EFFICACY OF LOW LEVEL LASER THERAPY ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCERS

Submitted by

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DISSERTATION SUBMITTED TO

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In

GENERAL SURGERY

UNDER THE GUIDENCE OF

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2020

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DR. ROHIT GHANASHYAM VAIDYA

LIST OF ABBREVATIONS

AGE	Advanced glycation end products
ABI	Ankle brachial index
DFU	Diabetic Foot Ulcer
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
ECM	Extra cellular matrix
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
eNOS	Endothelial nitric oxide synthase
EPC	Endothelial progenitor cells
FGF	Fibroblast growth factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
HbA1C	HaemoglobinA1C/ Glycosylated haemoglobin
HBO	Hyperbaric Oxygen
IDF	International Diabetes Federation
IGF-1	insulin-like growth factor 1
LLLT	Low level laser therapy
MCR	Microcellular rubber
MDP	Methylene disphosphonate
MMP	Matrix metalloproteinase

MTP	Meta-tarso-phalangeal
NOS	Nitric Oxide synthase
NO	Nitric oxide
NPWT	Negative pressure over the wound as therapy
PDGF	Platelet-derived growth Factor
PKC	Protein kinase C activation
ROS	Reactive oxygen species
SWMF	Semmes-Weinstein monofilament
TcPO2	Transcutaneous oxygen tension
TIMP	Tissue inhibitors of metalloproteinases
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
VPT	Vibration perception threshold

ABSTRACT

AIMS AND OBJECTIVES: To study the efficacy of low level laser (LLLT) on wound healing in Diabetic Foot ulcer and to test the hypothesis that LLLT will promote early healing of Diabetic Foot ulcer.

MATERIALS AND METHODS: Patients attending surgical OPD and/or admitted in BLDE(DU) Shri B.M.Patil Medical College Hospital and Research centre, Vijayapur with diabetic foot ulcers(Wagner's Grade I to III) during the period of October 2018-March 2020 were included in the study. A prospective comparative study was conducted with 30 patients to LLLT group (660 and 808 nm laser) and 30 patients to conventional (Saline) dressing group. All the cases were examined on day 1 and day 15. 'Primary efficacy end point' was complete ulcer closure. 'Secondary efficacy end point' include reduction in ulcer surface area over time and time to achieve ulcer closure by either skin grafting or secondary suturing.

RESULTS: Mean Age of the study group was 56.83±13.8 years with 76.66 % males. Majority of the cases were known diabetic since 5 to 10 years. There was poor glycemic control among the study subjects with mean HbA1c of 8.4%. There was 42% reduction in the size of ulcer among study group. There was average of 7 days i.e. 22% reduction in hospital stay in study group, compared to control group. Three ulcers in LLLT group healed by secondary intention while none in control group. Majority of the cases, ulcer closure was achieved by split thickness skin grafting.

CONCLUSION: Low level laser therapy in Diabetic Foot ulcers promotes early healing and reduces the hospital stay.

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INTRODUCTION

Diabetes mellitus (DM) is one of the main problems in health systems and a global public health threat that has increased dramatically over the past 2 decades[1,2]. According to epidemiological studies, the number of patients with DM increased from about 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and estimated if the situation continues, more than 360 million people by 2030. The total number of people in India with diabetes is estimated to be around 50.8 million in 2010, rising to 87 million by 2030 according to the International Diabetes Federation (IDF) [3].

Diabetic foot lesions are actually a complex triad of neuropathy, ischemia and infections with plantar aspect of the foot being the most common site for ulceration[4]. Recent studies have indicated multiple risk factors associated with the development of Diabetic Foot Ulcer (DFU)[5,6,7]. These risk factors are as follows: gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index and other co-morbidities such as retinopathy, diabetic peripheral neuropathy, peripheral vascular disease, high glycated haemoglobin level (HbA1C), foot deformity, high plantar pressure, infections and inappropriate foot self-care habits.[1,7,8]

Patients with DM are prone to multiple complications such as retinopathy, neuropathy, nephropathy, peripheral arterial disease and diabetic foot ulcer being a devastating chronic complication of Diabetes mellitus of them all. DFU is a common complication of DM that has shown an increasing trend over previous decades[7,8,9]. In total, it is estimated that 15% of patients with diabetes will suffer from DFU during their

lifetime. Although accurate figures are difficult to obtain for the prevalence of DFU, the prevalence of this complication ranges from 4%-27%.[10,11,14]

To date, DFU is considered as a major source of morbidity and the main cause in diabetic patients for hospitalization[1,7,16,18]. It is estimated that approximately 20% of hospital admissions among patients with DM are the result of DFU[19]. DFU can lead to infection of the limb, gangrene of foot, amputation or even death if necessary timely care is not given[19].

On the other hand, once DFU has developed, there is an increased risk of ulcer progression that may ultimately lead to amputation. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than patients without diabetes[10]. It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU[10]. Rough estimates are at about 1,00,000 lower limbs are amputated in India every year, of which at least seventy-five percent are neuropathic feet with secondary infections and are potentially preventable[17].

Diabetic foot ulcer commonly affects the toes followed by mid-foot. It usually starts with colonization of neuropathic or ischemic ulcers, traumatic wounds, small fissures between the toes or nail beds, wounds due to burns or chronic pressure. Diabetic foot ulcers can also develop secondary to cellulites, necrotizing fasciitis and abscess[15].

In addition, it is reported that every 30 second one leg is amputated due to DFU in worldwide[12]. Furthermore, DFU is responsible for substantial emotional and physical distress as well as productivity and financial losses that lower the quality of life[22]. Various modalities of wound healing products are in use to treat diabetic foot ulcers like growth

factors, skin substitutes, extracellular matrix protein, protease inhibitors, vasoactive compounds, platelet therapies, low level laser therapy etc. Techniques like Negative pressure over the wound as therapy (NPWT), local application of hyperbaric oxygen (HBO), and Autologous bone marrow cultured cell are also being increasingly used[5]. But around 80% diabetic patients are neuropathic and diabetic patients with a history of foot ulceration have abnormally high pressure under the foot[21].

Low level laser therapy (LLLT), also called soft laser, is known to supply direct biostimulative light energy to body cells with a wave-length between 600 and 1000 nanometers and power from 5 to 500 mill watts. The absorbed laser energy stimulates molecules and atoms of cells but does not cause rapid or significant increase in tissue temperature[72]. Different laser wavelengths have different depths of penetration into human tissue. Red laser has a deeper penetration depth than violet, blue, green, or yellow. Infrared and near infrared light are not visible, but it has been demonstrated to penetrate human tissue deeper than visible red light.

AIMS AND OBJECTIVES OF THE STUDY

1. To study the efficacy of low level laser on wound healing in patients with diabetic foot ulcer in terms of

a) Amount of granulation tissue fill up

b) Reduction in ulcer size

c) Time taken in ulcer healing

d) Duration of hospital stay

2. To Test the hypothesis that combined 660 and 808 nm laser phototherapy will promote early healing of diabetic foot ulcers

REVIEW OF LITERATURE

Diabetes is a chronic disease (International Diabetes Federation (IDF) 2012a) and according to IDF (2012b) projections in 2011 the prevalence of DM in the world was of 8.3% and it will increase to 9.90% by 2030. Furthermore, in 2011 the number of deaths related to DM was of 4.593.109 people (IDF 2012b)[11]

DFUs are lesions characterized by a break in skin continuity involving loss of epithelium, the hypodermis, the dermis and inner deeper tissue, and in some cases involve muscle and even bone (Reiber et al. 1998, Boulton 2004b)[12].

Neuropathy results from continued peripheral nerve damage of motor, sensory and autonomic fibres, that affect sensation, innervations of the muscles of the foot and its circulation (Reiber et al. 1998, Jeffcoate and Harding 2003, Merza and Tesfaye 2003, Boulton 2004b, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 2009).

Motor neuropathy causes muscle wasting, atrophy and weakness which leads to foot deformities, such as claw and hammer toe that in turn predispose the individual to restricted joint mobility, balance problems and gait instability (Reiber et al. 1998, Merza and Tesfaye 2003, Boulton 2004b, Cavanagh et al. 2005, Singh et al. 2005)[12].

Sensory neuropathy leads to decreased or loss of protective sensation to pain, pressure and loss of proprioception (inability to recognize the feet position) (Reiber et al. 1998, Merza and Tesfaye 2003, Boulton 2004b, van Deursen 2004)[12].

The loss of protective sensation places the individual at risk of continuously harming the foot without realising it (Laing 1998, Wu and Armstrong 2005).

Autonomic neuropathy refers to altered micro vascular blood flow that results in warm feet, and decreased sweat production, resulting in dry skin, predisposing callus formation, which is hyperkeratosis that develops around the ulcer, and skin breakdown (Reiber et al. 1998, Merza and Tesfaye 2003, Boulton 2004b, Lavery et al. 2008).

Nevertheless, other factors also play an important role in the development of FUs. DFUs are an important health issue that needs to be addressed. It is fundamental to implement prevention and treatment practices that will improve individuals' Quality of life (QoL) and bring better cost-effectiveness for the health services.

A study done by priyadarshini et al[14] concluded that Laser therapy is painless, cost effective procedure which induces faster granulation, wound contraction and reepithelialisation, thus accelerates complete wound healing.

A study done by Catherine N. et tl[15] on a group of 40 patients published concluded that all clinical studies included in their systematic review demonstrated improved healing outcomes of DFU with no adverse events using LLLT

A study conducted by Maura Cristina Porto FeitosaI et al[16] in Sao Jose dos Campos-SP, Brazil on a group of 60 patients and published in Acta Cirúrgica Brasileira journal on Effects of the Low-Level Laser Therapy (LLLT) as a modality for healing diabetic foot ulcers concluded that The low-level laser treatment seems to be an efficient method, viable, painless and of low costs concerning the tissue repair ulcers in a diabetic foot.

A study conducted by R. K.Mathur et al[17] on LLLT as an adjunct to regular therapy in the management of diabetic ulcers on a group of 30 patients and published in Lasers Med Sci. 2017 Feb, Department of Surgery, Mahatma Gandhi Memorial Medical College,Indore, MP, India on 14 November 2016 concluded that the wounds in subjects treated with LLLT contracted significantly more than the wounds in the non-treated group which indicates that LLLT is an effective modality to facilitate wound contraction in patients suffering from diabetes and can be used as an adjunct to conventional mode of treatment for healing of diabetic wound.

ANATOMY OF FOOT

The human foot combines mechanical complexity and structural strength. The ankle serves as foundation, shock absorber and propulsion engine. The foot can sustain enormous pressure (several tons over the course of a one-mile run) and provides flexibility and resilience.

The foot and ankle contain:

- 26 bones
- 33 joints
- More than 100 muscles, tendons and ligaments
- A network of blood vessels, nerves, skin and soft tissue.

These components work together to provide the body with support, balance and mobility. A structural flaw or malfunction in any one part can result in the development of problem elsewhere in the body.

Figure 1. BONES - MEDIAL VIEW

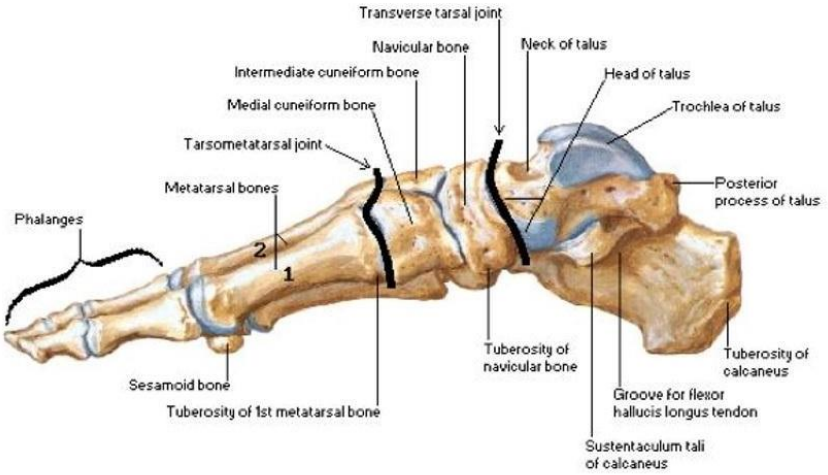
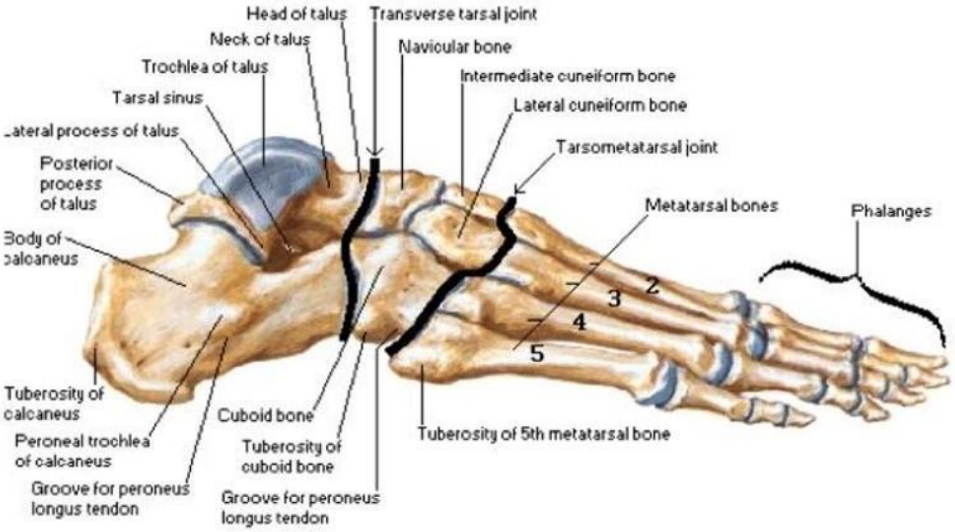


Figure 2. BONES - LATERAL VIEW



Skin

The skin of dorsum of the foot (hirsute) is thin and highly flexible, containing hair follicles, sweat glands and scanty sebaceous gland. Hairs are sparse and thick. It is less than 2mm thick and few fibrous septa penetrate to deeper fascial structures. The plantar skin (glabrous) is 5mm thick especially over those points which bear weight viz. heel, ball of big toe and lateral margins of the sole. It has no hair follicles of sebaceous glands but sweat glands are numerous. Hypodermis is composed of loose areolar connective tissue, most of this is collagenous and elastic fibers running parallel to the surface of the skin, but some are continuous with the fibers of dermis. Hypodermis is well supplied with blood vessels and nerve endings. Tactile sensation is exceptionally good in the sole.

The subcutaneous tissue in the sole as in the palm differs from that of the rest of body in being more fibrous, tough and stingy. Fibrous septa divide the tissue into small loculi which are filled with fluid fat under tension this makes a shock absorbing pad especially over the heel and over the tips of toes.

Deep fascia:

On the dorsum of the foot (fascia dorsalis pedis) is the thin layer continuous above with the inferior extensor retinaculum and at the sides of the foot; it blends with plantar aponeurosis, anteriorly it en-sheathes the dorsal tendons.

Plantar aponeurosis:

Cover the whole length of the sole. It arises posteriorly from the medial and lateral tubercles of calcaneous from the back of that bone below the insertion of the tendo-calcaneous. It spreads out over the sole and is inserted by five slips into each of the five toes. A very dense and strong intermediate part is known as plantar aponeurosis.

Parts of the Foot:

Structurally, the foot has three main parts:

The forefoot:

Forefoot is composed of five toes (called phalanges) and their connecting long bones (metatarsals). Each toe (phalanx) is made up of several small bones. The big toe (hallux) has two phalanges, two joints (interphalangeal joints) and two tiny, round sesamoid bones that enable it to move up and down. The other four toes each have three bones and two joints. The phalanges are connected to the metatarsals by five metatarsal phalangeal joints. The forefoot bears half the body's weight and balances pressure on the ball of the foot.

The Midfoot:

Forms the foot's arch, and serves as a "**shock absorber"**. The bones of the midfoot are cuboid, first, second, third cuneiform and navicular connected to the forefoot and the hind foot by muscles and the plantar fascia.

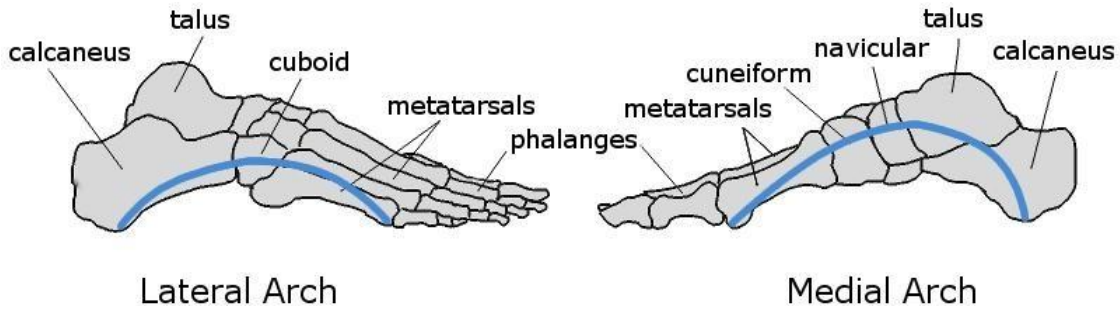
The Hind foot:

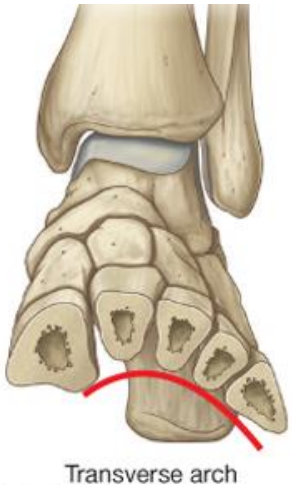
Hind foot is composed of three joints and links the midfoot to the ankle (talus). The top of the talus is connected to the two long bones of the lower leg (tibia and fibula), forming a hinge that allows the foot to move up and down. The heel bone (calcaneus) is the largest bone in the foot. It joints the talus to form the subtalar joint which enables the foot to rotate at the ankle. The bottom of the calcaneus is cushioned by a layer of fat.

The Arches:

The foot has three arches. The medial longitudinal arch is composed of the calcaneus, talus, navicular, cuneiforms, and the first three metatarsals. The lateral longitudinal arch is composed of the calcaneus, cuboid and the fourth and fifth metatarsals. The transverse arch is composed of the cuneiforms, the cuboid and the five metatarsal bones. The arches of the foot are maintained not only by the shapes of the bones as well as by ligaments. In addition, muscles and tendons play an important role in supporting the arches.

Figure 3. ARCHES OF FOOT





Muscles, Tendons and Ligaments:

There are 20 muscles in the foot that give the foot its shape by holding the bones in position and expand and contract to impart movement. The muscles in the sole of the foot are categorized into four layers: Muscles in the first layer include Flexor digitorium brevis, Abductor hallucis and Abductor digiti minimi. In the second layer are tendon of Flexor hallucis longus, Flexor digitorum accessories and the Lumbricals. In the third layer

are Flexor hallucis brevis, Adductor hallucis and Flexor digiti minimi brevis. In the fourth layer are peroneous longus tendon, Tendon of the tibialis posterior, 4 dorsal interossei and 3 plantar interossei.

Arteries of the sole of the foot:

Medial plantar artery:

This terminal branch of the posterior tibial artery arises beneath the flexor retinaculum. It ends by supplying the medial side of the big toe. During its course it gives off numerous muscular, cutaneous, and articular branches.

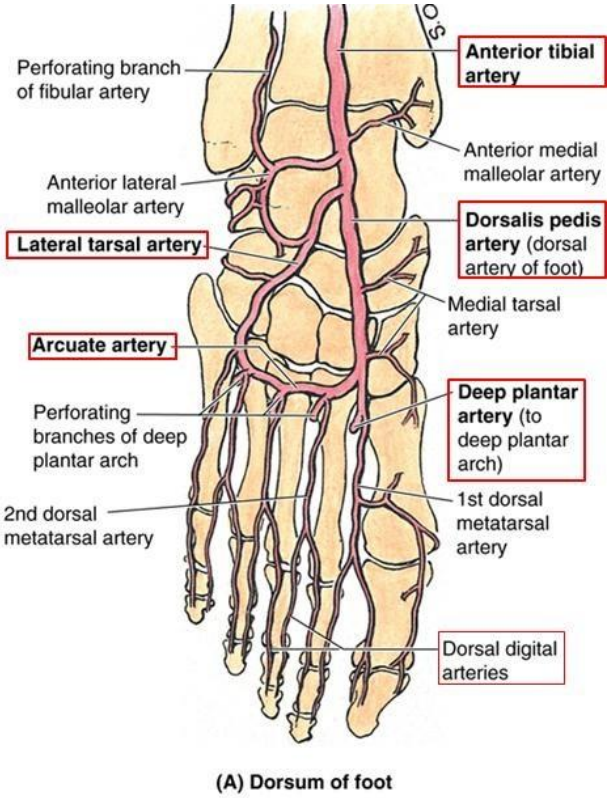
Lateral Plantar Artery:

Is the larger of the terminal branches of the posterior tibial artery. During its course, it gives off numerous muscular, cutaneous and articular branches. The plantar arch gives off plantar digital arteries to the adjacent sides of the lateral four toes and the lateral side of the little toe.

Dorsalis Pedis Artery*:*

On entering the sole between the two heads of the first dorsal interosseous muscle, the dorsalis pedis artery immediately joins the lateral plantar artery, gives the first plantar metatarsal artery, which supplies the cleft between the big and second toes.

Figure 4 : ARTERIAL SUPPLY



Veins of the Sole of the Foot:

Medial and lateral plantar veins accompany the corresponding arteries, and they unite behind the medial malleolus to form the posterior tibial venae comitantes.

Nerves of the Sole of the Foot:

Medial Plantar Nerve:

The medial plantar nerve is a terminal branch of the tibial nerve. It gives muscular branches to the abductor hallucis, the flexor digitorium brevis, the flexor hallucis brevis and the first lumbrical muscle. Cutaneous branches: Plantar digital nerves run to the sides of the medial three and one-half toes.

Lateral Plantar Nerve:

The lateral plantar nerve is a terminal branch of the tibial nerve.

Branches:

1. From the main trunk to the quadratic plantae and abductor digiti minimi; cutaneous branches to the skin of the lateral part of the sole.
2. From the superficial terminal branch to the flexor digiti minimi and the interosseous muscles of the fourth intermetatarsal space.
3. From the deep terminal branch supplies the abductor hallucis; the second, third and fourth lumbricals; and all the interossei, except those in the fourth intermetatarsal space.

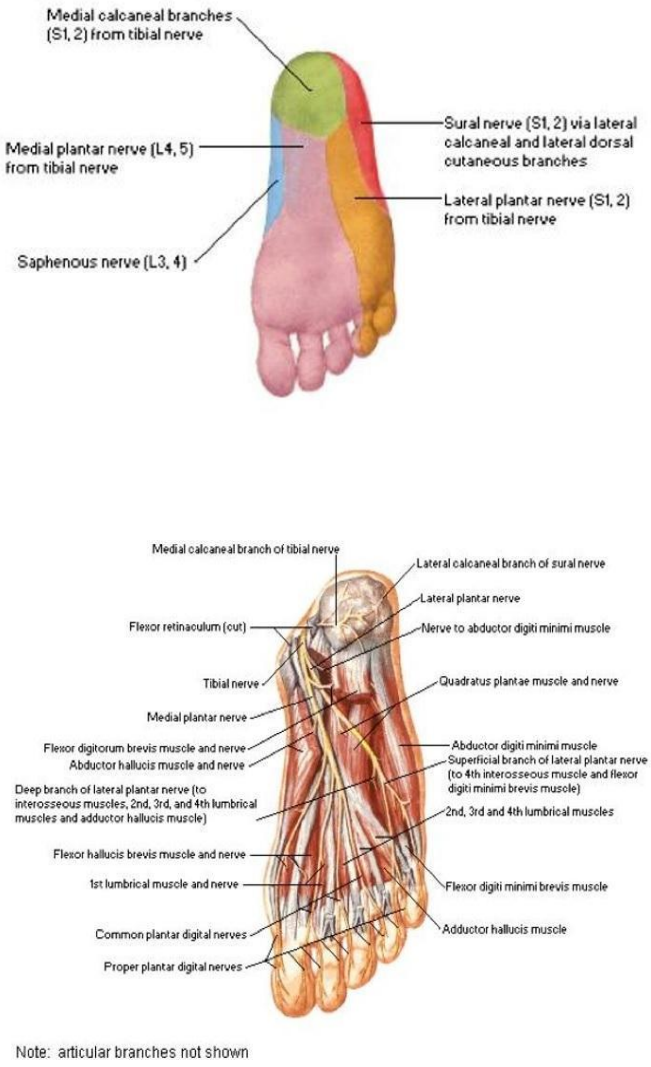


Figure 5 : NERVE SUPPLY

Dorsal venous arch:

The dorsal venous arch lies in the subcutaneous tissue over the heads of the metatarsal bones and drains on the medial side into the great saphenous vein. The great saphenous vein leaves the dorsum of the foot by the ascending into the leg in front of the medial malleolus. The small saphenous vein ascends into the leg behind the lateral malleolus.

Artery of the dorsum of the foot:

Dorsalis Pedis Artery:

The dorsalis pedis artery begins in front of the ankle joint as a continuation of the anterior tibial artery. It terminates by passing downward into the sole between the two heads of the first dorsal interosseous muscle, where it joins the lateral plantar artery and completes the plantar arch. The Branches are:

1. Lateral tarsal artery.

2. Arcuate artery

3. First dorsal metatarsal artery

Nerve supply of the dorsum of the foot:

Deep Peroneal Nerve:

It divides into terminal, medial and lateral branches. The medial branch supplies the skin of the adjacent sides of the big and second toes. The lateral branch supplies the extensor digitorium brevis muscle.

Spaces of the Foot:

Infections of the foot can be approached and drained effectively, with clinical importance of the 4 median fascial spaces on the plantar aspect of the foot and the 2 dorsal spaces.

***Four median Plantar Spaces**:*

1. The first space is located between the plantar aponeurosis and the flexor digitorium brevis.
2. The second space is situated between the flexor digitorium brevis and the conjoined long flexor tendons and quadrates plantae.
3. The third space is found between the flexor digitorium longus (with its associated lumbricals muscles) and the oblique head of the abductor hallucis.
4. The fourth deepest space is situated between the oblique head of the abductor hallucis muscle and the 2nd and the 3rd metatarsal bones and their interosseous muscles.

These spaces are bound both laterally and medially by dense connective tissue septa an infection may travel from one space to another. The sheaths of the entire flexor tendon extend from the toes and proximal to the distal head of the metatarsal bones; therefore within these sheaths either may remain local or break into one of the four spaces. The 3rd layer of the sole of the foot is enclosed inferiorly by the plantar fascia and superiorly by the metatarsal and small muscles and ligaments of the foot. It is continuous distally into the through the lumbricals and web space along with the long flexor tendons.

Propulsive action of the foot:

Standing immobile:

The body weight is disturbed via the heel behind and the heads of the metatarsal bones in the front.

Walking:

As the body weight is thrown forward, the weight is borne successively on the lateral margin of the foot and the heads of the metatarsal bones. As the heel rises the toes are extended at the metatarso-phalangeal joints and the plantar aponeurosis is pulled on thus heightening the longitudinal arches. The body is then thrown forwards

1. By the actions of the gastroenemius and soleus (and plantaris) on the ankle joint, using foot as a lever.
2. By the toes being strongly flexed by the long and short flexors of the foot, providing the final thrust forward.

The lumbricals and interossei contract and keep the toes extended so that they do not fold under pressure because of the strong action of the flexor digitorium longus. In this action the long flexor tendons also assist in Plantar flexing the ankle joint.

DIABETIC NEUROPATHY [11]

Diabetic neuropathy encompasses several neuropathic syndromes, the commonest of which is diabetic peripheral neuropathy (DPN), the main initiating factor for foot ulceration. In this study we are mainly considering DPN which is defined as "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and micro-vessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates". [12]

Foot ulcers in diabetic patients due to neuropathy result from two or more risk factors acting at a time. All three kinds of nerves i.e. sensory, motor and autonomic are affected in diabetic polyneuropathy.

Sensory neuropathy:

Insensate foot will be at risk of mechanical and thermal injuries as protective pain and temperature sensations will be lost. Reduction or absence of vibration sensation also will be there. Any trauma to foot goes unnoticed and patients wouldn't seek any treatment for it. Such wounds get infected easily as they remain exposed to outer environment and lead to diabetic foot complications. Sensory neuropathy is the most important prerequisite for foot ulcerations. Other factors contribute to foot ulceration only in presence of sensory neuropathy.

Motor neuropathy:

Motor neuropathy causes mild weakness of extensors initially. As the disease progresses there will be significant muscle atrophy especially in intrinsic(small) muscles of the foot and hand there will be limited joint movement. Patients may develop hammer toes or clawing of toes due to unopposed pulling of long extensors and flexor tendons and atrophy of small muscles. This also leads to increased plantar pressures at metatarsal heads. The fibrofatty tissues which act as cushions for metatarsal heads will be pushed forward due to deformities leading to further

increase in pressure and making these sites prone for callus formation and ulceration.

Autonomic neuropathy.

Autonomic neuropathy results in reduced or absent sweating consequently causing dry skin which cracks easily and leads to fissures easily predisposing patients for infection.

General or Systemic Contributions

- Uncontrolled hyperglycemia
- Duration of diabetes
- Peripheral vascular disease
- Blindness or visual loss
- Chronic renal disease
- Older age

Local tissues

- Peripheral neuropathy
- Structural foot deformity
- Trauma and improperly fitted shoes
- Callus

- History of prior ulcer / amputation
- Prolonged elevated pressures
- Limited joint mobility

IMMUNOPATHY IN DIABETIC FOOT: [33]

Immune functions are altered at various levels in individuals with diabetes, which comprise the immunopathy of diabetes, that result in development of ulcers and delayed wound healing.

Factors that contribute to an impairment in diabetic wound healing include prolonged inflammation, persistent infection, imbalanced proteolytic activity, improper formation and remodeling of the ECM(extra cellular matrix), reduced growth factors, poor angiogenesis and various cell type and stem cell dysfunction, cellular senescence and reduced re epithelialization.[63]In addition both cell mediated and antibody mediated immune functions are impaired in diabetic patients.

Nonhealing wounds fail to progress through the normal phases of wound repair, but instead remain in a chronic inflammatory state. Imbalances in wound proteases and their inhibitors in chronic wounds, because of sustained production of inflammatory mediators and influx of inflammatory cells, prevent matrix synthesis and remodeling, essential for progression to a healed wound. [65]

Nonhealing ulcer keratinocytes are hyperproliferative in both basal and suprabasal layers of the epidermis giving rise to parakeratosis and hyperkeratosis, indicating impaired differentiation. [65]

Fibroblasts from diabetic foot ulcers exhibit major changes including altered morphology, ECM

deposition, increased apoptosis, and diminished response to growth factors, reduced proliferation and reduced migration. [64]

An imbalance between ECM protein synthesis and remodeling by Matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs) is seen in DFUs. Increased MMP production causes ECM degradation.[65] Increase in MMPs with reduced concentrations of TIMP-2 in patients with DFUs, compared to traumatic wounds of nondiabetic patients, suggesting that the increased proteolytic environment reduces ECM formation and contributes to the failure of diabetic wounds to heal.[65]

Other common causative factors for chronic wounds include deregulation of certain cytokines, growth factors and their receptors and corresponding signaling molecules. Examples of these include TGF-β(Transforming growth factor-beta), FGF(Fibroblast growth factor), insulin-like growth factor 1 (IGF-1), interleukins, VEGF(vascular endothelial growth factor), TNF-α(Tumor necrosis factor alpha), PDGF(human platelet-derived growth factor), EGF(Epidermal growth factor), EGFR(Epidermal growth factor receptor), granulocyte-macrophage colony stimulating factor (GM-CSF), and receptors such as TGF-β receptors, EGFR, and bone morphogenetic protein receptor. [73]

Impaired angiogenesis and vasculogenesis, as a result of deregulation and cleavage of growth factors, and their receptors leads to insufficient oxygenation and suboptimal delivery of nutrients to the wound contributing to poor diabetic wound healing. [66]

Elevated levels of advanced glycation end products (AGEs) in serum of diabetic individuals result in a subclinical chronic inflammatory state and affects synthesis of collagen. Hyperglycemia has been shown to elevate oxidative and inflammatory stress via ROS (reactive oxygen species) and tumor necrosis factor alpha (TNF-α), sustaining inflammation [64]

BIO MECHANICS OF DIABETIC FOOT

Majority of ulcers in diabetics are consequence of mechanical trauma unnoticed by patients due to neuropathy. Commonest sites are in forefoot. Ulcers occur at sites of high pressure on either plantar or dorsal surfaces and are caused by ill-fitting footwear over bony prominences and toe deformities.

NORMAL WEIGHT BEARING:

The weight of the body, during walking, is borne mostly by one leg at a time. When the foot first touches the ground while walking, heel bone (calcaneus) takes all weight, however, the other foot as well, is still sharing some of the body weight. As soon as the heel is firmly on the ground, other foot leaves the ground.

The forefoot then comes to the ground but the lateral border of the foot takes on the weight first, transmitting it through cuboid bone and base of 5^{th} metatarsal. Thus, the weight is transmitted from calcaneus, cuboid and base of 5^{th} metatarsal and heads of all metatarsal. As the other foot swings forward, the whole weight is on forefoot. Finally, strong contraction of toes pushes the body forward.

While the foot is standing on the ground, it is rather like an arch, sparing the mid foot from weight bearing. The intricate mechanism, involving the joints of the foot, ligaments, muscles, bones and the resilient plantar tissue makes walking and running comfortable and does not lead to any foot problems.

WEIGHT BEARING IN DIABETIC NEUROPATHY:

Chronic hyperglycemia and poly neuropathy lead to certain functional and structural changes in the foot. Chronic hyperglycemia causes non enzymatic glycosylation of proteins causing limited joint mobility, reduction in elastic tissues in plantar skin and underlying collagen tissue.[51] Foot deformities occur as a result of atrophy of the intrinsic muscles of foot and previous scars and toe amputations alter the architecture of the foot.

Loss of elasticity, flexibility and free joint movements lead to a relatively rigid and unstable foot with altered weight bearing areas. Bony prominence develops underneath the foot pushing fibro fatty shock absorbing tissue forward, exposing the condyles of metatarsal heads. The combination of the various risk factors in presence of neuropathy increase the plantar pressure significantly in forefoot and hallux and increases the risk of foot ulceration.

HOW DOES FOOT INJURY OCCUR?

In normal individuals, peak pressure in foot ranges between 50 - 300 K Pascals, lowest being on mid foot and highest being on heel and heads of three Meta tarsal and hallux. In diabetic patients, plantar pressures are increased 2- 3 folds. The ulceration occurs because of combined effect of increased pressure and loss of pain sensation. The risk of foot ulceration also depends on the activity, use of protective foot wears of the individual. Elevated plantar pressure is now accepted as major factor in pathogenesis of plantar ulcers in diabetics.[6]

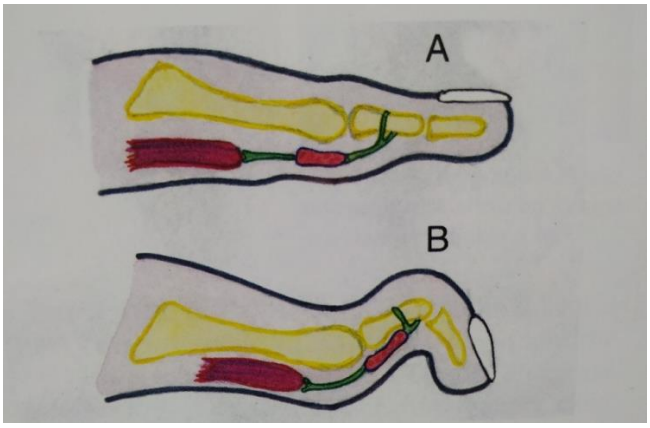


Figure 6. Normal position of fibro fatty tissue B. Fibrofatty tissue pushed forward in diabetics

Some regions of plantar tissue become ischaemic when foot is loaded. When the foot is lifted from the ground, the pressure is released and capillaries opened and restoring blood circulation. When normal person stands for some time, he feels uncomfortable and hence changes the position but in patients with diabetic neuropathy, due to loss of pain sensation, they stand still for more time, so the capillaries get occluded causing tissue ischaemia resulting in tissue injury. Recovery of this ischemia is also affected in diabetics, because of altered micro circulation. Dorsiflexion at first Meta-tarso-phalangeal (MTP) joint is essential during 'toe off' phase of gate. When ability to dorsiflex, the foot is limited as in Hallux Rigidus, very high pressure develops under Hallux explaining the high prevalence on ulcers on pulp of great toe. In addition, soft tissue metatarsal cushions are displaced distally leaving condyles of metatarsal heads exposed.

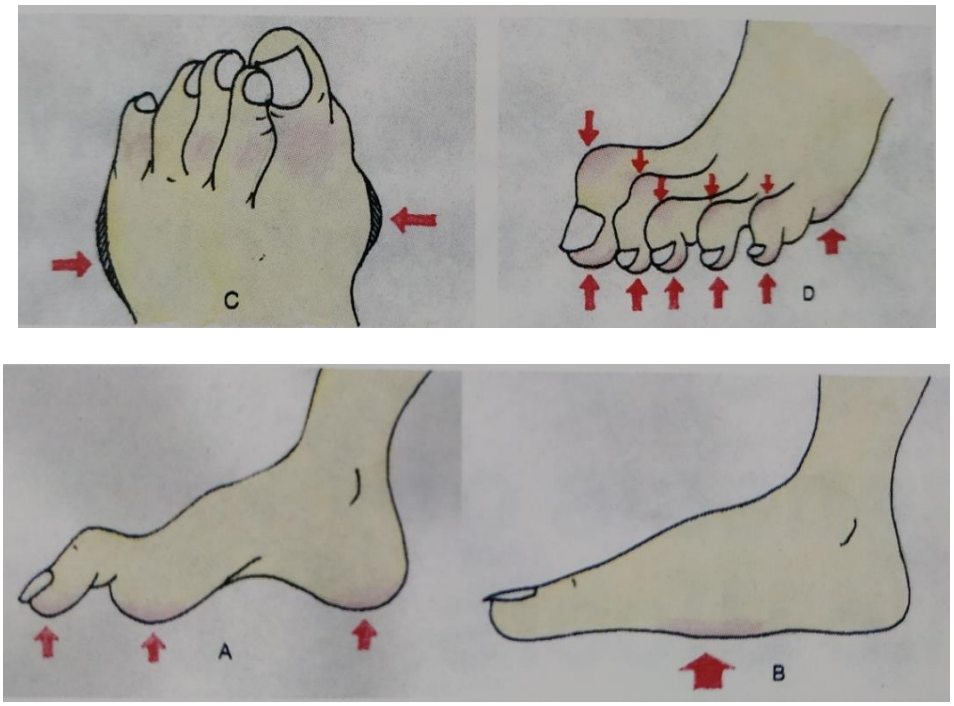


Figure 7. AREAS OF HIGH RISK FOR ULCERATION.

Total weight bearing area of foot is reduced significantly, increasing the pressure on limited weight bearing surface. Presence of scar from previous ulcers is a leading risk factor for future ulceration as soft; elastic tissue is replaced by hard and non-elastic scarred tissue which tears easily.

Plantar callus is common at elevated pressure sites which adds on to increased pressure further. Shear i.e. horizontal movement between skin below and the bone above is altered in previously ulcerated foot and in presence of callus as the scarred tissue is fixed, elastic and does not move horizontally with bone above it leading to foot ulcers.

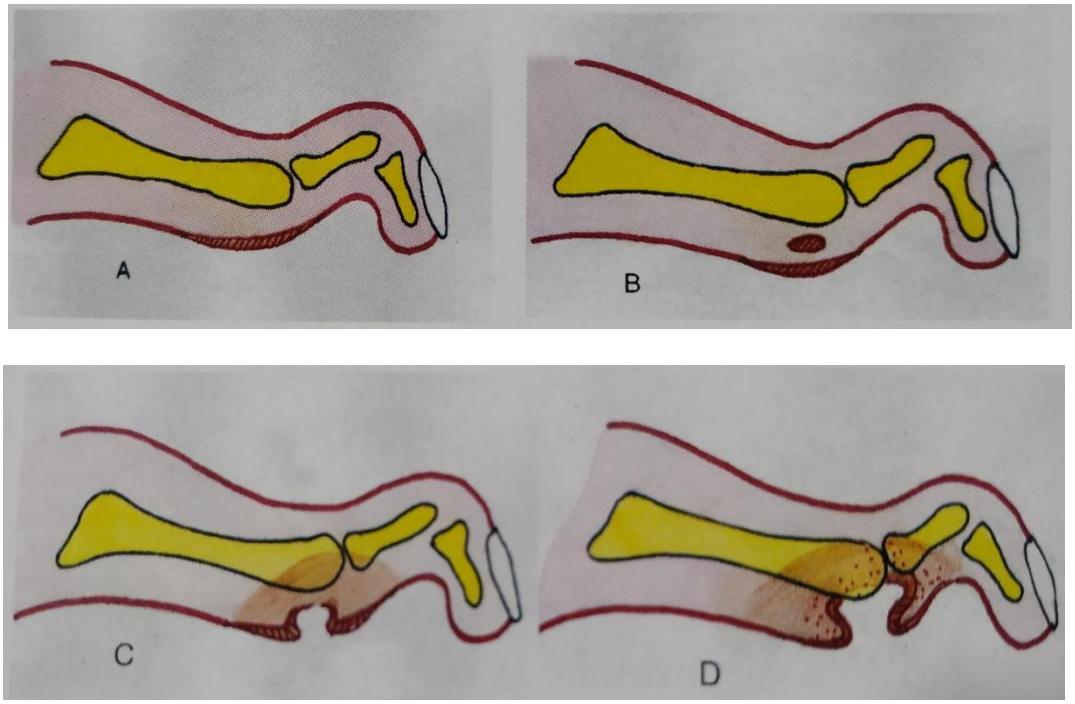


Figure 8. Stages of foot ulcer A. Callus B. Soft tissue damage C. Ulceration D. Infection

On running or walking for a long distance, the foot is subjected to repetitive stress and gradually becomes inflamed and hotter. The normal person adopts by changing posture of foot allowing the shift of pressure and thus inflammation. In insensitive foot, inflammation increases until finally tissue breaks downs and ulcerates.

MECHANISMS OF INJURY

Internal mechanism: Associated with structural deformities of the foot anatomy which are favored by sensory, motor and autonomic neuropathy disorders. Together, limited joint mobility and structural alterations are caused by glycosylation of collagen and thickening of the peri aarticulares structures that are produced for a disorder in the production of elastin (tendons, ligaments, articular capsule and, etc.), at subtalar, metatarsal and metatarsophalangeal head levels. Because the diabetic condition invariably involves hyperglycemia, non-enzymatic glycation of collagen and a deterioration of elastin, fibronectin, proteoglycans, epithelial cells and other proteins are noteworthy in wound healing during repair sequence. [74]

External mechanism: Related to chronic trauma of the soft tissues of the foot that precipitate the onset of an injury on the same structures that later produce the wound. These mechanisms, together with risk factors, do not act independently to cause ulcers. They require the combination of numerous events (sometimes fewer than others) to produce wounds in different areas of the foot, different sizes and different components. In fact, the most important factors that produce foot injury and lesion of the extracellular basement matrix of the skin are: neuropathy, deformity, trauma, peripheral circulation failure, inflammation, dryness and calluses on the foot. [74]

The accumulation of the principal components corresponds to the causal pathways that result in diabetic foot ulcer when applying the Rothman model of causation. [54] These factors that are insufficient on their own, combined will ultimately result in the formation of a diabetic foot ulcer; the interaction of a number of component causes may result in

sufficient cause for ulceration. The most common causes interact between one another to result in ulceration in the diabetic foot. These risk factors are: neuropathy, deformity, trauma and impaired healing (present in 63% of cases) [74]

PATHWAY OF FOOT ULCERATION

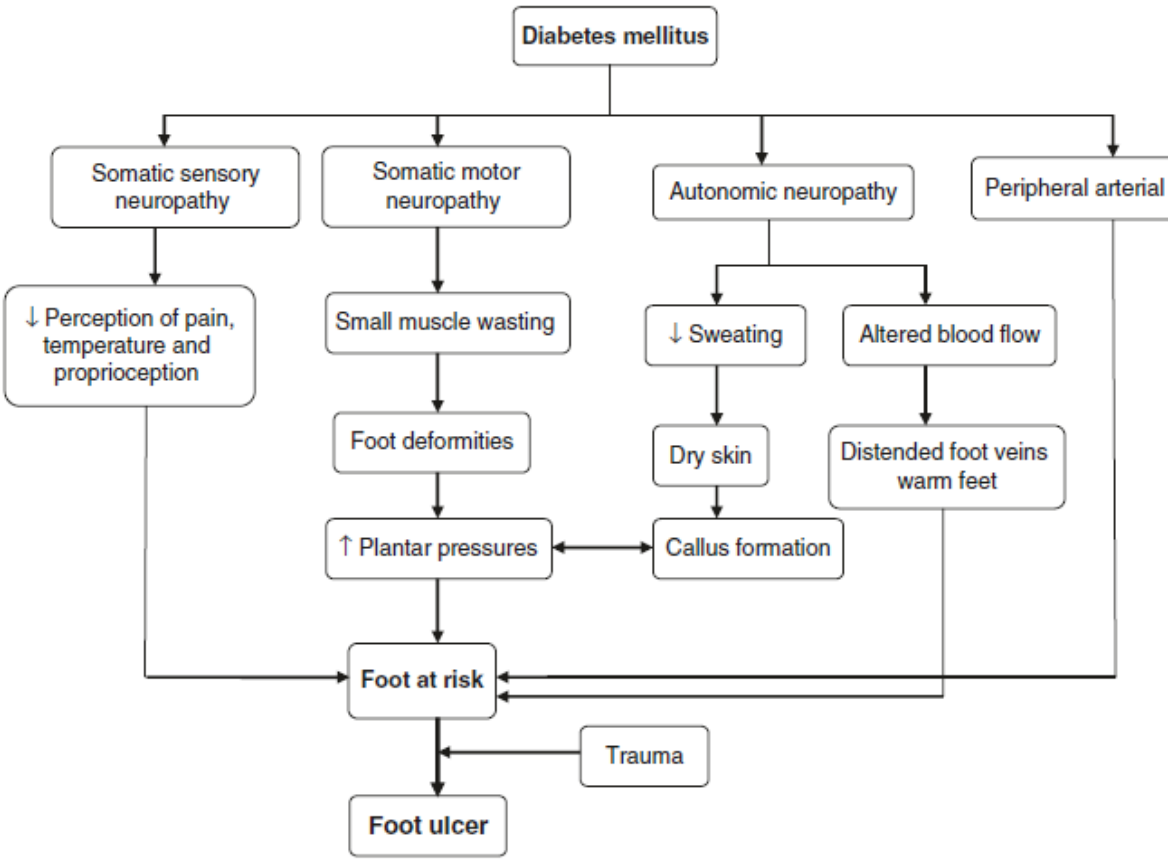


Figure 9. Pathway of foot ulceration

RISK FOR INFECTION

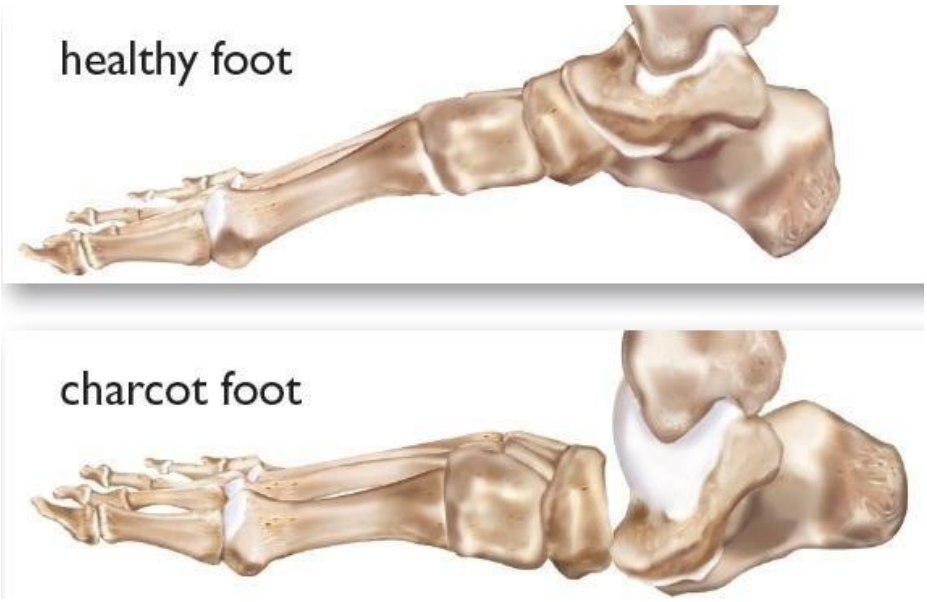
Infections are common in diabetic patients when compared to normal foot[31]. It is proven that diabetic foot infections are **"polymicrobial"** in nature. Hyperglycemia with impaired immunologic responses, superadded neuropathy and peripheral arterial disease are predisposing factors. There is impaired ability of leukocytes and ischemia also affects the ability to fight infections because delivery of antibiotics to the site of infection is impaired. Consequently, infection can spread rapidly, and produce significant and irreversible tissue damage. Even in the presence of adequate arterial perfusion, underlying peripheral sensory neuropathy will often allow the progression of infection through continued walking or delay in recognition.

RISK FOR CHARCOT JOINT DISEASE

Less than 1% diabetes will develop Charcot joint disease[37]. One large population based prospective study found an incidence of about 8.5 per 1,000 persons with diabetes per year; The incidence of reported Charcot cases is likely to be underestimated because many cases go undetected, especially in the early stages.

Primary risk factors for this are the presence of dense peripheral sensory neuropathy normal circulation, and history of preceding trauma often minor on nature

Figure 10. CHARCOT DEFORMITY



RISK FOR AMPUTATION

The risk of leg amputations in diabetic patients is from 2% to 16% [(38)]. While peripheral arterial disease may not be an independent risk factor for ulcer, it can be significant risk factor for amputation. PAD affecting the feet and legs is present in 8% of adult diabetic patients at diagnosis and in 45% after 20 years. The incidence of amputation is 4 to 7 times greater for diabetic than the counterparts[(37)]. Impairment of arterial is another risk factor. Early diagnosis, control of risk factors, and medical management as well as timely revascularization may aid in avoiding limb loss.

While infection is not implicated in the pathway of ulceration, it is a significant risk factor in the pathway to amputation. Poor wound healing, sepsis, or infection can lead

to tissue necrosis and gangrene, requiring amputation[38].Another frequently described risk factor for amputation is chronic hyperglycemia.

The link between degree of glucose control and incidence of numerous diabetic complications has been established in many studies. Complications include peripheral neuropathy, micro-angiopathy, microcirculatory disturbances, impaired leukocyte phagocytosis, and glocosylation of tissue proteins. Aggressive glucose control, management of co-morbidities, and lower extremity care will indeed lower overall risk for amputation.

The best predictor of amputation is a history of previous amputation. A past history of ulceration or amputation increases the risk for further ulceration and amputation. Up to 34% patients develop new ulcer within 1 year and the 5 year rate of recurrence is 70%[40]. The recurrence rate is higher for patients with a previous amputation because of abnormal distribution of plantar pressures and altered osseous architecture.

ASSESSMENT OF THE DIABETIC FOOT

The foot manifestations of diabetes are well documented. Recognition and early treatment of diabetic foot disorders require the skills of a doctor to diagnose, manage, treat and counsel the patient. A multidisciplinary team approach promotes effective treatment, thereby improving outcomes and decreasing the risk of amputation[41].

The evaluation involves careful assimilation of the history and physical findings and necessary diagnostic procedures. Screening tools may be valuable in evaluating the foot and assessing the risk level. Identification of abnormal findings can improve the prognosis for a favourable outcome.

History

A through medical and foot history must be obtained from the patients. The history should address several specific diabetic foot issues

Medical History

Global History

- Diabetes- duration
- Glycaemia management
- Cardiovascular, renal and ophthalmic evaluations

- Other co-morbidities
- Treating physician
- Nutritional status
- Social habits alcohol, tobacco, drugs
- Current medications
- Allergies
- Previous hospitalization/ surgery

Foot Specific history

General

- Daily activities including work
- Footwear
- Chemical exposures
- Callus formation
- Foot determines
- Previous foot infections, surgery

- Neuropathic Symptoms
- Claudication/ rest pain

Wound ulcer history

- Location
- Duration
- Inducing trauma
- Infection
- Hospitalization
- Wound care
- Off loading techniques
- Wound response
- Patient compliance
- Interference with wound care (family or social problems for patient)
- Previous foot tissue or surgery
- Charcot foot previous or active

- Charcot treatment

Physical Examination

All patients require a pedal inspection by a health care practitioner at least once annually[41]. Patients with high risk require more frequent evaluations. It begins with an evaluation of extremities. Any problem can then receive closer scrutiny. Key components of the foot examination are presented below

Vascular Examination

- Palpation of pulses: common femoral, popliteal, Dorsalis pedis, posterior tibial
- Hand held Doppler examination
- Skin/limb colour changes: cyanosis, erythema, pallor, dependendent rubor
- Presence of edema
- Temperature gradient (ipsilateral and contralateral extremity)
- Dermal thermometry
- Ischemic changes: Skin atrophy, thin, smooth, parchment like skin, abnormal wrinkling, absence of hair growth, onychodystrophy

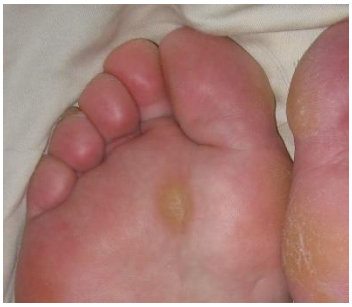
Neurological examination

- Vibration perception: Tuning fork 125 Hz/cps, measurement of vibration perception threshold (biothesiometer)
- Light pressure Semmes-Wenstein 10gm monofilament
- Light touch: cotton wool
- Two point discrimination
- Pain: pin prick (sterile needle)
- Temperature perception: hot and cold
- Deep tendon reflexes: patella, Achilles
- Clonus testing
- Babinski's test
- Romberg's test

Dermatological examination

Figure 11: Diabetic foot lesions

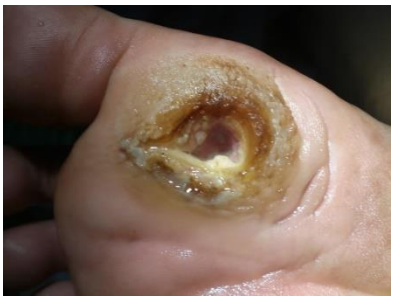
- Skin appearance



o Color, texture, turgor, quality

o Dry skin

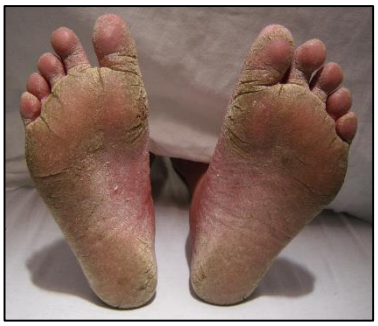
- Calluses



o Discoloration/ subcallus hemorrhage

Fissures (especially posterior heel) Nail appearance

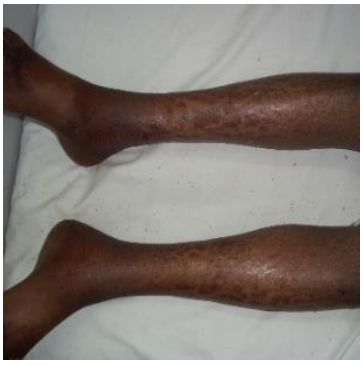
o Onychomycosis, dystrophic gryphotic



o Atrophy or hypertrophy

o Paronychia

- Hair growth



- Ulceration, gangrene, infection

o Note location, size, depth, infection status, etc

- Interdigital lesions
- Tinea pedis
- Markers of diabetes
    - o Shin spots: diabetic dermopathy
    - o Necrobiosis lipodica diabeticorum
    - o Bullosum diabeticorum
    - o Granuloma annulare
    - o Acanthosis nigricans

Muskuloskeletal examination

- Biomechanical abnormalities
- Structural deformities
    - ➢ Hammer toe, bunion, tailor’s bunion
    - ➢ Hallux limitus/ rigidus

  - Flat or high arched feet
  - Charcot deformities
  - Post surgical deformities (amputations)
- Prior amputation
- Limited joint mobility
- Tendo-Achliles contractures/ equinus
- Gait evaluation
- Muscle group strength testing
  - Passive and active non weight bearing
  - Foot drop
  - Atrophy: intrinsic muscle atrophy
- Plantar pressure assessment
  - Computerized devices
  - Harris ink mat, pressure sensitive foot mat

Foot wear examination

- Type of shoe (athletic, oxford, comfort etc)
- Fit
- Depth of toe box
- Shoe wear, pattern of wear
- Lining wear
- Foreign bodies
- Insoles, orthoses.

Laboratory investigations [78]

The standard procedure involves measuring blood glucose level and urine for glucose and ketones.

Other investigations like full blood count, blood urea, electrolytes, and creatinine levels should be monitored regularly. Glycosylated hemoglobin (HbA1C) is important to gauge the patient's overall glycemic control as HbA1c shows the mean blood sugar concentration best over previous weeks to months.

Hepatic and renal function tests are necessary for monitoring the patient's metabolic status. ESR can be done to assess the presence and response to treatment of infections like osteomyelitis.

Routine wound cultures are not recommended since all wounds harbour microorganisms. However in the presence of invasive infection, cultures from the deeper tissue will help to identify the causative microorganisms.

Imaging [13]

In case of diabetic foot, it is hard to assess the depth of the ulcer especially when there is pus and slough covering it. Also, it is hard to determine the extent of deep infection as the rubor of inflammatory response is minimal in subfascial sepsis.

X rays are helpful to determine the depth of foot ulceration and to assess presence of bone infection or neuroarthropathy. Radiographs may reveal bony erosions, fractures, subluxation/dislocation of multiple joints, osteosclerotic features or united fractures.

Magnetic Resonance Imaging has emerged as a popular investigation for many of the foot problems. In Diabetic foot it is especially useful to detect infection. It is used to evaluate the extent of foot infection by revealing the depth of ulceration, edema and localized fluid collections in the soft tissues, joints and tendon sheaths. Positron emission tomography demonstrates a high specificity for osteomyelitis.

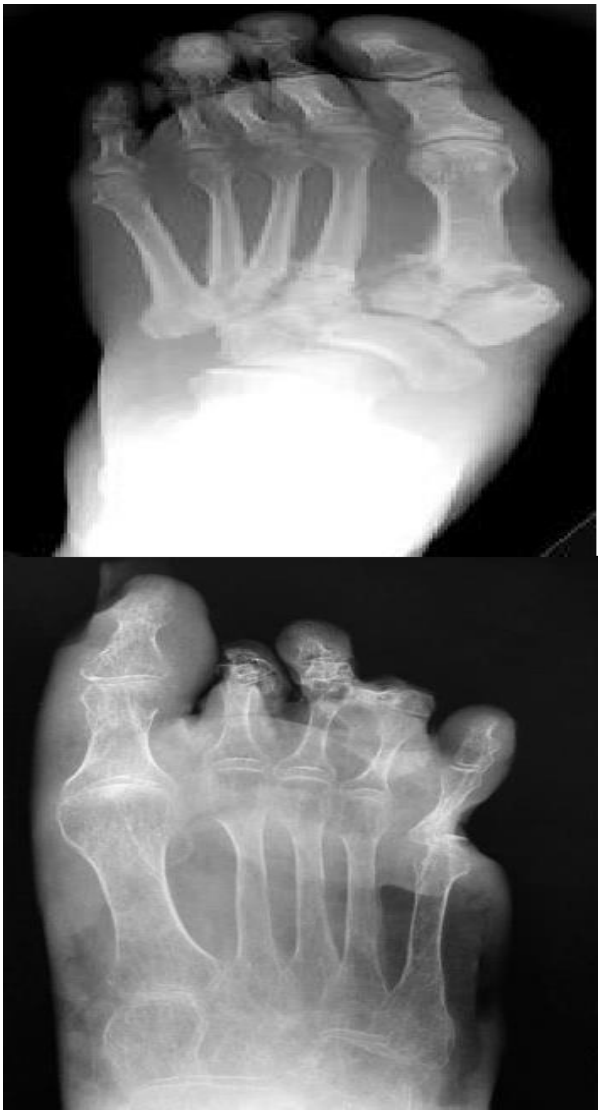


Figure 12. Osteomyelitic changes in diabetic foot x-ray AP- view.

Other investigations [49]

Most of the DFUs may have silent osteomyelitis. Newman et al. found Indium-111 leukocyte scan to be 89% sensitive for diagnosing osteomyelitis in DFUs.

Ankle brachial index (ABI) or toe-brachial index can be used to determine the extent of the vascular problem. Values below 0.9 suggests an obstruction while ABI less than 0.4 is

associated with tissue necrosis and a significant risk for amputation.

Screening ABI every 5 years in patients with diabetes without any signs/symptoms of vascular insufficiency has been recommended.

Pulse oximetry has also been reported to be as effective as ABI and the sensitivity of the test will be improved if used together with ABI.

The transcutaneous oxygen tension method is a reliable indicator of skin perfusion as periwound cutaneous perfusion is the critical physiological determinant of ulcer healing. TcPO2 less than 20mmHg has been associated with early wound healing failure.

Other investigations to detect vascular insufficiency include measuring absolute toe pressure, continuous-wave Doppler Ultrasonography, duplex ultrasonography, pulse volume recordings and angiography (CT, MRI or contrast).

Pedobarography is a study of foot pressure and has been widely used in the research of diabetic foot.

In-shoe and barefoot peak plantar pressure measurement has also been suggested to assess foot at-risk and prevent ulcers.

Technetium 99 methylene disphosphonate (Tc-99 MDP) bone scans are used to detect osteomyelitis. Although highly sensitive, it has low specificity. To improve the specificity, white blood cells can be labelled with Tc-99 hexamethylpropyleneaminoxime (tc-99 HMPAO), Indium-111 oxime or gallium-67 citrate.

CT scans may be indicated in the assessment of suspected bone and joint pathology. CT offer good anatomy visualization and resolution of bone with osseous fragmentation and joint subluxation. MRI is usually preferred over CT for osteomyelitis because of its enhanced resolution and its ability to visualize any infectious process. When arthropathy is present, the T1 and T2 bone images are "hypo intense". Increased signal on T2 bone images is seen is osteomyelitis.

PET scan is a upcoming new technique for differentiating osteomyelitis from neuropathic arthopathy. A meta-analysis comparing the diagnostic accuracy of PET scanning with bone leucocyte scanning found that PET scans are most accurate for diagnosing osteomyelitis, with a sensitivity of 96% and specificity of 91%.

Vascular evaluation

The lower extremity must be assessed for vascular risk factors. The indications for vascular intervention include an ABI of less than 0.7, toe blood pressures less than 40mmHg, or transcutaneous oxygen tension (TcPO2) levels less than 30mmHg [45,46].

Hand held Doppler:

A hand-held Doppler probe is a small, portable ultrasound machine designed to detect blood flow. It works by transmitting high frequency sound waves (typically 8–10MHz) through the tissues and collecting the reflected signal. The change in frequency detected by the Doppler machine is output as an audible signal (sound), and it is this sound which indicates

the presence of blood flow to the operator. It can be used to detect blood flow in pedal arteries when pulsations are not clinically palpable. It can also be used to measure systolic blood pressure in peripheral arteries of ankle and arm hence to calculate ankle brachial index (ABI).

Figure 13. HAND HELD DOPPLER

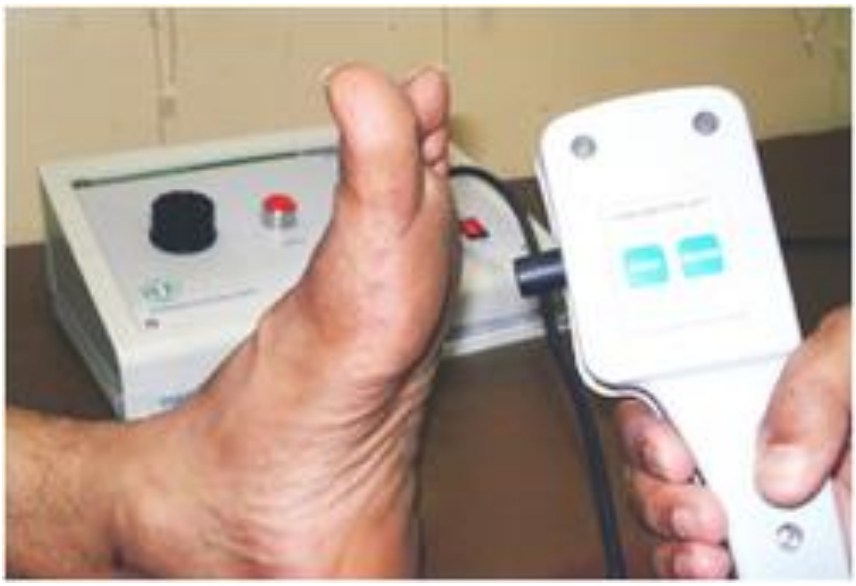


Figure 14. BIOTHESIOMETER

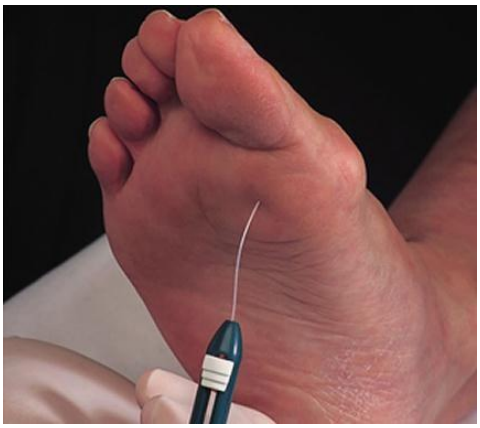
Neurological evaluation

10g Semmes Weinstein monofilament: Florence Semmes and Sidney Weinstein developed a set of nylon monofilaments to measure the sensory loss in the hands of patients with brain injury. Inability to sense 5.07/10g Semmes Weinstein monofilament will be considered as loss of protective sensation. Pressure sensation loss using the 10g monofilament has high predictive value of ulceration.

Vibration perception threshold:

Degeneration of intra-epidermal nociceptors [C-fibres and A-delta fibres] leads to pain insensitivity. So, measuring the vibration perception at the feet is a test recommended for diabetic neuropathy. The Biothesiometer (also known as VPT meter or Neurothesiometer) is a handheld device with a rubber tactor that vibrates at 100 Hz.

IMAGE 15. SEMMES WEINSTEIN MONOFILAMENT



Plantar foot pressure assessment

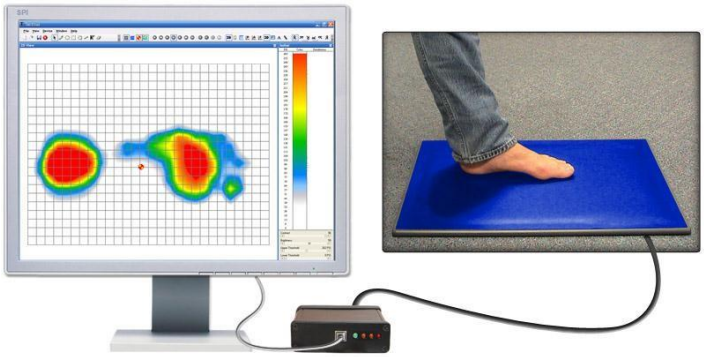
Semi quantitative estimation of plantar pressures can be carried out using HARRIS MAT FOOT IMPRINT on which the patient's foot leaves impression in different states. Although the test is specific but not very sensitive.

Quantitative measurement of plantar pressures is now possible with many devices commercially available e g: Podia scan. All these devices require computer and special software.

For the recording and the evaluation of the plantar pressure distribution, there are in the market special platform like apparatus (pedobarographs or FPPs), which consist of digital sensors and calculate the force per square area (N/cm2) (pressure in KPa). The amplitudes of the applying forces attributed analogously through a RGB color scale (with the highest pressures draw red and the lowest draw blue). As a result, a full image of the loading plantar area of the foot can be acquired,

with the specific coloration based on the recorded pressures. For the pressure distribution the subject adapts an upright standing (static) position (usually a quite bipedal stance), barefoot for some seconds.

IMAGE 16. HARRIS MAT



THE HEALTHY DIABETIC FOOT : PREVENTION

Preventing is best accomplished through a multi disciplinary . It is a a co-ordinated process of care. Patient and family education is the primary role in prevention. This involves regular glucose assessment, insulin administration, diet, daily foot inspection and care, proper footwear. Therapeutic shoes which have pressure relieving insoles and high toe boxes must be used. Diabetic patients must be educated about risk factors and the importance of foot care. This includes the need for self-inspection, appropriate foot hygiene, and surveillance, monitoring foot temperature, proper footwear, good diabetic control and prompt recognition and professional treatment of newly discovered lesions.

Classification of ulcers

Appropriate classification of the foot wound facilitates proper treatment and be generally predictive of expected outcomes. Several systems of ulcer classification are currently in use. The easiest system is to classify lesions as neuropathic, ischemic or neuro-ischemic, with descriptors of wound size, depth and infection[(5)]. Although no single system has been universally adopted, the classification system most often used was described and popularized by Wagner. In the Wagner's system, foot lesions are divided into six grades based on the depth of the wound and extent of tissue necrosis

Another hybrid system, is the PEDIS system, which includes five basic characteristics: perfusion, infection, extent/size, depth/tissue loss and sensation. While

this system has yet to be validated, it provides the benefit of having been developed by a consensus body. Imaging studies play an important role in the assessment and evaluation of the diabetic foot ulcer

WAGNER CLASSIFICATION SYSTEM

Grade 0	Foot symptoms like pain only
Grade 1	Superficial ulcers
Grade 2	Deep ulcers
Grade 3	Ulcer with bone involvement
Grade 4	Forefoot gangrene
Grade 5	Full foot gangrene

TREATMENT OF DIABETIC ULCERS: GUIDING PRINCIPLES

The primary goal for diabetic foot ulcers is to obtain wound closure. The Wound Healing Society defines a chronic wound as one that has failed to proceed through an orderly and timely repair process to produce anatomic and functional integrity.

A chronic wound is defined as one where the healing cascade has been disrupted at some point, leading to prolonged inflammation and failure to re- epithelialize and allowing for further breakdown and infection.

Standard care for DFU is ideally provided by a multidisciplinary team by ensuring glycemic control, adequate perfusion, local wound care and regular debridement, off-loading of the foot, control of infection by appropriate antibiotics and management of comorbidities. Educating patients helps in preventing ulcers and their recurrence.

Tissue management/ wound bed preparation

Debridement: debridement of a necrotic tissue is an integral component in the treatment. Undermined tissue or closed wound spaces will otherwise harbor bacterial growth. Debridement serves various important functions- removal of necrotic tissue and callus, reduction of pressure, evaluation of the wound bed and reduction of bacterial burden. Debridement facilitates drainage and stimulates healing.

Ulcers heal faster when the wound is clean as the devitalized necrotic tissues hinder cell migration and predispose it to infection and prohibit healing. Debridement of the wound

may hasten healing by removing the dead necrotic tissue, particulate matter, or foreign materials, and reducing bacterial load.

The conventional way is to use a scalpel and excise all unwanted tissues including callus and eschar (sharp debridement). Since the necrotic tissue often extends beyond the ulcer bed, some authors recommend liberal debridement of deeper tissue beyond the ulcer boundary.

The limiting factors of sharp debridement include inadvertent bleeding, poor pain tolerance by the patient and lack of any objective markers to differentiate impaired and healthy tissue to ascertain the extent of debridement.

Other methods of wound debridement include physical debridement using wet-to- dry dressings; hydrodissection or hydrocision with the use of high pressure saline beam; enzymatic debridement using enzymes like collagenase and papain as ointment preparations; autolytic debridement with the use of moisture retaining dressings; and biological debridement with use of larvae of common green bottle fly (Lucilia sericata).

Maggot therapy is recommended for DFUs when surgical debridement and antibiotics fail to improve tissue healing.

Occasionally sharp debridement is combined with other forms of debridement to achieve ulcer healing.

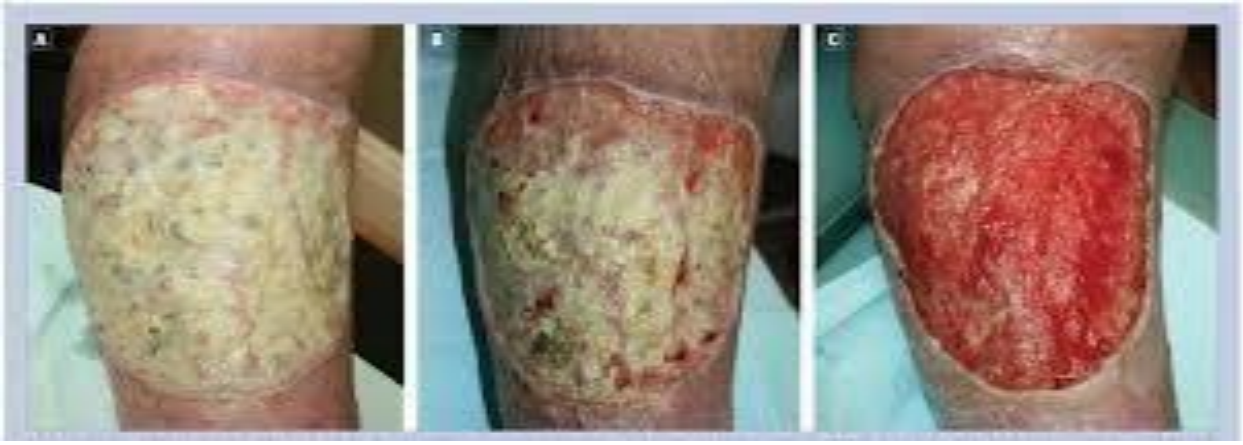


Figure 17. ULCER POST DEBRIDEMENT

***Growth factor therapy*:** chronic ulcers have demonstrated benefits from autologous platelets releasates or genetically engineered products such as recombinant DNA platelet derived growth factor becaplermin gel[(60)]. These agents promote chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes and other components that help wound healing.

***Bioengineered tissues**:* These have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers in the US- ApligrafTM and DermagraftTM. These can provide the cellular substrate and molecular components necessary to accelerate wound healing and angiogenesis[(62)]. They function both as biologic dressings and has delivery systems for growth factors and extra cellular matrix components through the activity of live human fibroblast contained in their dermal element.

Bilayered skin substitutes: These include bilayered skin equivalents (ApligrafTM) and cultured composite skin (OrcelTM). ApligrafTM has been shown to significantly benefit

in the wound closure [62,63]. Extracellular matrices are generally derived from devitalized tissues to produce an immunologically inert acellular dermal matrix.

Adjunctive modalities: regenerative tissue matrix (GraftJacketTM) is a new therapy used in diabetic foot ulcers. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bio active components and structure of dermis.

Hyperbaric Oxygen (HBO) has been found to be a useful adjunctive therapy for DFUs and is associated with decrease in amputation rates [124,125]. The beneficial role of topical oxygen therapy in treating chronic wounds has also been documented.

Negative Pressure Wound Therapy (NPWT): Has become a common adjunctive treatment modality. It involves creating a sub-atmospheric pressure at the wound site and draining out the exudates. It improves oxygenation, cellular proliferation and wound granulation and reduces bacterial load and inhibitory cytokines.

A study found better efficacy and decreased amputation rate with the use of negative pressure wound therapy compared to moist dressings (hydrogels, alginates) in the management of DFUs.

Figure 18. VAC DRESSING

OFF LOADING Diabetic foot patients will have high pressure points due to deformities caused by motor neuropathy leading to muscle atrophy and loss of cushion over sole. Most commonly high-pressure points are found at great toes and 1st metatarsal heads. As the diabetic foot patients have sensory neuropathy the trauma occurring to these high-pressure points goes unnoticed and eventually, they develop ulcers over these high-pressure points.

Reducing the pressure over foot is one of the important factors in management of foot ulcers. This is achieved by various techniques which are called as offloading techniques following are the various forms of offloading.

1. Bed rest: absolute bed rest is ideal form of offloading, but practically it is not acceptable.
2. Wheel chair: This is useful in patients who have ulcers are present on both limbs.
3. Crutches: It is one of cheap and easily available method of off-loading but difficult to use by elderly patients. Patient needs to be trained regarding proper use and to avoid falls accidents, especially on chairs.

4. Total contact slab: It works on the principle that it distributes the pressure of sole equally by uniform contact of foot to cast there by increasing the weight bearing area and minimizing the pressure over ulcer.it is contraindicated in infected ulcers.
5. Air cast: This is a bi-valve cast. Two parts are joined a Velcro strapping. Inside it is lined with four air cells which can be inflated with domestically used hand pumps through four valves.
6. Temporary shoes. Temporary readymade shoes with cushioned insole such as microcellular rubber.

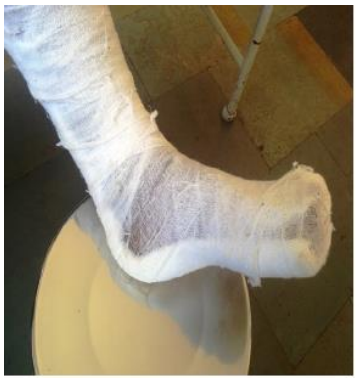


Figure 19. TOTAL CONTACT SLAB.

Figure 20. REMOVABLE CAST WALKER

Laser surgery is a type of surgery that uses a laser (in contrast to using a scalpel) to cut tissue. Examples include the use of a laser scalpel in otherwise conventional surgery, and soft-tissue laser surgery, in which the laser beam vaporizes soft tissue with high water content. Laser surgery is commonly used on the eye. Techniques used include LASIK, which is used to correct near and far-sightedness in vision, and photorefractive keratectomy, a procedure which permanently reshapes the cornea using an excimer laser to remove a small amount of the human tissue.

Types of surgical lasers include carbon dioxide, argon, Nd:YAG laser, and potassium titanyl phosphate, among others.

Effects

1. Photochemical effect: clinically referred to as photodynamic therapy. Photosensitizer (photophrin II) is administered which is taken up by the tumor tissue and later irradiated by laser light resulting in highly toxic substances with resultant necrosis of the tumor. Photodynamic therapy is used in palliation of oesophageal and bronchial carcinoma and ablation of mucosal cancers of Gastrointestinal tract and urinary bladder.

2. Photoablative effect: Used in eye surgeries like band keratoplast, and endartectomy of peripheral blood vessels.

3. Photothermal effect: this property is used for endoscopic control of bleeding e.g. Bleeding peptic ulcers, oesophageal varices

4. Photomechanical effect: used in intraluminal lithotripsy

Applications

Soft tissue: Soft-tissue laser surgery is used in a variety of applications in humans (general surgery, neurosurgery, ENT, dentistry, orthodontics and oral and maxillofacial surgery as well as veterinary surgical fields. The primary uses of lasers in soft tissue surgery are to cut, ablate, vaporize, and coagulate. There are several different laser wavelengths used in soft tissue surgery. Different laser wavelengths and device settings (such as pulse duration and power) produce different effects on the tissue. Some commonly used lasers types in soft tissue surgery include erbium, diode, and CO2. Erbium lasers are excellent cutters, but provide minimal hemostasis. Diode lasers (hot tip) provide excellent hemostasis, but are slow cutters. CO2 lasers are both efficient at cutting and coagulating.

Dermatology and plastic surgery: A range of lasers such as erbium, dye, Q switch lasers, and CO2 are used to treat various skin conditions including scars, vascular and pigmented lesions, and for photorejuvenation. The laser surgery for dermatology often bypasses the skin surface. The principle of laser surgery for dermatologic problems is based on SPTL (selective photothermolysis). The laser beam penetrates the skin until it encounters chromophore which absorbs the laser beam. After absorption of the laser beam, heat is generated to induce coagulation, necrosis of the targeted tissue, this results in the removal of unwanted tissue by laser surgery. Laser resurfacing is a technique in which covalent bonds of a material are dissolved by a laser. Lasers are also used for laser-assisted lipectomy.

Eye surgery: Various types of laser surgery are used to treat refractive error. LASIK, in which a knife is used to cut a flap in the cornea, and a laser is used to reshape the layers underneath, is used to treat refractive error. IntraLASIK is a variant in which the flap is also cut with a laser.

In photorefractive keratectomy (PRK, LASEK), the cornea is reshaped without first cutting a flap. In laser thermal keratoplasty, a ring of concentric burns is made in the cornea, which causes its surface to steepen, allowing better near vision Lasers are also used to treat non-refractive conditions, such as phototherapeutic keratectomy (PTK) in which opacities and surface irregularities are removed from the cornea and laser coagulation in which a laser is used to cauterize blood vessels in the eye, to treat various conditions. Lasers can be used to repair tears in the retina.

Endovascular surgery: Laser endarterectomy is a technique in which an entire atheromatous plaque in the artery is excised. Other applications include laser assisted angioplasties and laser-assisted vascular anastomosis.

Foot and ankle surgery: Lasers are used to treat several disorders in foot and ankle surgery. They are used to remove benign and malignant tumors, treat bunions, debride ulcers and burns, excise epidermal nevi, blue rubber bleb nevi, and keloids, and the removal of hypertrophic scars and tattoos. A carbon dioxide laser (CO2) is used in surgery to treat onychocryptosis (ingrown nails), onychauxis (club nails), onychogryposis (rams horn nail), and onychomycosis (fungus nail).

Gastro-intestinal tract:

- Peritoneum-Laser is used for adhesiolysis.

- Peptic ulcer disease and oesophageal varices - Laser photoablation is done.

- Coagulation of vascular malformations of stomach, duodenum, and colon.

- Lasers can be effectively used to treat early gastric cancers provided they are less than 4 cm

and without lymph node involvement. Lasers are also used in treating oral submucous fibrosis.

- Palliative laser therapy is given in advanced oesophageal cancers with obstruction of lumen. Recanalisation of the lumen is done which allows the patient to resume a soft diet and maintain hydration.
- Ablative laser therapy is used in advanced colorectal cancers to relieve obstruction and to control bleeding.
- Laser surgery used in hemorrhoidectomy, and is a relatively popular and non-invasive method of hemorrhoid removal.
- Laser-assisted liver resections have been done using carbon dioxide and Nd:YAG lasers.
- The ablation of liver tumors can be achieved by selective photovaporization of the tumor.
- Endoscopic laser lithotripsy is a safer modality compared to electrohydraulic lithotripsy.

Oral and dental surgery: The CO2 laser is used in oral and dental surgery for virtually all soft-tissue procedures, such as gingivectomies, vestibuloplasties, frenectomies, and operculectomies. The CO2 10,600 nm wavelength is safe around implants as it is reflected by titanium, and thus has been gaining popularity in the field of periodontology. The laser may also be effective in treating peri-implantitis.

Spine surgery: Laser spine surgery first began seeing clinical use in the 1980s and was primarily used within discectomy to treat lumbar disc disease under the notion that heating a bulging disc vaporized enough tissue to relieve pressure on the nerves and help alleviate pain.

Since that time, laser spine surgery has become one of the most marketed forms of minimally invasive spine surgery, despite the fact that it has never been studied in a controlled clinical trial to determine its effectiveness apart from disc decompression.

Thoracic surgery: In thoracic surgery, surgical laser applications are most often used to remove pulmonary metastases and tumors of different primary localizations. Other areas of application are surgical sectioning of the parenchyma, anatomic segmental resections, removal of tumors from the thoracic wall and abrasion of the pleura parietalis. Since the introduction of surgical lasers, the amount of potentially surgically resectable pulmonary nodules has significantly increased. Compared to laser surgery, other conventional surgical methods such as segmental or wedge resections with surgical stapling will normally lead to a bigger loss of lung tissue, especially in patients with multiple pulmonary nodules methods.

Other surgery: The CO2 laser is also used in gynecology, genitourinary, general surgery, otorhinolaryngology, orthopedic, and neurosurgery.

Hard tissues: Lasers are used to cut or ablate bones and teeth in dentistry.

LLLT: Mitochondria are thought to be a likely site for the effects of laser, leading to increased ATP production, modulation of reactive oxygen species, and induction of transcription factors. These effects in turn lead to increased cell proliferation and migration (particularly by fibroblasts)[16]

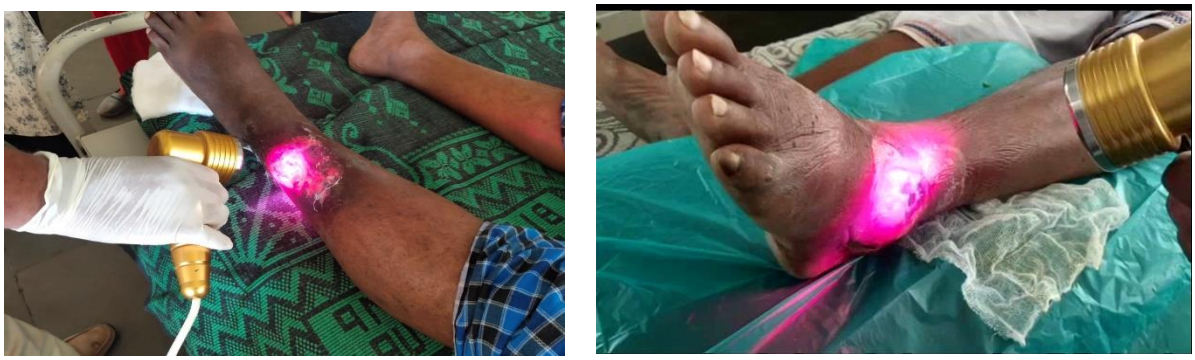
Various LLLT devices have been promoted for use in treatment of several musculoskeletal conditions including carpal tunnel syndrome (CTS), fibromyalgia, osteoarthritis, and

rheumatoid arthritis. They have also been promoted for temporomandibular joint (TMJ) disorders, wound healing, smoking cessation, and tuberculosis. LLLT appears to be effective for preventing oral mucositis in recipients of a stem cell transplant with chemotherapy.

Other Uses of LLLT:

- **Musculoskeletal:** LLLT is useful in the treatment of both acute and chronic neck pain.
- **Mouth:** To treat chronic periodontitis and to speed healing of infections around dental implants
- **Hair loss:** LLLT has been studied as a treatment for hair loss.
- **Stem cells:** An ongoing area of research is the application of LLLT for increasing cell proliferation, including stem cells.

Figure 21. LLLT OVER DIABETIC ULCER



Regardless of the modality selected, the patient should not return to an unmodified shoe until complete healing of the ulcer has occurred. Furthermore, any shoe that has resulted in the formation of an ulcer should never again be worn by the patient[20].

MATERIALS AND METHODS

The study was conducted at BLDE(DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR after obtaining ethical clearance from Ethical Committee.

Type 2 DM patients with ulcers of grade I to grade III as per Wagner grading System were included.

Patients were randomised into two groups of study and control group on the basis of alternate numbers.

The nature of therapy to be given was explained to the patients and written informed consent obtained from them before enrolment.

Patients in the study group received treatment with LLLT. Ulcer bed with edge was exposed locally with red laser (660nm) and IR laser (808nm) cluster probe. About 2-4J/cm2 for 10 minutes delivered on alternate day basis. Saline dressing done for covering after exposure and controls were treated with conventional therapy alone. Course of antibiotic treatment and slough removal was done whenever needed.

The size, depth and culture status of the ulcer was assessed on Day 1 and day 15. Duration of stay in hospital noted.

SOURCES OF DATA

Patients admitted in surgery ward or attending OPD with Diabetic foot ulcer (unilateral/bilateral) at **BLDE(DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR** from November 2018 to June 2020 were considered in the study.

METHODS OF DATA COLLECTION

- The patients were allocated alternatively into study and control groups.
- And while allocating cases, age of patient, duration of DM and size of the ulcer were matched.
- A proforma was used to collect all the relevant data from the patients.
- Detailed history was taken; thorough clinical examination and investigations will be performed on all the patients included in the study.
- All the cases were followed up till discharge and subsequently for a follow up till wound healing.
- "Primary efficacy end point" was complete ulcer closure and "Secondary efficacy end point" was time taken to achieve ulcer closure by either secondary suturing or skin grafting.

STUDY DESIGN

Comparative study

SAMPLE SIZE

- On the basis of a study the anticipated mean±sd of Ulcer area at day 1 vs Ulcer area at day 15 was 13.74±11.88 and 3.97±5.41 resp. the minimum **sample size is 25 per group** with 95% level of significance and 90% power.

Formula used is

$$N = 2\left[\frac{\left(Z_{1-\propto/2} + z_{\beta}\right) * S}{d}\right]^2$$

$Z_{1-\propto/2}$ Level of significance=95%

$Z_{1-\beta}$--power of the study=90%

d=clinically significant difference between two parameters

S= Common standard deviation

Statistical analysis

- Data represented using Mean ±SD, percentages and diagrams
- Significant difference between quantitative data found using unpaired t test/ Wilcoxon signed rank test to compare with control group.

- Significant difference between quantitative data was found using paired t test/ Wilcoxon paired signed rank test to compare day1 result with day15 result.
- Significant difference between Qualitative data was found using Chi square or Fisher's Exact test

INCLUSION CRITERIA

- Diabetic ulcers that come under Wagner's grade I to III.

EXCLUSION CRITERIA

- Patients on medications such as corticosteroids, immunosuppressant or chemotherapy
- Diabetic patients with foot ulceration resulting from electrical, radiation burns
- Pregnant or nursing mothers.
- Case of diabetic foot ulcers with skin cancer.
- Those with clinical signs of ischemia and ABI less than 0.7
- Patients associated with critical illness that need intensive care.

DESCRIPTION OF THE PROCEDURE STEP BY STEP:

-All patients admitted to the surgical ward and/or attending Surgery OPD were subjected to detailed evaluation, complete haemogram and HbA1c levels.

- Detailed work up of the diabetic foot was done by

- Hand held doppler
- Semmes Weinstein monofilament
- Harris mat
- Digital biothesiometer

-Ulcer size was calculated by obtaining the impression of ulcer floor on a sheet of cellophane paper and then transferring the imprint onto a graph paper OR by multiplying the largest length of the ulcer by the second largest length perpendicular to it.

Depth was described as deep if full thickness skin is involved and superficial if not extending till subcutaneous plane.

The ulcer size was measured on day 1 and day 15.

-Patients with evidence of slough were subjected to repeated surgical debridement.

-Objective assessment of vascularity was done by careful palpation of peripheral pulses.

-Systemic antibiotics were administered based on culture sensitivity reports.

-Insulin/oral hypoglycaemic agents (OHA) used to maintain a good glycaemic control.

-Adequate glycaemic and infection control achieved.

- LLLT was commenced.

-An LLLT device with a multidiode cluster probe of 660nm and 808nm wavelength light.

The dose of exposure calculated to deliver 2–4 J/cm2 at 100 mW,

5 kHz, from a distance of 10cm, alternate day for 15 days. Both the patients and administrators will wear laser safety goggles to prevent damage to their eyes.

The ulcer floor and edge were exposed to laser.

The ulcer was covered with Saline dressing.

Pressure off-loading was carried out in patients with plantar ulcers.

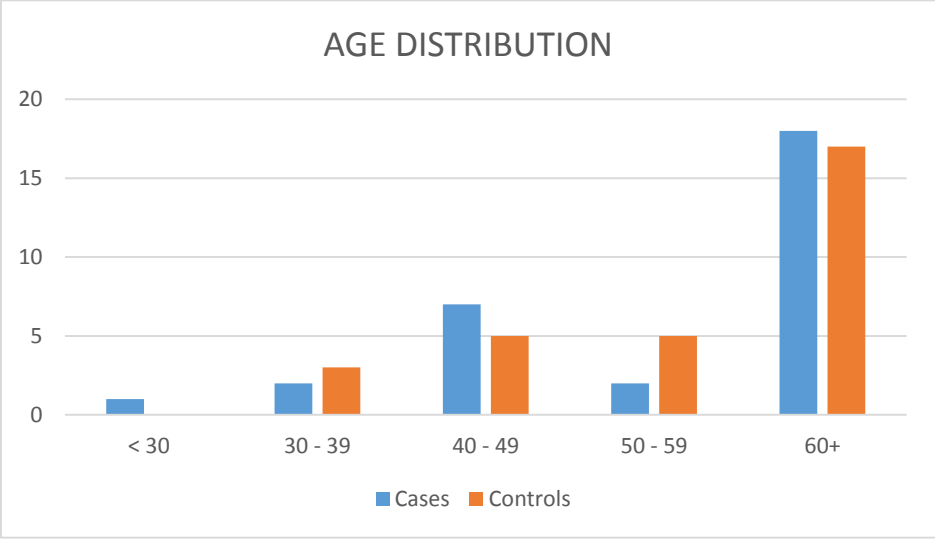
Simultaneously, these patients were educated about various aspects of Diabetes Mellitus treatment including dietary restrictions, exercise and foot care in order to prevent recurrence.

RESULTS

Table 1: Age distribution among the study population

Age(Years)	Study group		Control group	
	No. of patients	Percentage	No. of patients	Percentage
< 30	1	3.3	0	0
30 - 39	2	6.7	3	10.0
40 - 49	7	23.3	5	16.7
50 - 59	2	6.7	5	16.7
60+	18	60.0	17	56.7
Total	30	100.0	30	100.0

Figure 22: Age Distribution

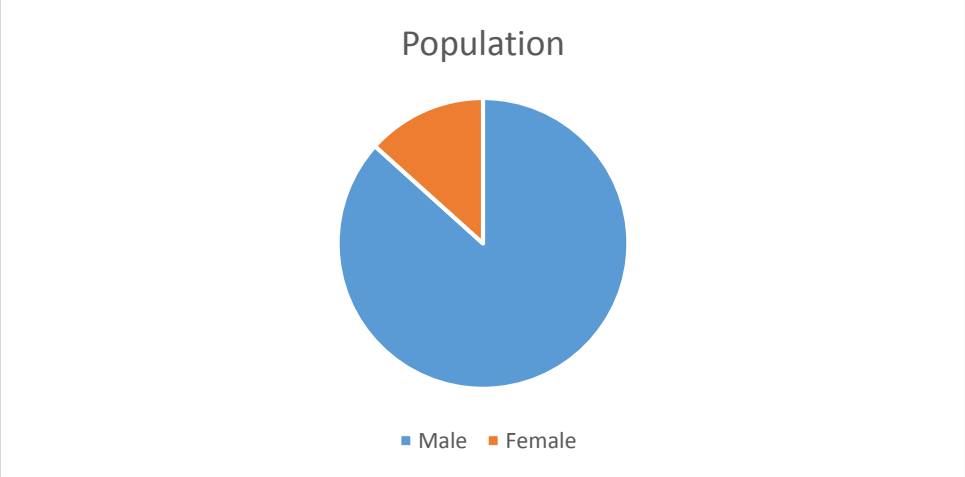


Most of the patients of Diabetic foot in the study were in the age group of 6th decade and above.

Table 2: Gender distribution among the study population

Gender	Study group		Control group		Chi square test	P value
	No. of patients	Percentage	No. of patients	Percentage		
Female	4	13.3	4	13.3	X^2=0.000	P=1.00
Male	26	86.7	26	86.7		
Total	30	100.0	30	100.0		
Insignificant						

Figure 23: Gender distribution among the study population



There is male dominancy in development of diabetic foot.

Table 3: Distribution of patients according to **Cause of Wound**

Cause of Wound	Study group		Control group		Chi square test	P value
	No. of patients	Percentage	No. of patients	Percentage		
Injury	15	50.0	14	46.7	X^2=0.0667	P=0.7961
Spontaneous	15	50.0	16	53.3		
Total	30	100.0	30	100.0		
Insignificant						

There is equivocal distribution of causes of diabetic foot ulcers i.e., following trauma and spontaneous.

Table 4: Distribution of patients according to Site of Ulcer

Site of Ulcer	Study group	Control group
	No. of patients	No. of patients
Heel	5	4
Leg	14	16
Metatarsal head	0	1
Toes	6	2
Dorsum of foot	5	7
Total	30	30

Most common site of Diabetic foot lesions was around the ankle followed by dorsum of foot.

Figure 24 : Distribution of patients according to Site of Ulcer

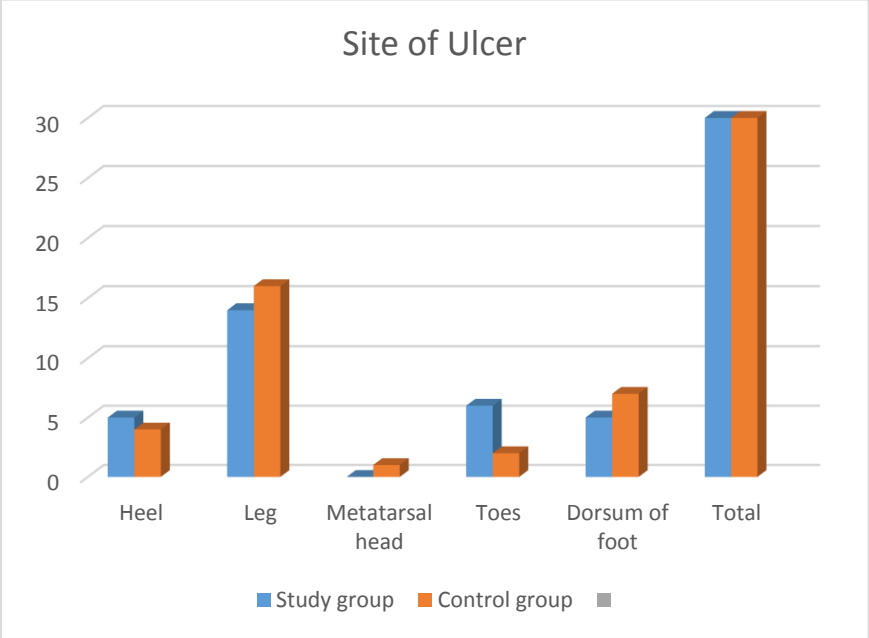


Table 5: Comparison between Mean BMI of Study group and Control group

	Study Group	Control Group
Mean BMI	27.8	26.5
Insignificant		

Table 6: Comparison of FBS and PPBS among study and control groups

	Study group		Control group		P value
	Mean	SD	Mean	SD	
Fasting blood sugar (mg/dL)	182.900	33.424	171.66	27.293	P=0. 53
Post prandial blood sugar (mg/dL)	212.657	36.919	195.54	29.744	
Insignificant					

Table 7: Comparison of HbA1c (%) between study and control groups

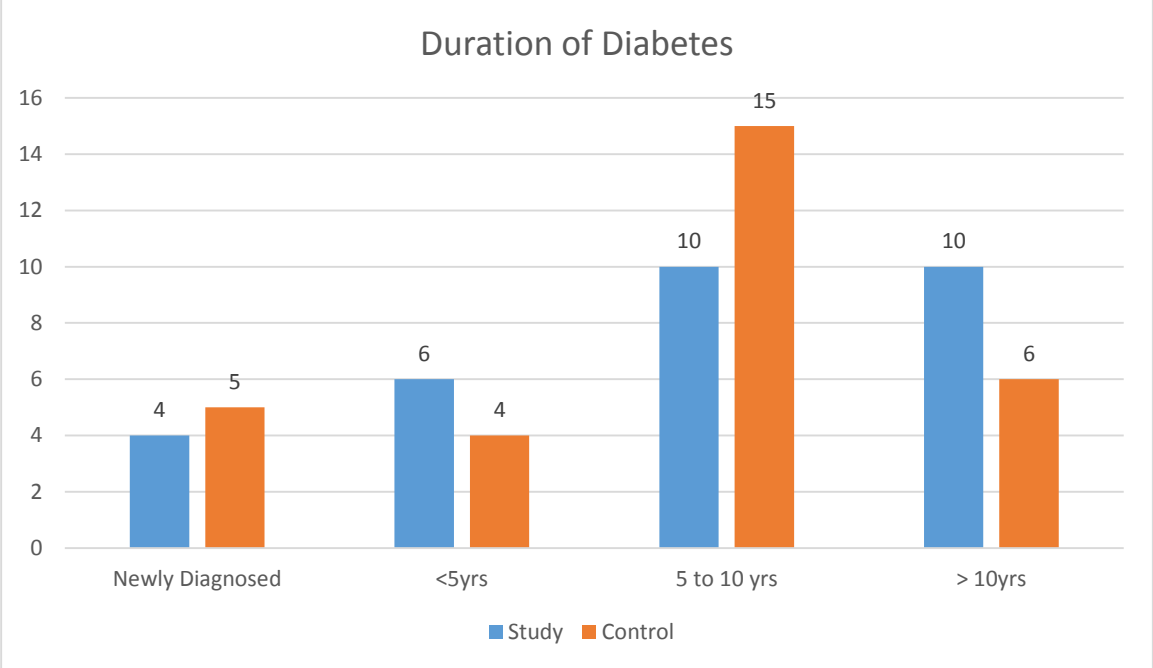
HbA1c (%)	Study Group		Control group		Mean difference (%)	Mann Whitney U test	P value
	Mean	±SD	Mean	±SD			
HbA1c (%)	8.463	1.816	8.386	1.057	0.077(0.91%)	U=358.500	P=0. 452
Insignificant							

The risk of diabetic foot increases with increase in BMI and poor Glycemic control.

Table 8: Duration of Diabetes among the Study and Control Group

	Study	Control
Newly Diagnosed	4	5
Less than 5yrs	6	4
5 to 10yrs	10	15
More than 10 yrs	10	6

Figure 25: Duration of Diabetes among the Study and Control Group

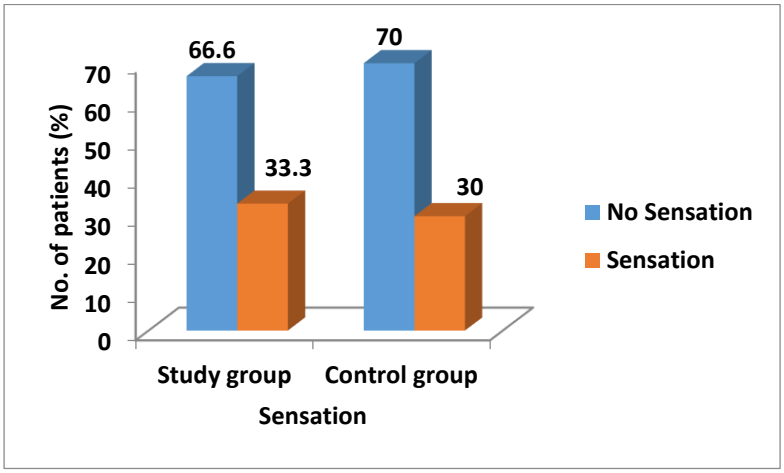


Most of the cases in the study have Diabetes for 5 to 10 years.

Table 9 : Distribution of patients according to Sensation

Sensation	Study group		Control group		Chi square test	P value
	No. of patients	Percentage	No. of patients	Percentage		
No Sensation	20	66.6	21	70.0	X^2=0.0770	P=0.7844
Sensation	10	33.3	9	30.0		
Total	30	100.0	30	100.0		
Insignificant						

Figure 26: Distribution of patients according to Sensation



There is equivocal distribution of causes of diabetic foot ulcers i.e., following trauma and spontaneous. But since there is loss of peripheral sensations in diabetic patients, minor traumas can be missed by the patient.

Table 10: Distribution of patients according to Infection

Infection	Study group		Control group		Chi square test	P value
	No. of patients	Percentage	No. of patients	Percentage		
E. Coli	1	3.3	1	3.3	X^2=2.206	P=0.6979
No Growth	14	46.7	10	33.3		
Pseu	5	16.7	4	13.3		
S. Aure	9	30.0	12	40.0		
Strept	1	3.3	3	10.0		
Total	30	100.0	30	100.0		
Insignificant						

Most Cultures on admission were sterile, followed by Staph aureus as the most common organism

Table 11: Comparison of Age (Years) between study and control groups

Age(Years)	Study Group		Control group		Mann Whitney U test	P value
	Mean	±SD	Mean	±SD		
Age (Years)	56.83 yrs	13.859	58.53 yrs	13.151	U=420.50	P=0.662
Insignificant						

Mean age of patients in study and control were almost comparable.

Figure 27: Mean ulcer area -between study and control groups

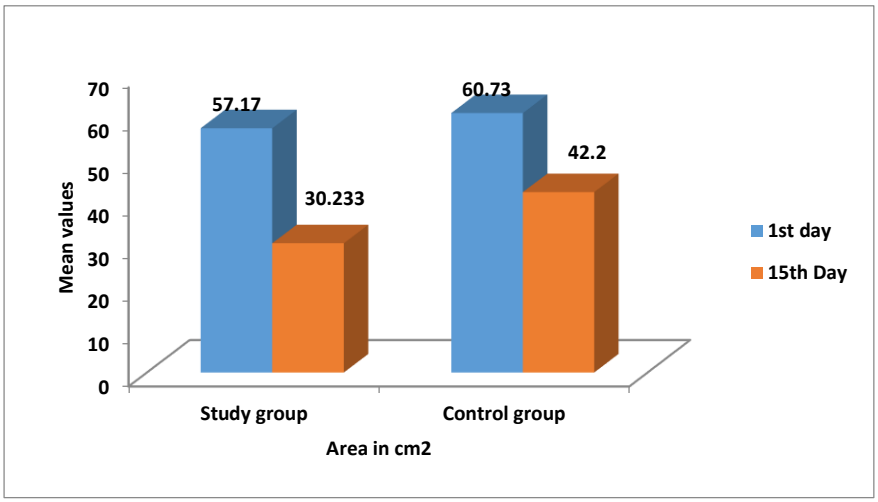


Table 12: Comparison of ulcer area between 1st and 15th days in Study and control groups

	1st day		15th day		Mean difference (%)	Wilcoxon signed rank test	P value
	Mean (cm2)	±SD	Mean (cm2)	±SD			
Study group	57.17	57.357	30.233	34.8541	3.56(5.86)	Z=4.785	P=0.0001*
Control group	60.73	35.821	42.200	27.3602	11.97(28.36%)	Z=4.785	P=0.0001*
*: Highly significant							

There is Significant decrease in ulcer area, on 15th day in cases compared to control.

Table 13: Distribution by amount of Granulation at 15th day in study group and control group

Granulation at 15th day	**Control Group**		**Study Group**		**p value**
	N	**%**	**N**	**%**	
Complete	2	6.7%	23	76.66%	<0.001*
Partial	8	26.7%	7	23.33%	
No	20	66.7%	0	0.0%	
Total	30	100.0%	30	100.0%	
*Significant					

Low level laser therapy facilitates faster granulation tissue fill up compared to conventional dressing.

Table 14: Distribution of cases by the method of ulcer closure

	Study group	Control Group
Secondary Intention	3	0
Secondary Suturing	1	1
Split thickness Skin grafting	26	29

Majority of the patients in our study underwent Split thickness skin grafting.

Figure 28: Distribution of patients according to mode of wound closure

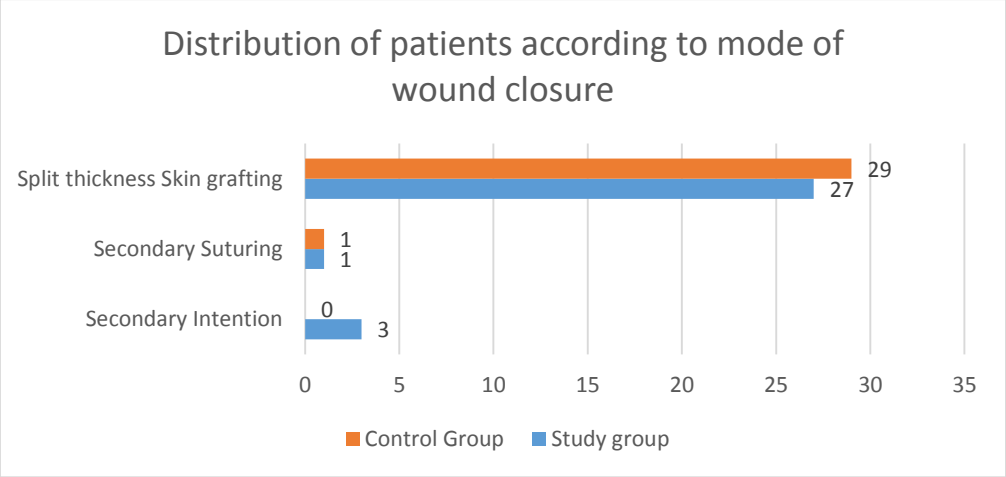
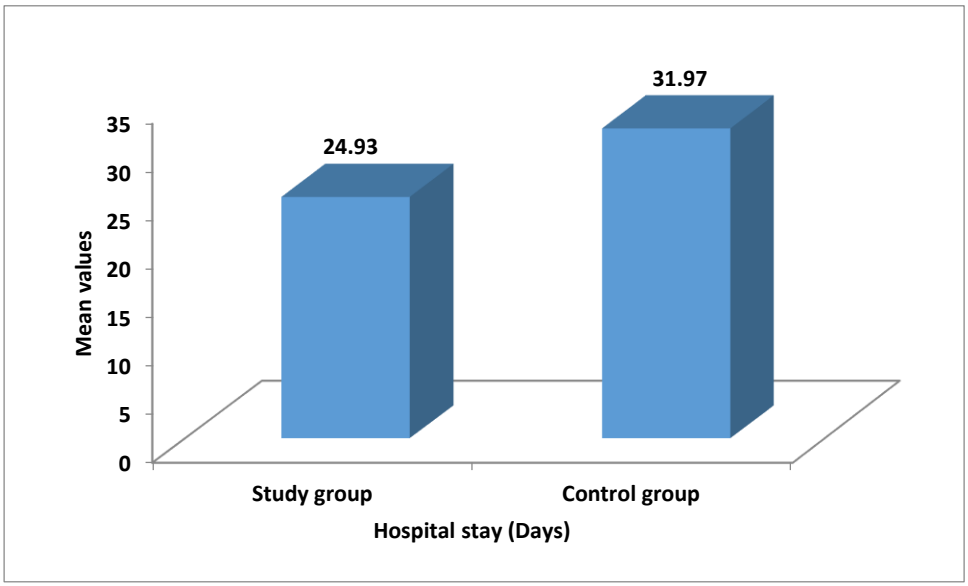


Table 15: Comparison of Hospital stay (Days) between study and control groups

Hospital stay (Days)	Study Group		Control group		Mean difference (%)	Mann Whitney U test	P value
	Mean	±SD	Mean	±SD			
Hospital stay (Days)	24.93	3.383	31.97	3.596	7.04(22.02%)	U=7.803	P<0.001*
*: Highly significant							

Figure 29: Comparison of Hospital stay (Days) between study and control groups



LLLT has significantly reduced hospital stay, with early uptake for Skin graft or secondary suturing.

DISCUSSION

In this study, it is noted that about 60% of the patients in study group and 56.7% of patients included in the control group belong to the age group of 60+ yrs of age suggesting that diabetic foot ulcers are more common in older age groups. 50% of the ulcers included in this study were over the leg.

The mean age of the patients in years included in this study were 56.83±13.8 and 58.53±13.15 for the study group and control group respectively. This is found to be in slightly higher with the mean age of patients as in different similar studies conducted like 52.1±8.940 years noted in Lenifa Priyadarshini M. J. et al 2018.

	Mean Age
Our Study	56.83±13.8 years
Lenifa Priyadarshini M. J. et al 2018	52.1±8.940 years
R. K. Mathur et al 2016.	54.6±9.9 years

The sex ratio of the patients included in the study showed a male preponderance with 87 % of patients included in the study being males. Other similar studies also noted high number of male patients included in the study with 88% in David Armstrong et al 2005 and 82.4 % in Lindy Begg et al 2016.

	Gender
Our Study	76.66 %
Lenifa Priyadarshini M. J. et al 2018	62%
R. K. Mathur et al 2016.	75 %

The mean BMI of the patients included in this study were 27.8 and 26.5 respectively for study group and control group respectively, which was comparably same in both groups. Therefore, it predicts higher incidence among people with increased BMI. Almost all the patients in the study were above the normal BMI range. Similar studies also show high BMI among the study subjects indicating obesity as a risk factor for development of diabetic foot ulcers.

There is also poor glycemic control among the study subjects with mean FBS of 182mg/dl and post prandial blood sugars of 212.6 mg/dl. Also the mean HbA1c was 8.463% indicating, poor glycemic control as the major cause of ulcers and poor healing.

The most common site for ulceration in the patients included in both the groups collectively was the leg with incidence of 50%. These results were again consistent with the findings of study conducted by Lenifa Priyadarshini M. J. et al 2018 with heel ulcerations at 35% and base of 1st metatarsal head at 23%.

	Ulcer over leg
Our study	50%
R. K. Mathur et al 2016.	54%

It was observed that the patients who were included in the study and patients in general who are found to have a tendency to develop foot ulcerations were chronically diabetic. In our study more than 85% of the patients were known to be on diabetic medication for more than 5yrs and possibly undiagnosed diabetic for a much longer time. This was again noted in almost all the studies that conducted studies on diabetic foot.

Almost all patients in the study groups were uncontrolled diabetic and on irregular treatment with mean FBS values of 182.9±33.4 and mean HBA1c of 8.463±1.8.

In our study, majority 42% had NG, followed by 30% has S. aureus, followed by 16% had pseudomonas, followed by 8% had streptococci, and 4% had E.coli.

Study by Chalya et al (127) showed that Eight out of 12 (66.7%) cultured specimens had positive bacterial growth within 48 hours of incubation while 4 (33.3%) had negative bacterial growth. One out of 8 cultured specimens (12.5%) had pure bacterial growth while seven (87.5%) had polymicrobial bacterial growths. Staphylococcus aureus was the most frequent microorganism isolated 4 (50.0%), followed by Escherichia coli 3 (37.5%) and Klebsiella pneumoniae 2; (25.0%). Pseudomonas spp and Proteus spp were the least bacteria isolated.

The present study identified Staphylococcus aureus, coliforms, and Pseudomonas as infective agents in DMFU. The exact same pattern of Staphylococcus aureus, coliforms, and Pseudomonas aeruginosa was reported by Otu A A et al (131) and even by Edo and Eregie et al(132) in Benin, Nigeria, as common isolates from in nongangrenous diabetic ulcers.

The finding of Staphylococcus aureus to be the commonest organism to be isolated in the present study is in agreement with Okunola et al. (133) who reported Staphylococcus aureus to be the most commonly isolated organism on wound swabs of DMFU patients in Oshogbo, Nigeria

Zubair et al.(67) in a study in India also reported that Staphylococcus aureus was the most common isolate, accounting for 28%, followed by Escherichia coli 26.6%, Pseudomonas aeruginosa 10.6%, and beta haemolytic Streptococcus spp. 6.6%.

Study by Benkhadoura M et al (136) showed that Staphylococcus aureus was the most common (164, 45.3%) pathogen isolated, followed by Pseudomonas spp. (131, 36.2%). Fungal co-infection was seen in 59 cases (16.3%).

Although the initial mean wound area for the study group was more compared to the control group, on day 15, it is lower than the control group ($p < 0.001$). Wounds were also observed for the presence of granulation and pus. It was observed that the majority of the wounds study groups had reduced pus discharge and exhibited healthy granulation. In contrast, the wound that received conventional treatment comparatively more pus and lesser granulation and required more debridement and dressing changes.

Healing rate of the ulcers in this study when compared between the conventional dressing were found to be statistically significant with healing of more than 40% in the study group and P value of <0.001. The average healing time in study was 24.93±3.38 days while control was 31.97±3.596 days which is significant P<0.001.

Three cases showed complete healing of ulcer by secondary intension in this study, while no ulcer in control group healed completely. It is also observed that the study group was on an average taken up 7 days (p<0001) early for skin grafting as compared to the control group. Study conducted by Priyadarshini LMJ et al on 30 subjects also showed complete ulcer closure in five cases in study group.

	Healing by secondary intension
Our Study	3
Priyadarshini LMJ et al	5

The mean reduction in the ulcer size in the study after 14 days was 42%. This is similar to the LLLT studies conducted by other studies by Priyadarshini LMJ et al and R. K. Mathur et al of 39% and 41% respectively.

In the study, a combination of 660nm and 808nm wavelength of Low level laser was used. Lenifa Priyadarshini M. J et al used single wavelength 660nm low level laser and another study by R. K. Mathur et al also used a single wavelength 660nm low level laser in their study. Both studies reported a mean reduction of 39% and 40% reduction in size of ulcer by the end of 15^{th} day. This is comparable to this study which reported 42% reduction.

	Ulcer Area reduction
Our Study	42 %
Priyadarshini M. J. et al 2018	39%
R. K. Mathur et al 2016.	41 %

The average hospital stay in our study among the study group was 24.9 days with reduction in average hospital stay by 7 days. Other studies by by Priyadarshini LMJ et al showed similar reduction in the hospital stay by average of 6 days.

The study population had Diabetes for a mean age of 11.5 years while the control group had Diabetes for 9.4 years and minimum age of Diabetes was 3yr, suggesting increased incidence of ulcers with years of diabetes.

In this study there was reduction in the hospital stay be mean of 7.04 days i.e 22.02% which is highly significant. Other studies by Priyadarshini M. J. and R. K. Mathur et al report 25% and 20% reduction of mean hospital stay. This result is comparable to the present study and suggests faster recovery of the ulcers with no additional burden. Low level laser therapy provides significant benefit to the diabetic patients, even those with poor glycemic control and slow healing ulcers. All the study cases showed improvement in the ulcer healing, irrespective of the previous healing status suggesting that the low level laser helps in stimulation of granulation and healing even in chronic diabetic foot ulcers.

	Reduced Hospital stay
Our Study	22.02%
Lenifa Priyadarshini M. J. et al	25%
R. K. Mathur et al	20 %

Thus low level laser therapy can be considered as an additional modality in the treatment of diabetic ulcers. As they help in granulation and ulcer contraction without any observable side effects; systemic or local. Addition of low level laser therapy along with the conventional modalities provides good treatment outcomes.

Study conducted by Priyadarshini M. J. and R. K. Mathur et al also reported no significant cost burden along with patient compliance and reduced hospital stay.

SUMMARY

- Most of the patients of Diabetic foot in our study were in the age group of 6th decade and above.
- Mean age of patients in study and control group were almost comparable.
- There is male dominancy in development of diabetic foot.
- There is equivocal distribution of causes of diabetic foot ulcers i.e., following trauma and spontaneous. But since there is loss of peripheral sensations in diabetic patients, minor traumas can be missed by the patient.
- Most common site of Diabetic foot lesions was around the ankle followed by dorsum of foot.
- The risk of diabetic foot increases with increase in BMI and poor Glycemic control.
- Most of the cases in the study have Diabetes between 5 to 10 years.
- Most cultures on admission were sterile followed by S. aureus as most common organism.
- Low level laser therapy facilitates faster granulation tissue fill up compared to conventional dressing.
- LLLT causes significant reduction in surface area of ulcer in a shorter duration.
- LLLT has significantly reduced hospital stay, with early uptake for Skin graft or secondary suturing.
- Majority of patients in our study underwent Split thickness skin grafting.

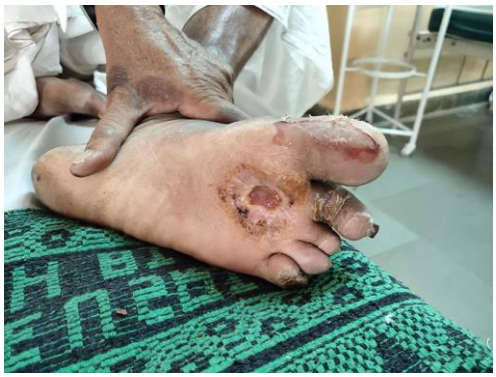
CONCLUSION

Exposure by Low level lasers at the site of ulcer promotes early healing of diabetic foot ulcers.

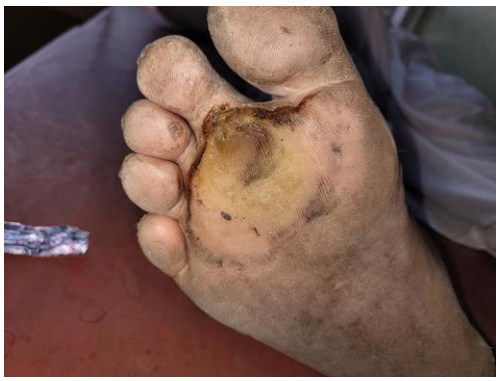
IMAGES TAKEN DURING THE STUDY

CASE-1

Day-1

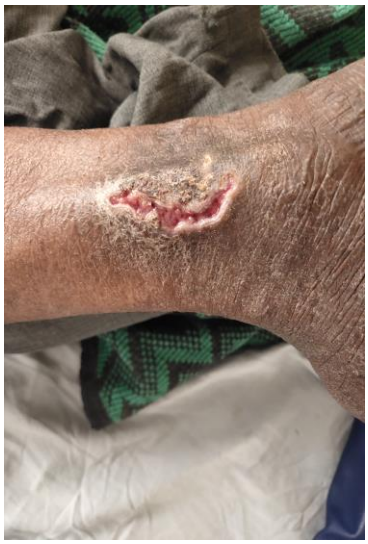


Day-15

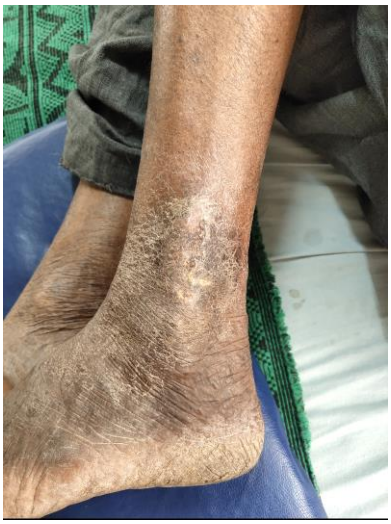


CASE-2

Day-1

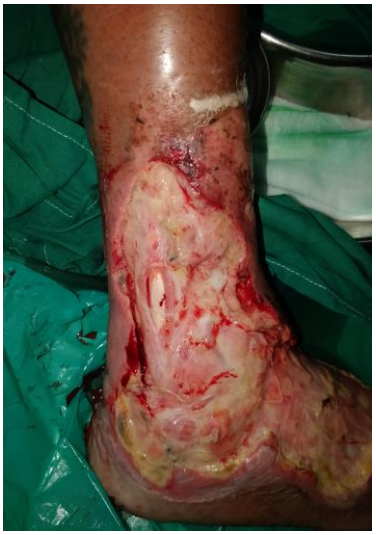


Day-15

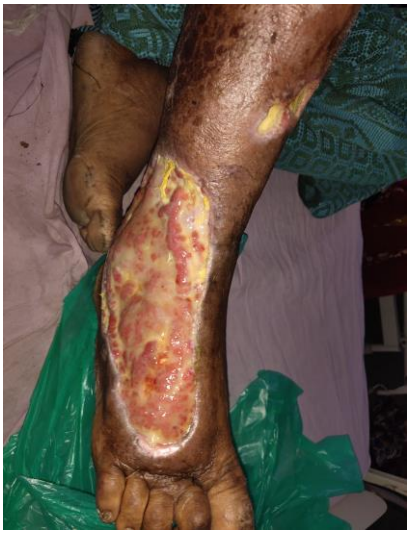


CASE-3

Day-1

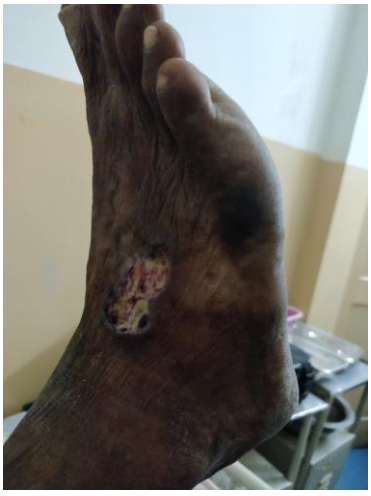


Day-15

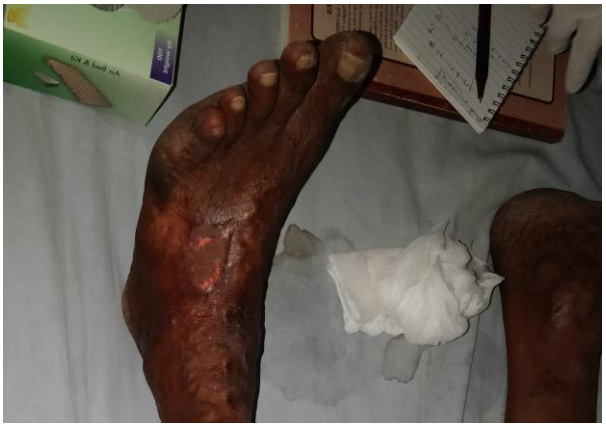


CASE-4

Day-1

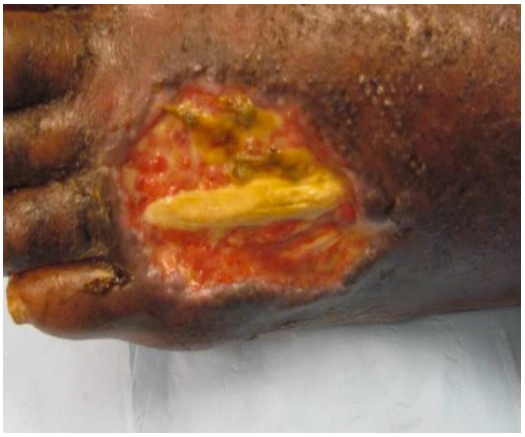


Day-15

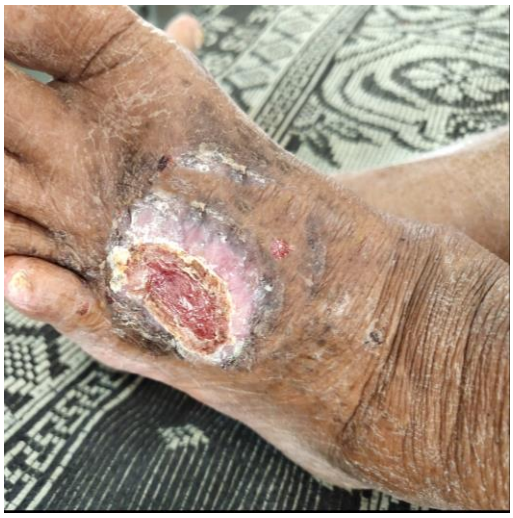


CASE-5

Day-1



Day-15



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ANNEXURES

ANNEXURE I – ETHICAL CLEARANCE CERTIFICATE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/No:286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : Efficacy of low level laser therapy on wound healing in patients with Diabetic foot ulcers.

Name of P.G. Student : Dr Rohit Ghanashyam Vaidya
Department of General Surgery

Name of Guide/Co-investigator: Dr M.S.Kotennavar, Professor of Surgery

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College, VIJAYAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

ANNEXURE II

INFORMED CONSENT FORM

TITLE OF THE PROJECT:

"EFFICACY OF LOW LEVEL LASER THERAPY ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCERS"

NAME OF THE INVESTIGATOR: DR. ROHIT GHANASHYAM VAIDYA

NAME OF THE GUIDE: DR. MANJUNATH. S. KOTENNAVAR

PROCEDURE: LOW LEVEL LASER EXPOSURE TO ULCER BASE AND EDGES ON ALTERNATE DAY BASIS FOLLOWED BY CONVENTIONAL DRESSING FOR 15 DAYS

CONFIDENTIALITY OF RECORDS:

I understand that medical information produced by this study will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of only by a code number. The code key connecting name to numbers will be kept in a

the medical records, but will be stored in the investigator's research file and identified separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time **Dr Rohit Ghanashyam Vaidya** is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me to keep it and for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or

may withdraw consent and discontinue participation in the study at any time without

prejudice to my present or future care at this hospital.

I also understand that **Dr. ROHIT GHANASHYAM VAIDYA**, will terminate my participation in this study at any

time after he has explained the reasons for doing so and has helped arrange for my continued care

by my own physician or therapist, if this is appropriate

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my

participation in this study, if such injury were reported promptly, then medical treatment

would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of

my legal rights.

I have explained to _____ the purpose of this

research, the procedures required and the possible risks and benefits, to the best of my ability

in patient's own language

Date: Dr. M.S.Kotennavar Dr.Rohit Ghanashyam Vaidya

(Guide) (Investigator)

Participant's name: **Address:**

TITLE OF THE PROJECT:

"EFFICACY OF LOW LEVEL LASER THERAPY ON WOUND HEALING IN PATIENTS WITH DIABETIC FOOT ULCERS"

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

_____ _____

(Participant) (Date)

_____ _____

(Witness to signature) (Date)

_____ _____

(Investigator to signature) (Date)

ANNEXURE III

PROFORMA

CASE/CONTROL

NAME: CASE NO.:

AGE: IP NO./ OP NO. :

SEX: DOA:

RELIGION: DOD:

OCCUPATION: WEIGHT: BMI:

ADDRESS:

CHIEF COMPLAINTS WITH HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

- DIABETES MELLITUS:

    Duration

        Treatment

- HYPERTENSION:
- HISTORY OF ANY DRUG INTAKE:

PERSONAL HISTORY:

- DIET:
- APPETITE:
- SLEEP:
- HABITS:

FAMILY HISTORY:

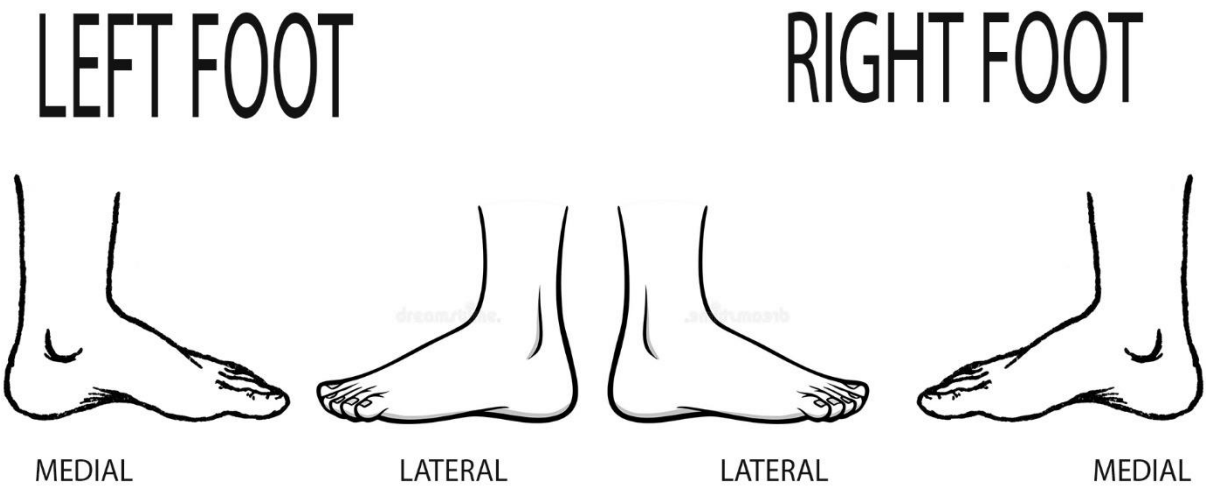
GENERAL PHYSICAL EXAMINATON:

VITALS

- PULSE RATE:
- BLOOD PRESSURE:
- RESPIRATORY RATE:

- TEMPERATURE:

- LOCAL EXAMINATION:



- INSPECTION OF FOOT WITH ULCER

  SITE:

  SIZE:

  SHAPE:

  SURROUNDING SKIN:

  FOOT DEFORMINTY:

  SURFACE AREA OF:

ULER DEPTH OF :

- PALPATION

SENSATION:

FILAMENT:

BIOTHESIOMETER:

PULSATIONS:

HAND HELD DOPPLER:

- PRESSURE POINTS (HARRIS MAT):

CLINICAL DIABETIC FOOT GRADING (WAGNER'S):

OTHER SYSTEMIC EXAMINATION:

- RESPIRATORY SYSTEM:
- CARDIOVASCULAR SYSTEM:
- CENTRAL NERVOUS SYSTEM:
- PER ABDOMINAL EXAMINATION:

INVESTIGATIONS:

- BLOOD HB:

  TC: DC:

  BT: CT:

- URINE ALBUMIN:
- SUGAR:
- MICROSCOPY:
- KETONE BODIES:
- HIV : HBSAg:

- GLYCEMIC LEVELS

  RBS:

  FBS: PPBS:

  HBA1C:

- PUS CULTURE AND SENSITIVITY:

- COLOUR DOPPLER:

- XRAY FOOT AP AND OBLIQUE VIEW:

- ECG:

- ECHOCARDIOGRAPHY (WHENEVER REQUIRED)

FINAL DIAGNOSIS:

FOLLOW UP:

Day 1

Day 15

COMMENTS:

ANNEXURE IV – MASTER CHART

Sr No	Name	Sex	Age (Years)	IP No	Cause of wound	Duration (Years)	Side of Ulcer	Site of Ulcer	BMI	Size in cm^2	Fasting blood sugar (mg/dL)	Post prandial blood sugar (mg/dL)	HbA1c	Sensations	Culture	1ST Day area in cm^2	15th day area in cm^2	Granulation	Ulcer fill-up	Mode of Closure	total duration in days
CASES																					
	Babu	M	60	29316	T	6	R	T	27	6x4	258.8	264.7	7.80	-	EC	24	14	Hl	C	STS	21
2	**Shivappa**	M	42	30363	T	2	L	H	27	8x5	214	236	8.20	+	N	40	23	Hl	C	STS	25
3	**Nanagouda**	M	55	31177	S	8	L	DF	29.1	16x14	186	201	7.60	-	ST	224	130	Uh	P	STS	28
4	**Aniket**	M	30	32596	T	8	R	L	27	18x9	154	202	8.70	+	N	172	100	Hl	C	STS	23
5	**Husen**	M	60	33810	S	Nw	L	T	24	4x2	184	162	8.00	-	P	8	0	Hl	P	SI	24
6	**Ramachandra**	M	45	34682	T	4	R	H	24.3	10x5	212	296	7.20	+	SA	50	32	Hl	C	STS	20
7	**Mallarao**	M	66	42876	S	5	R	T	26	18x12	136	202	8.30	-	N	216	130	Hl	P	STS	22
8	**Kashinath**	M	48	2379	S	5	L	L	25	8X5	182	188	9.60	+	N	40	18	Hl	C	STS	25
9	**Laxmi**	F	65	5926	T	15	R	T	25.9	10X6	182	206	7.60	+	SA	60	22	Hl	C	STS	24
10	**Madiwalapagoud**	M	70	15992	S	9	L	T	24.9	12x10	200.2	212	8.90	-	N	120	60	Hl	P	STS	24
11	**Sadiq**	M	62	15997	S	Nw	L	L	27.8	12x6	128	212	7.60	-	P	72	42	Hl	P	STS	22
12	**Vijay jaganath**	M	47	16297	T	6	R	H	25	8x4	158	200.8	9.50	+	SA	32	0	Hl	P	SI	28
13	**Sachin**	M	50	12420	S	10	L	L	25.1	10x8	174	188	10.2	-	P	80	44	Hl	C	STS	28
14	**Lokesh Indi**	M	60	53474	T	4	L	L	27	6x4	212	263	9.0	+	P	24	0	Hl	C	SS	25
15	**Vadiraj Kittur**	M	63	28371	S	10	L	L	24	8x6	212	254	8.2	+	SA	48	25	Hl	C	STS	30
16	**Devibai Lalu**	F	75	26015	T	4	R	DF	26.1	6x6	254	326	8.78	+	N	36	20	Hl	P	STS	31
17	**Chandrabhaga**	F	70	25560	T	Nw	L	H	24.1	12x10	156	198	8.20	+	SA	120	72	Uh	C	STS	27
18	**Gousiddappa**	M	80	26775	T	8	L	L	24	6x8	188	216	9.90	-	N	48	25	Hl	C	STS	24
19	**Vijaykumar**	M	26	27626	S	4	L	L	23.4	6x6	202	212	8.40	-	SA	36	18	Hl	C	STS	19
20	**Ramu Galave**	M	75	26003	S	10	R	DF	23	3x3	130	162	7.65	-	N	10	0	Hl	C	SI	21
21	**Ishwarappa**	M	60	37084	T	6	R	L	27.1	6x4	156	192	9.30	-	N	24	12	Hl	C	STS	28
22	**Vijaykumar**	M	76	38788	S	12	R	T	24.2	10x4	182	188	8.20	-	N	40	18	Hl	C	STS	24
23	**Sangabassappa**	M	34	40116	T	Nw	L	L	28.3	6x8	136	186	9.70	-	SA	48	22	Hl	C	STS	25
24	**Suresh Pattar**	M	43	40585	S	18	L	L	26.1	5*6	186	200.2	8.90	-	SA	30	12	Hl	C	STS	26
25	**Amogeppa**	M	60	41524	S	9	R	H	24.6	5x3	217	222	9.20	-	N	15	8	Hl	C	STS	28
26	**Basanna**	M	65	67543	T	15	L	L	26.1	5*4	156	182	9.90	-	P	20	9	Hl	C	STS	21
27	**Rajesh**	M	45	67854	T	2	L	L	26.8	3x3	199	207	7.60	-	SA	9	0	Hl	C	STS	21
28	**Sunanda**	F	46	36854	S	8	R	L	26.7	4x4	152	183	11.1	-	N	16	7	Hl	C	STS	23
29	**Prajwal**	M	66	87765	T	7	L	DF	28.1	8x4	168	184	9.2	-	N	32	17	Hl	C	STS	32
30	**Ganesh**	M	61	67546	S	12	R	DF	25.1	7x4	212	234	8.6	-	N	21	11	Hl	C	STS	29

CONTROLS																					
31	**Prakash**	M	35	34536	T	8	R	L	27	13x12	183	219	9.9	-	N	156	120	Uh	C	STS	35
32	**Gangamma**	F	60	37440	S	12	L	T	25.3	10x7	173	186	9.0	-	P	70	60	Hl	No	STS	33
33	**Siddanna**	M	70	41937	S	Nw	R	M	25.3	12x6	158	184	8.4	+	ST	72	58	Hl	No	STS	34
34	**Shobha**	F	35	38959	T	1	R	T	24.7	8x6	138	160	11	-	N	48	39	Hl	No	STS	36
35	**Seetaram**	M	68	5773	S	5	L	L	28	14x10	201	218	9.6	+	SA	140	112	Hl	No	STS	30
36	**Irasangawwa**	F	50	8516	S	8	L	L	26.2	6x6	160	194	8	-	N	36	24	Uh	No	STS	36
37	**Laxman**	M	60	8400	T	9	L	L	25.1	12x10	172	199	6.6	-	ST	120	75	Hl	No	STS	32
38	**Arun**	M	46	21973	T	Nw	R	L	26	12x10	188	206	6.6	-	EC	120	78	Uh	No	STS	30
39	**Nagarjun**	M	80	22796	T	3	R	H	24.9	8x6	178	193	7.5	+	SA	46	30	Uh	No	STS	35
40	**Sangappa**	M	46	5927	S	7	R	L	26.1	6x4	193	211	8.6	-	SA	64	32	Hl	No	STS	35
41	**Lalemasha**	M	65	6066	T	10	R	L	26.2	10x4	156	184	8.0	+	N	40	25	Hl	No	STS	30
42	**Gundappa**	M	70	6662	S	Nw	L	L	25	6x6	162	188	8.2	-	P	36	24	Hl	No	STS	31
43	**Channayya**	M	70	8256	S	12	R	DF	25.2	10x8	139	178	9.2	-	N	80	50	Hl	No	STS	27
44	**Shaila**	F	34	10191	T	6	L	DF	26.2	6x4	153	162	8.2	-	N	24	0	Hl	No	SS	28
45	**Mallappa**	M	40	60493	T	7	R	H	28	8x6	148	184	9.9	+	N	46	28	Uh	No	STS	33
46	**Kashinath**	M	63	26818	S	9	R	DF	25.6	12x10	219	233	7.4	-	SA	120	86	Uh	P	STS	29
47	**Gagganath**	M	65	25544	T	8	R	L	25.6	8x6	170	201.2	7.0	+	P	46	32	Hl	No	STS	29
48	**Rayappa**	M	65	27607	S	Nw	R	L	26	8x6	155	188	8.3	+	SA	46	34	Hl	No	STS	31
49	**Shivappa**	M	75	28450	T	12	L	DF	24.8	10x6	177	194	9.3	+	ST	60	40	Hl	P	STS	29
50	**Huvappa**	M	75	25554	T	12	L	L	26.1	10x4	160	178	8.7	-	SA	40	32	Hl	C	STS	32
51	**Manjunath**	M	76	37158	S	10	R	L	26.1	10x6	132	184	8.4	-	SA	60	40	Uh	P	STS	34
52	**Vishwanath**	M	48	39703	T	8	R	DF	27.3	6x4	144	165	8.6	-	N	24	15	Hl	No	STS	38
53	**Nagappa**	M	54	54	T	Nw	R	H	24.8	6x8	152	178	7.2	+	SA	48	36	Hl	P	STS	34
54	**Basayya**	M	75	40633	T	9	L	L	26.3	6x6	187	160	8.2	-	P	36	22	Uh	P	STS	32
55	**Ramnath**	M	60	42423	T	4	L	DF	26.1	6x4	212	296	9.2	-	SA	26	18	Hl	No	STS	37
56	**Sangamesh**	M	61	84545	S	10	L	L	27.2	8x6	130	162	8.6	-	N	46	29	Hl	P	STS	35
57	**Alfat**	M	45	87543	T	6	L	H	27.1	6x4	153	162	8.2	-	N	24	15	Hl	No	STS	35
58	**bhagesh**	M	54	637865	S	9	R	L	26.8	8x8	219	233	7.4	-	SA	64	40	Hl	P	STS	30
59	**kushalappa**	M	55	87656	S	9	R	L	26.2	6x4	219	233	7.4	-	SA	24	14	Hl	No	STS	28
60	**Ibrahim**	M	56	67980	S	9	R	L	26.7	10x6	219	233	10.4	-	SA	60	42	Hl	P	STS	21

KEY TO MASTER CHART

1. **Sex:** M- male
   F- Female
2. **Cause of wound:** Tr- Trauma
   S- Spontaneous
3. **Site of Ulcer:** M- Metatarsal
   H- Heel
   L- Leg
   T- Toe
   DF- Dorsum of foot
4. **Mode of Closure:** SI- Secondary Intention
   SS- Secondary Suturing
   STS- Split thickness skin Grafting
5. **Ulcer fill-up:** C- Complete P- Partial
6. **Granulation:** Hl- Healthy Uh- Unhealthy
7. **Nw:** Newly Diagnosed case of Diabetes