23	O	A	24.5	288	9.7	MRSA	MRSA	10.54	2	10.54	0.00	0.00
24	O	A	18.4	144	6.8	P.AERUGINOSA	K.OXYTOCA	2.56	2	2.48	0.08	3.13
25	I + O	P	28.6	130	5.6	P.AERUGINOSA	P.AERUGINOSA	75.9	2	73.62	2.28	3.00
26	O	A	28.3	200	7.1	E. FAECALIS	Negative	3.76	2	3.58	0.18	4.79
27	I + O	P	27.9	165	6.4	Negative	Negative	98.56	2	96.49	2.07	2.10
28	I + O	P	26.6	294	11.3	Negative	Negative	71.68	2	70.88	0.80	1.12
29	I + O	A	23.4	160	7.2	K.PNEUMONIAE	Negative	138.3	2	135.76	2.54	1.84
30	O	P	23.8	226	8.6	COAG.NEG STAPH.	Negative	6.56	2	6.39	0.17	2.59