Screening Tests For Neuropathy In Diabetic Patients With "Foot At Risk"

by

DR.NINGAPPA SOGALAD

Dissertation submitted to

In partial fulfillment for the degree of

MASTER OF SURGERY

IN

GENERAL SURGERY

Under the guidance of

DR MANJUNATH KOTENNVAR. M.S.(SURG)

PROFESSOR

DEPARTMENT OF GENERAL SURGERY

BLDE (DEEMED TO BE UNIVERSITY)

SHRI B. M. PATILMEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE

VIJAYAPUR – 586103

2019

LIST OF ABBREVATIONS

AGE	Advanced glycation end products
AKT	ATP dependant tyrosine kinase
DFU	Diabetic Foot Ulcer
DM	Diabetes mellitus
DNE	Diabetic Neuropathy Examination score
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
GTT	Glucose tolerance test
HbA1C	HaemoglobinA1C
HFMI	Harris mat foot imprint
IDF	International Diabetes Federation
IGF-1	insulin-like growth factor 1
LDI	Laser Doppler imaging
MCR	Microcellular rubber
MMP	Matrix metalloproteinase
NCV	Nerve conduction velocities
NCS	nerve conduction study

NOS	NO synthase
NO	Nitric oxide
NPV	Negative predictive value
PDGF	Platelet-derived growth Factor
PKC	Protein kinase C activation
PPV	Positive predictive value
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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Title: SCREENING TESTS FOR NEUROPATHY IN DIABETIC PATIENTS WITH "FOOT AT RISK"

Background and objectives: Diabetes mellitus (DM) is one of the public health problems of the whole world. Prevalence of DM is increasing rapidly worldwide and it is reaching the epidemic proportions. Diabetes leads to many macro vascular complications like coronary artery diseases, peripheral vascular disease, stroke etc. And it also causes micro vascular complications leading to end organ damage like cardiomyopathy, nephropathy, retinopathy and neuropathy. This study is about selecting proper tools to identify tests for neuropathy in diabetic patients with "Foot at risk".

Methodology: Observational analytical study conducted among 40 patients with h/o diabetic foot ulcer (Group A) and 120 patients without h/o diabetic foot ulcer (Group B) with Diabetes Mellitus attending Surgery/Medicine OPD or admitted in Surgery/Medicine wards during the study period from October 2017 to May 2019 were considered in the study. Data analyzed using SPSS software version 16. The association between the DM and neuropathy was tested using Chi-square test and Fisher's exact test. p value <0.05 was considered as significant. Sensitivity, specificity, positive predictive value, negative predictive value, % of false positive, % of false negative and accuracy of the screening test were calculated.

Results: The mean age of the study participants in Group A was 59.25 ± 12.22years and that of Group B was 61.98 ± 10.65years. Illiteracy, co-morbidities like Hypertension, Dyslipidemia and Heart disease were associated with patients of Group A. As the duration of diabetes (>10years) increases the probability of foot ulceration was more. Probability of getting foot ulceration was more among

patients with uncontrolled diabetes. DPN diagnosis by verbal questionnaire method showed the sensitivity of 87.5% & specificity of 91.67%. By Semmes-Weinstein 10G monofilament wire testing showed the sensitivity of 75% & specificity of 77.5% and by Biothesiometer showed the sensitivity of 72.5% and specificity of 86.67%.

Conclusion: Annual screening of diabetic patients for diabetic neuropathy by verbal questionnaire method had the higher sensitivity and specificity, followed by Semmes- Weinstein 10G monofilament wire testing and Biothesiometer.

Key words: Diabetes mellitus, Screening, Diabetic neuropathy, Micro vascular complications

INTRODUCTION

Diabetes mellitus (DM) is one of the public health problems of the whole world. Prevalence of DM is increasing rapidly worldwide and it is reaching the epidemic proportions.[1,2]According to International Diabetes Federation (IDF), it was estimated that 82million adults aged 20-79years are living with DM in South East Asia region in 2017.[3] In India, population of people with diabetes was around 50.8 million in 2010 and is excepted to be up to 87 million by 2030.[4]

Diabetes leads to many macro vascular complications like coronary artery diseases, peripheral vascular disease, stroke etc. And it also causes micro vascular complications leading to end organ damage like cardiomyopathy, nephropathy, retinopathy and neuropathy. The various forms of diabetic neuropathy include peripheral neuropathy, mononeuropathy, polyneuropathy multiplex, 3rd cranial nerve palsy, thoraco-abdominal neuropathy and diabetic autonomic neuropathy.[5]

Diabetic Foot Ulcer (DFU), being devastating chronic complication of DM and it is actually a complex triad of neuropathy, ischemia, and infections. DFU has shown an increase in the trend over previous decades. About 15% of patients with diabetes are estimated to suffer from DFU during their life time. [4]It is difficult to obtain accurate figures of prevalence of DFU, however the previous studies have shown the prevalence of this complication to be around 4%- 27 %. [6-8]

DFU is a major source of morbidity and leading cause of hospitalisation in patients with diabetes. It is estimated that approximately 20% of hospital admissions are the result of DFU among the diabetic patients.[9] If untreated, DFU may progress and ultimately may lead to amputation. Also, DFU is associated with substantial emotional and physical distress.[9]

Peripheral sensory neuropathy is one of the strongest risk factors for foot ulceration and amputation in diabetic patients. Peripheral neuropathy also forms a permissive environment that allows repetitive tissue injury. Peripheral neuropathy includes sensory, motor and autonomic neuropathy. The notion that neuropathy is generally necessary to produce diabetic foot ulcer is well established. However, the methods for testing and identification of loss of protective sensation have been quite variable and ill defined.

This study is about selecting proper tools to identify tests for neuropathy in diabetic patients with “Foot at risk”. Here “Foot at risk” means foot of diabetic patients which are at risk of developing diabetic foot ulcers mainly as a result of diabetic neuropathy, ischemia, immunopathy and high-pressure points.

Hence, with diabetes mellitus being so prevalent in India, it is important to have a clear-cut strategy on assessing neuropathy and determining which group of patients are at risk of developing diabetic foot ulcer so that proper preventive measures can be taken. Very few studies are conducted to identify proper tools for the screening of neuropathy in diabetic patients. Therefore, the present study has been undertaken.

AIMS AND OBJECTIVES

AIMS

To identify proper tools for screening of neuropathy in diabetic patients with "foot at risk".

"Foot at risk" means foot of diabetic patients which are at risk of developing diabetic foot ulcers mainly as a result of diabetic neuropathy, ischemia, immunopathy and high-pressure points.

OBJECTIVES

To assess the sensitivity, specificity and prediction value of **3 tests** for diabetic neuropathy;

1. Question verbal neuropathy score.
2. Semmes-Weinstein 10 G monofilament wire testing.
3. Vibration perception threshold testing by Biothesiometer.

REVIEW OF LITERATURE

The modern term “Diabetes mellitus” was mentioned in ancient times as “Madhumeha”, which shows the prevalence of diabetes in India even before 2500 BC. Though, there is no evidence about the prevalence of the disease, a recent article hypothesized that even in ancient times it could have been quite common in India. [4]

Diabetic peripheral neuropathy is defined as "the presence of signs and/or symptoms of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".[4]

Patients with type 2 DM may present with the history of distal polyneuropathy associated with few years of poor glycemic control. Most of the times, the patients would have already developed neuropathy at the time of diagnosis. Thus, the onset of diabetic peripheral neuropathy is early in type 2 diabetes mellitus.

As diabetic peripheral neuropathy can lead to serious consequences including disability and amputation, it has to be diagnosed at the earliest. These patients require more frequent follow-up, proper foot examination and the need for regular self-care.

ANATOMY OF FOOT [10]

The human foot provides the mechanical complex and the structural strength to the body. Ankle acts as the foundation, a propulsion engine and a shock absorber. 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 together.
- Nerves, blood vessels, skin and soft tissue.
- These structures work together to provide mobility, balance& support to the body. A structural flaw or malfunction in any one part can result in the problem elsewhere in the body.

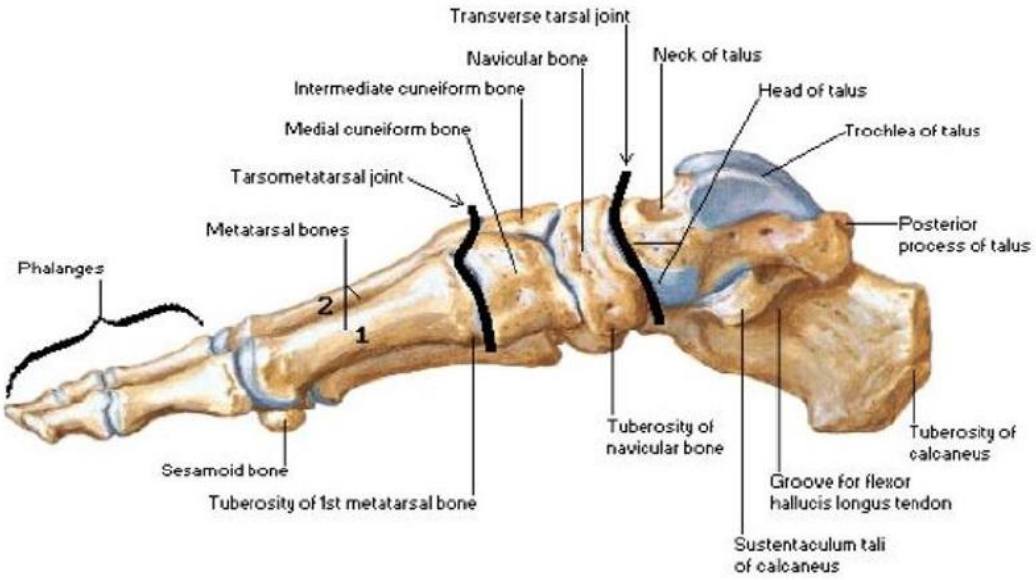


Figure 1: BONES - MEDIAL VIEW

SKIN

Skin of the dorsum of the foot (hirsute) is thin and highly flexible, containing hair follicles, sweat glands and scanty sebaceous glands. 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 over those points which are weight baring viz. heel, ball of big toe and the lateral margins of sole. It has no hair follicles and sebaceous glands but sweat glands are numerous. Hypodermis is composed of loose areolar connective tissue, most of this is collagenous and elastic fibres running parallel to the surface of the skin, but some are continuous with the fibres 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:

The dorsum of the foot has the thin layer continuous above with inferior extensor retinaculum and at the sides of the foot it blends with plantar aponeurosis and anteriorly it en-sheathes the dorsal tendons.

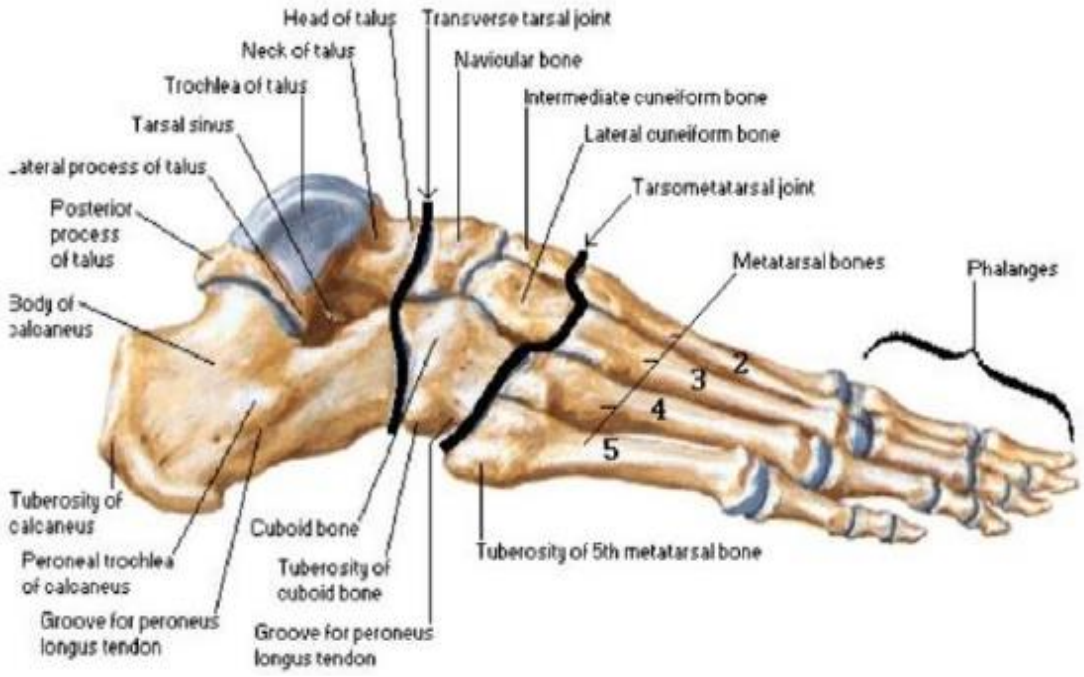


Figure 2: BONES - LATERAL VIEW

Plantar aponeurosis:

Cover the whole length of the sole. It arises posteriorly from the medial and lateral tubercles of calcaneus from the back of that bone below the insertion of the tendo-calcaneus. It spreads out over the sole and is inserted by five slips into each of the five toes. The 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 phalanges and their connecting long bones are known as metatarsals. Each phalanx is made of several small bones. Hallux, the big toe has two phalanges, two interphalangeal joints and two sesamoid bones that enable it to move up and down. The remaining four phalanges have three bones and two joints each. The phalanges are connected to the metatarsals by five metatarsophalangeal joints. The forefoot bears half of the body weight and also balances pressure.

The Midfoot:

It forms the arch of foot 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 it links the midfoot to the ankle (talus). The top of the talus is connected to two long bones of the lower leg (tibia and fibula), forming a hinge which allows the foot to move up and down. Calcaneus, the heal bone is the largest bone of the foot and joins 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 calcaneus, talus, navicular, cuneiforms, and first three metatarsals. The lateral longitudinal arch is composed of calcaneus, cuboid and fourth and fifth metatarsals. The transverse arch is composed of cuneiforms, cuboid and the five metatarsal bones. In addition, muscles and tendons plays an important role in supporting the arches.

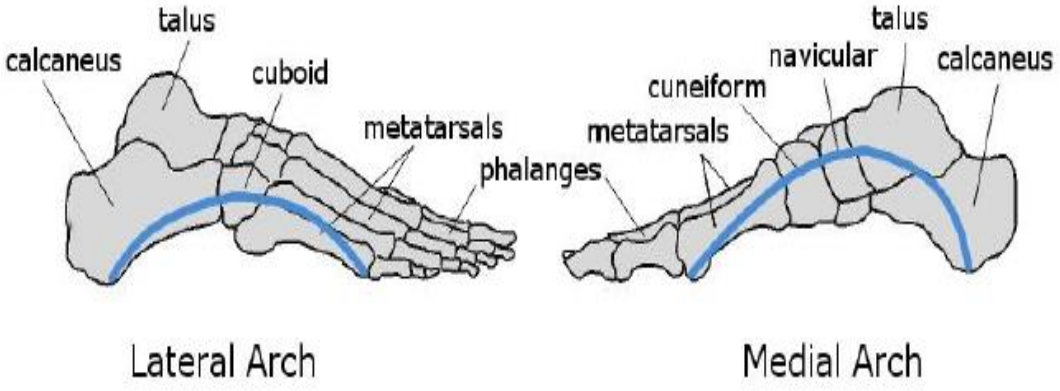


Figure 3: ARCHES OF FOOT

Muscles, Tendons and Ligaments:

There are 20 muscles in the foot that give shape to the foot by holding the bones in position and they 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 digitorum 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 and numerous muscular and cutaneous branches

Lateral Plantar Artery:

It is the largest 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 lateral four toes and lateral aspect of the little toe.

Dorsalis Pedis Artery:

In the sole, between the two heads of the first dorsal interosseous muscle, the dorsalis pedis artery joins to the lateral plantar artery, forming the first plantar metatarsal artery. **Veins of the Sole of the Foot:**

Foot is drained by the medial and the lateral plantar veins, which unite behind the medial malleolus to form posterior tibial venae comitantes.

Nerves of the Sole of the Foot:

Medial Plantar Nerve:

Terminal branch of the tibial nerve is the medial plantar nerve which gives muscular branches to the abductor hallucis, flexor digitorium brevis, 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:

It is another terminal branch of tibial nerve.

Branches:

1. From the main trunk to the quadratic plantae and abductor digiti minimi; cutaneous branches to the skin of the lateral aspect of the sole.

2. From the superficial terminal branch to the flexor digiti minimi and the interosseous muscles of fourth intermetatarsal space.

3. From the deep terminal branch supplies to the abductor hallucis; the second, third and fourth lumbricals; and to all the interossei, except those in the fourth intermetatarsal space.

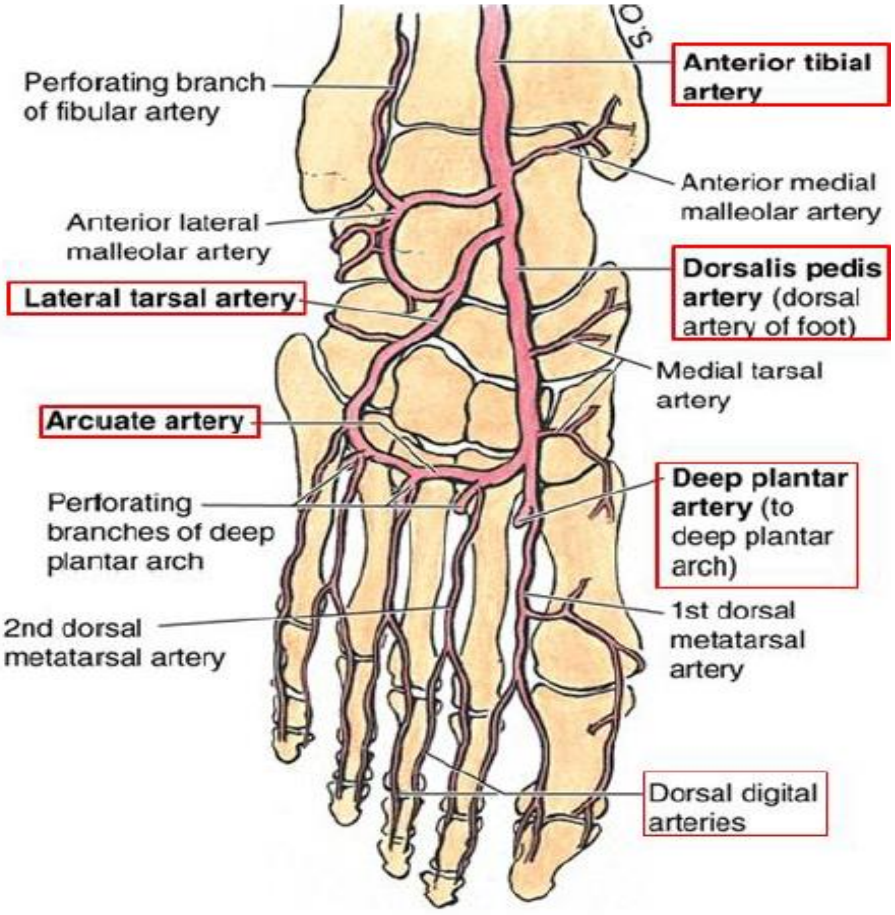


Figure 4: ARTERIAL SUPPLY OF FOOT

Dorsal venous arch:

The dorsal venous arch drains in to the great saphenous vein. The great saphenous vein leaves the dorsum of the foot by ascending along the leg in front of the medial malleolus. The short saphenous vein lies behind the lateral malleolus.

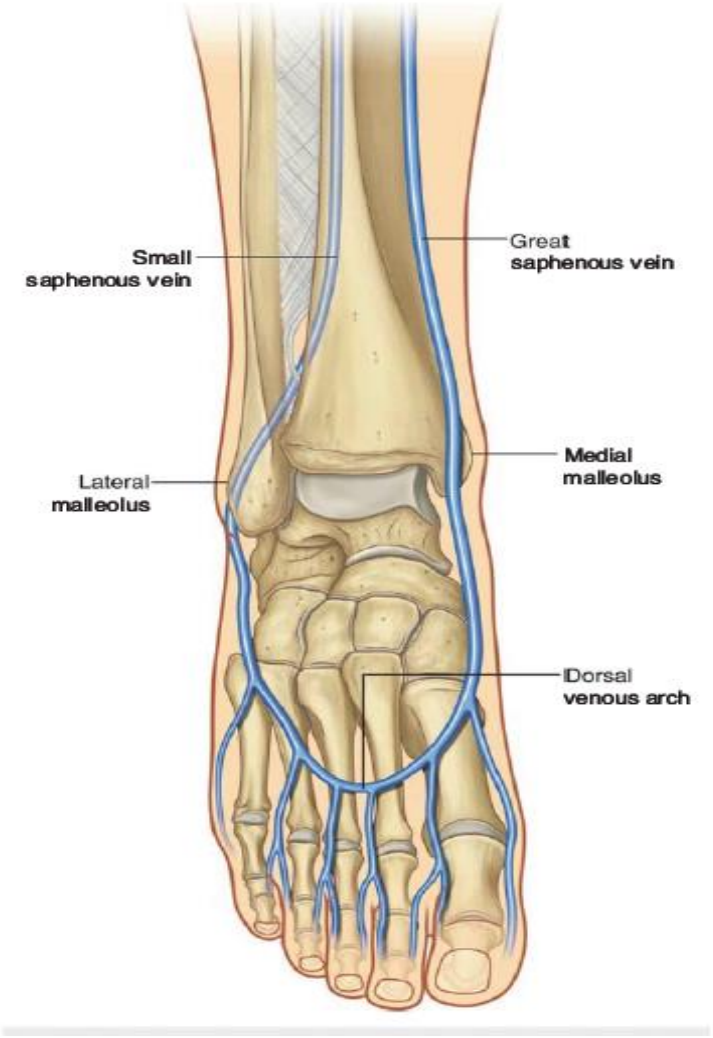


Figure 5: SUPERFICIAL VEINS OF FOOT

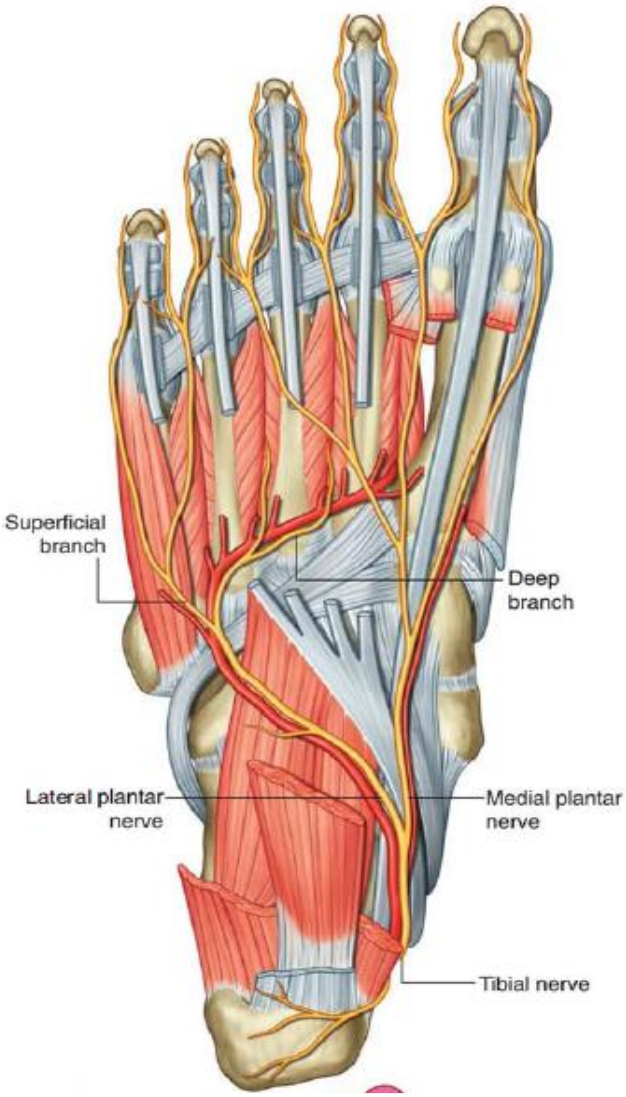


Figure 6 : Nerve supply of foot.

Spaces of the Foot:

Infections in the foot can be approached and drained effectively. Grodinsky has emphasized the clinical importance of the 4 median fascial spaces of the plantar aspect of the foot and the 2 dorsal spaces.

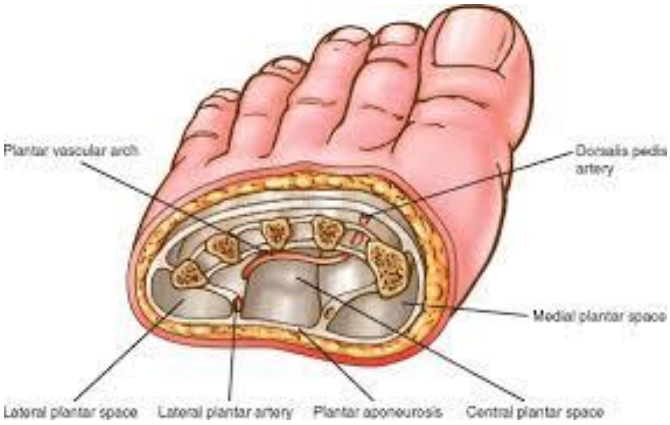
Four median Plantar Spaces:

1. The first space is located between the plantar aponeurosis and flexor digitorum brevis.

2. The second space is between the flexor digitorum brevis and conjoined long flexor tendons and quadrates plantae.

3. The third space is between the flexor digitorum longus (with its associated lumbricals muscles) and the oblique head of the abductor hallucis.

4. The fourth deepest space is between the oblique head of the abductor hallucis muscle and the 2nd and the 3rd metatarsal bones and their interosseous muscles.



Cross-section of foot
1 – 5: metatarsal bones
A: central plantar space
B: deep interosseous (dorsal) space
C: lateral plantar space
D: medial plantar space
9 foot compartments; all interconnected

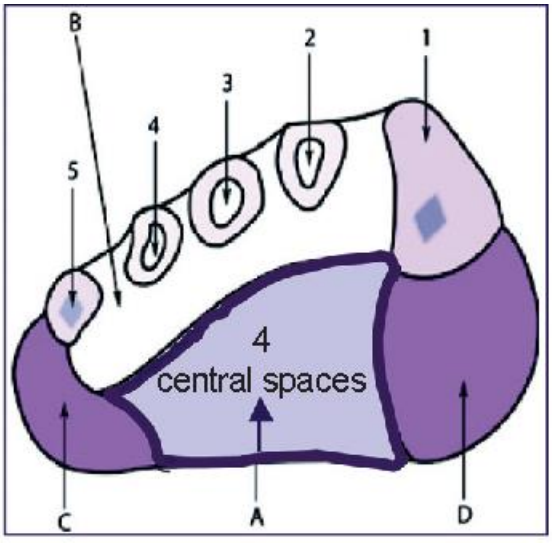


Figure 7: CROSS SECTION OF FOOT

These spaces are bound both laterally and medially by dense connective tissue septa, any infection may travel from one space to another. The sheaths of the entire flexor

tendon extend from the toes and to the proximal part of the distal head of metatarsal bones; therefore, within these sheaths, infection may remain local or break into one of the four spaces. The 3rd layer of 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 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 to the heads of the metatarsal bones in the front.

Walking:

As the body weight is thrown forward, the weight is borne on the lateral margin of the foot and the heads of 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 and the body is then thrown forwards

1. By the actions of gastrocnemius and soles (and plantaris) on the ankle joint, using foot as a lever.
2. Also by the toes which is strongly flexed by the long and short flexors of the foot, proving the final thrust forward.

The lumbricals and the interossei contract to keep the toes extended so that they do not fold under pressure because of the strong action of the flexor digitorum longus. In this action, the long flexor tendons assist for Plantar flexing of 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.

EPIDEMIOLOGY:

The wide variation in prevalence of symmetrical diabetic polyneuropathy is because of lack of consistency in criteria for the diagnosis, variable methods used in the selection of patients for study, and differing assessment techniques. In addition, careful neurologic examination is extremely important because many patients with DPN are initially asymptomatic. Additional diagnostic techniques, such as autonomic or quantitative sensory testing, may help in a higher recorded prevalence. [13,14]

In a cohort study conducted by Pirart et al, out of 4400 Belgian patients with DM, 7.5% patents had already developed neuropathy at the time of diagnosis of diabetes. After 25 years, the number with neuropathy raised to 45%. In United Kingdom, the prevalence of diabetic neuropathy among the hospital clinic population was noted to be around 29%. [15]

Sex difference in diabetic neuropathy: Both women and men are affected equally. Males with type 2 diabetes are prone to develop diabetic peripheral neuropathy earlier than female patients and morbidity due to neuropathic pain is more in females than in males.

Diabetic neuropathy and advancing age: Though diabetic neuropathy can occur in any age, it is more commonly seen in elderly and with increase in duration & severity of diabetes.

ETIOLOGY:

The following are the risk factors [16,17]:

- Prolonged hyperglycemia
- Increase in age
- Hypertension
- Duration of DM
- Dyslipidemia
- Smoking
- Increase in alcohol intake
- HLA DR 3/4 phenotypes.

Peripheral neuropathies in patients with primary DM which includes both type 1 and type 2 and secondary diabetes of various causes, suggest that hyperglycemia as a common etiological mechanism. This thought has been proven by strong support from the Diabetes Control and Complications Trial (DCCT). The association between peripheral neuropathy and impaired glucose tolerance has developed as further evidence of a dose-dependent effect of hyperglycemia on nerves, although relationship remains an area of some controversy for type 2 diabetes and prediabetes. [18,19]

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY:

The factors which precipitate the development of diabetic neuropathy are not clearly understood, and several hypotheses have been proposed. [20-22] It is accepted to be a multifactorial process. Symptoms developing in DPN depend on multiple

factors such as total hyperglycemic exposure and other risk factors such as elevated lipids, blood pressure smoking and high exposure to other potentially neurotoxic agents such as ethanol. Genetic factors may also play a role. [16]

Other important biochemical mechanisms in the development of the symmetrical forms of diabetic neuropathy likely include

1. Advanced glycation end products
2. Oxidative stress
3. Nitric oxide reactivity to blood vessels
4. Polyol pathway
5. Other contributing factors.

Advanced glycation end products: Advanced glycation end products (AGE) are formed because of non-enzymatic reaction of glucose which are in excess with proteins, nucleotides, and lipids. These products interfere with nerve cell metabolism and axonal transport and thus play a role in disrupting neuronal integrity and repair mechanisms. [23]

Oxidative stress: In diabetes, there is increased production of free radicals formed via several mechanisms that are poorly understood. These free radicals cause direct damage to blood vessels which compromise the blood supply and lead to nerve ischemia and facilitation of AGE reactions. Though the mechanisms underlying this process are poorly understood, use of the antioxidant alpha-lipoic acid may hold promise for improving neuropathic symptoms. [24,25]

Nitric oxide reactivity to blood vessels: Nitric oxide (NO) is a key regulatory molecule with broad metabolic, vascular, and cellular effects. [26,27] Activation of NO synthase (NOS) is under insulin control through the AKT (ATP dependent tyrosine kinase) pathway, the regulation of NO metabolism is important in

diabetics. NO generation disturbance because of insulin resistance may also affect the vascular response. [28] Hyperglycemia play a key role in the decreased NO production in type 2 diabetes because high glucose per se inhibit endothelial NOS activity through a protein kinase C–associated mechanism. [29]

DM-2 induces endothelial dysfunction by reducing the bioavailability of endothelial cell-derived NO. eNOS (endothelial nitric oxide synthase) is an important target for high glucose adverse effects on EPC (endothelial progenitor cells) number and activity. eNOS deactivation in diabetic EPCs resulted in excessive superoxide anion production and in reduced NO. An inverse relationship exists between the reduced NO bioavailability in EPCs and the patients' plasma glucose and HbA1c levels. This reduction in NO bioavailability could be attributed to enhanced oxidative stress in DM-2 patients, which is known to damage the protein signaling pathways that lead to NO production. [30]

Related contributing factors: The other co-contributors to these disturbed biochemical processes include altered gene expression which causes altered cellular phenotypes, changes in cell physiology which alters endoskeleton structure or cellular transport, reduction in neurotrophins, and nerve ischemia. [31] Thus in future, pharmacologic intervention targeting one or more of these mechanisms may be successful. Vascular injury and/or autoimmunity plays a major role in the pathogenesis of diabetic neuropathy. [32]

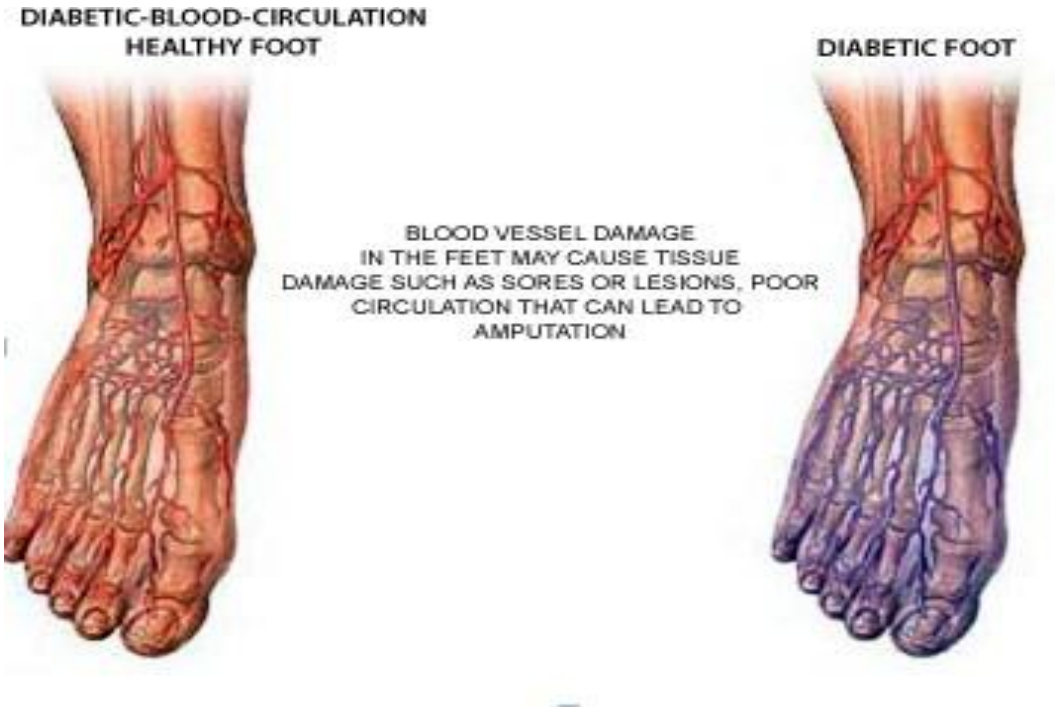


Figure 8: DIABETIC FOOT

SYMPTOMS:

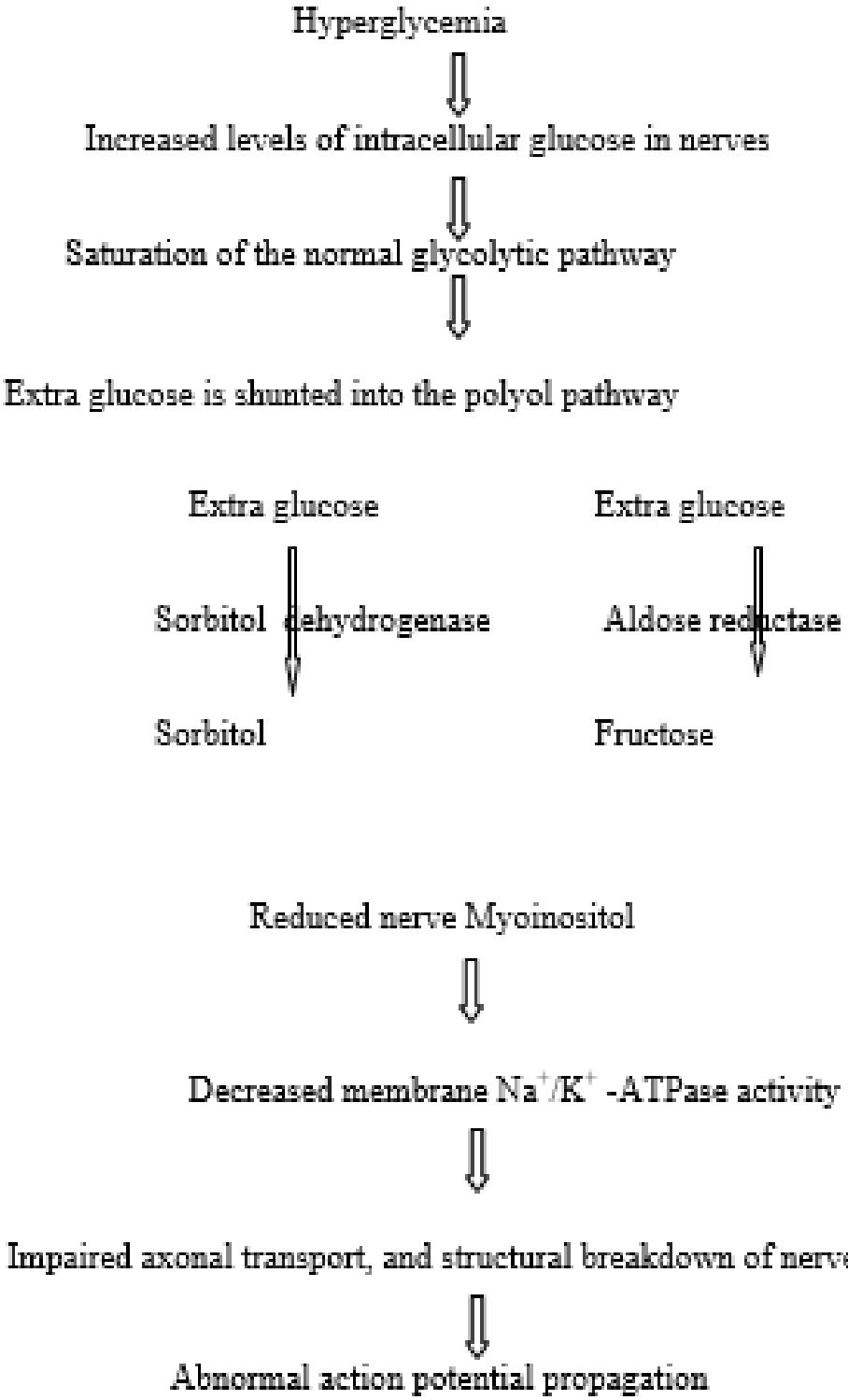
Tingling, numbness, prickling, pins and needles, burning sensation, cold, buzzing, deep stabs, cramps, exaggerated sensitivity to touch. These symptom often worsen at night.

Touch sensitivity: There will be increased sensitivity to touch, tingling or numbness in the feet, toes, legs or hands.

Muscle weakness:

Chronically elevated blood sugars will cause damage to the nerves and also the muscles supplied by them, which leads to muscle weakness. Hence patients complain of difficulty in walking and also in grabbing things.

Polyol pathway [33]



Thus to improve nerve conduction aldose reductase inhibitors are used[34].

Balance problems: Patients may feel unsteady gait or uncoordinated when they walk. This is due to the muscle damage.

Foot ulcers:

Diabetic foot ulcers are classified according to **Wagner's grading** as follows

Grade 1: Superficial Diabetic Ulcer

Grade 2: Ulcer Extension

a. Involves ligament, tendon, joint capsule or fascia

b. No abscess or Osteomyelitis

Grade 3: Deep ulcer with abscess or osteomyelitis

Grade 4: Gangrene to portion of forefoot

Grade 5: Extensive gangrene of foot

PROGNOSIS:

Morbidity and complication rates are more in patients with uncontrolled sugar levels as compared with the patients with controlled diabetes. Repetitive injuries in the affected areas may lead to skin breakdown, infection and progressive ulceration resulting in amputation and death.

PREVENTION OF DIABETIC NEUROPATHY:

The following steps may prevent or slow the progression of diabetic neuropathy.[34]

- Control hyperglycemia
- Normal blood pressure
- Regular Exercise
- No smoking
- Limited amount of alcohol intake
- Healthy diet and normal weight

DIABETIC PERIPHERAL NEUROPATHY – DIFFERENTIAL DIAGNOSIS

- Vitamin B-6 intoxication
- Pernicious anaemia
- Uraemia
- Alcoholism
- Chemical toxins
- Nerve entrapment and compression of benign etiology
- Hepatitis
- Idiopathic
- Congenital (various hereditary sensory motor neuropathies)
- Para neoplastic syndrome
- Syphilis
- HIV/AIDS
- Medication (e.g., chemotherapy, isoniazid)
- Spine disease (e.g., radiculopathy, stenosis, arteriovenous [AV]fistula)

SCREENING AND INVESTIGATIONS:

- Hemoglobin A1c and fasting plasma glucose
- Nerve conduction study
- Semmes Weinstein monofilament
- Vibration perception threshold using Biothesiometer
- Neuropad, a new indicator test
- Skin biopsy
- Plantar thermography
- Scoring systems eg; Diabetic neuropathy symptom score, neuropathy

disability score, neuropathy symptom score etc.

HemoglobinA1C and fasting plasma glucose

HaemoglobinA1C (HbA1C) and fasting blood glucose constitute important laboratory screening tests. HaemoglobinA1C measurement reflects the adequacy of recent diabetes control; that is past three months which in turn is lifespan of RBC. These levels are mostly elevated in patients with diabetic neuropathies.

A glucose tolerance test (GTT) may be more helpful in borderline cases. Urine analysis is also helpful to screen for nephropathy and proteinuria.

American Diabetes Association has recommended annual foot exam of diabetic neuropathy. To evaluate a patient for neuropathy, clinicians need to ask patients about signs and symptoms, perform a thorough physical exam, including deep tendon reflexes, motor strength and vibration; as well a nerve conduction velocities (NCV), a diagnostic test.

Nerve conduction study:

A nerve conduction study (NCS), also called a nerve conduction velocity (NCV) test- it is the procedure to measure the speed of electrical impulse conduction through a nerve. This procedure determines whether nerves are normal/nerve damage and destruction.

The nerve conduction velocity is related to the diameter of the nerve and the degree of myelination. There is an insulation around the nerve by the myelin sheath. A nerve which is functioning normally transmits the impulses stronger and faster than a damaged nerve. Normal conduction velocity will be in the range of approximately 50 to 60 meters per second and it may vary between individuals and

also between different nerves. NCS help to detect the presence, location, and extent of diseases that damage the nerves.

NCS helps in the evaluation of following diseases or conditions like

- Guillain-Barré syndrome
- Carpal tunnel syndrome
- Charcot-Marie-Tooth disease
- Herniated disk disease
- Chronic inflammatory polyneuropathy and neuropathy
- Sciatic nerve problems
- Peripheral nerve injury

Pattern of nerve damage will be depicted in nerve conduction studies. In patients with diabetes, even in absence of clinical symptoms of neuropathy, the nerve conduction studies show abnormalities. Few studies have shown that, the severity of electro physiologic abnormalities is proportional to the clinical symptoms and it also predicts the morbidity related to diabetes. Tkac found in 1998 that, NCV levels could improve with glycemic control. These studies are the most sensitive, reliable and reproducible measure of nerve function.

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. This was done in the year 1960. Inability to sense 5.07/10g Semmes Weinstein monofilament will be considered as loss of protective sensation.

Monofilament gauge is derived from the logarithm of the applied force in milligrams and the value is fixed to be 5.07.[35] The buckling force of 10grams for

the 5.07 monofilament, which was the force felt by the patient when the monofilament bends.

Monofilaments, also known as Semmes-Weinstein monofilaments, were originally designed to diagnose sensory loss associated with leprosy. [36] Semmes Weinstein monofilament examination is a low cost, non-invasive, rapid and easy to apply test often used in clinical testing and for self-assessment.[37] Pressure sensation loss using the 10g monofilament has high predictive value of ulceration. [38] All over the world it is accepted that 10 g monofilament is a screening tool for sensory loss and it is also proved to be efficient in number of studies. [39,40] The use of 5.07/10 g SWMF is generally accepted but there is no standard method for application of SWMF.

The other drawback was there are no guidelines for the application of monofilaments. The same is depicted in the other research studies. Young and Booth, in their studies identified that filaments manufactured by some companies did not buckle at 10g of force. But some filaments buckled at <8 g and could give erroneous results.

Vibration perception threshold:

Degeneration of intra-epidermal nociceptors [C-fibres and A-delta fibres] leads to pain insensitivity. These fibres conduct the vibration impulses undergo axonal degeneration with subsequent lack of function. [41, 42] Hence the patients present with loss of vibration sensation in diabetic neuropathy. So, measuring the vibration perception at the feet is a test recommended for diabetic neuropathy. [43,44] So the assessment of VPT is the one of the recommended standardized sensory testing methods in the diagnosis of diabetic neuropathy. Elevated VPT is an effective

predictor of neuropathic foot ulceration, the most common cause for hospital admission and amputation of lower limb among the patients with diabetes. [45]

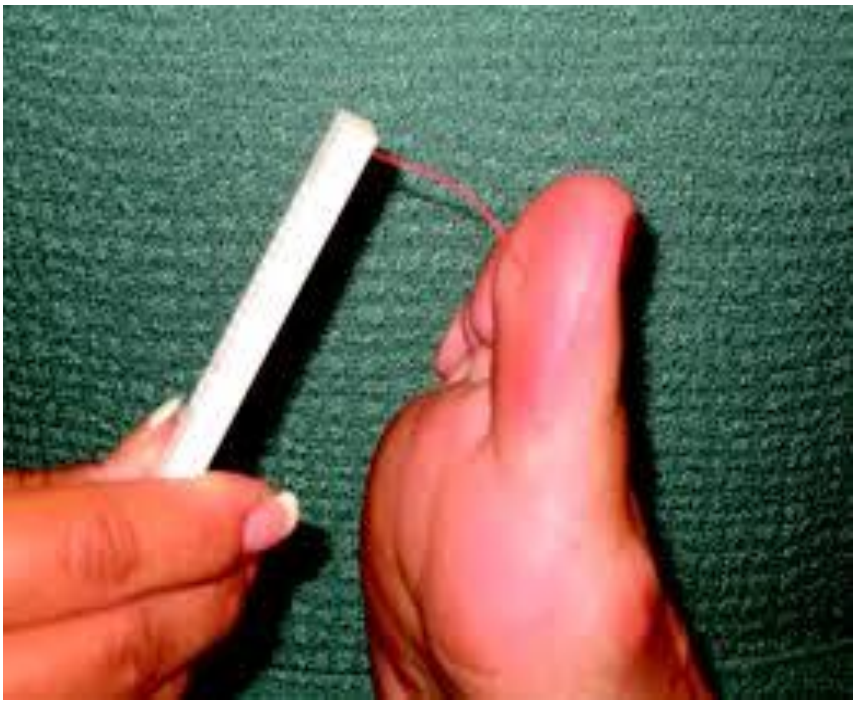


Figure 9: SEMMES-WEINSTEIN MONOFILAMENT

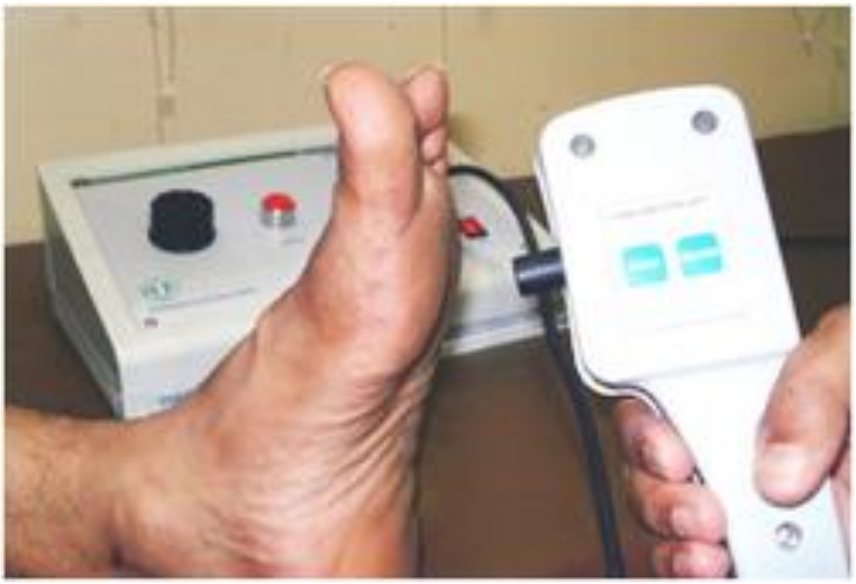


Figure 10: BIOTHESIOMETER

Studies have shown that VPT was simple, reliable and this has led biothesiometer[46,47] comparable to NCS in diagnosing peripheral neuropathy.

Biothesiometer: A Biothesimeter is a semiquantitative tool to assess large fiber neuropathy. It was devised by Willium Frohring (1893-1959) from Cleveland, Ohio. The Biothesiometer (also known as VPT meter or Neurothesiometer) is a handheld device with a rubber tactor that vibrates at 100 Hz. The handheld unit is connected by an electrical cord to a base unit. This unit contains a linear scale which displays the applied voltage, ranging from 0 to 50 V. The device is held with the tactor balanced vertically on the pulp of the toe. The voltage amplitude is then increased on the base unit until the patient can perceive a vibration. A mean of three readings (measured in Volts) is generally used to determine the vibration perception threshold for each foot. "Loss of protective sensation" with VPT has commonly been considered to be about 25 V. Based on vibration perception threshold diabetic neuropathy hence risk of developing foot ulcer can be graded as no or mild risk if VPT is less than 15volts and moderate risk if VPT is 16 to 24 volts and high risk if VPT is equal to or more than 25 volts. [48]

University of Texas Subjective Peripheral neuropathy verbal questionnaire.[38] It includes four queries to identify the presence of burning, formication, numbness and paresthesia

The four queries include

1. Do your feet ever feel numb?
2. Do your feet ever tingle, as if electricity were traveling into your foot?
3. Do your feet ever feel as if insects were crawling on them?
4. Do your feet ever burn?

A positive answer to any one of the 4 verbal question constituted 1 point. A negative answer constituted 0 points.

The widely used examination scores for diabetic neuropathy are the Neuropathy Impairment Score in the Lower Limbs (NISLL)[50], Neuropathy Disability Score (NDS)[51],the Neuropathy Deficit Score [52], the Clinical Examination Score of Valk (CE-V)· [54] and the Michigan Neuropathy Screening Instrument (MNSI) [53],

Neuropad, a new indicator test:

Neuropad was a new diagnostic test proved to have high sensitivity in diagnosing DPN [55,56] It is a simple adhesive indicator test that has been found to be suitable for patient self-examination at home. The principle underlying the procedure was to test the function of the unmyelinated C fibers, responsible for the function of the sweat glands by the color indicator. Patients were allowed to relax for a period of 10 minutes at a room temperature of 25°C. Neuropad test indicators are to applied to both the soles at the level of the first through the second metatarsal heads. The time taken for color change from blue to pink was recorded for 10seconds. Dryness of the skin of the feet correlates with foot ulceration. Few studies have showed that 95% of the patient with foot ulceration had dryness of the skin over the feet using NCS.

Plantar thermography:

Infrared computerized thermography was a modern diagnostic technique method of DPN. This method includes visualization, documentation and measurement of the infrared rays along the human body. According to studies conducted by Stefan-Boltzmann, the emission of infrared rays was proportional to the skin temperature and it was directly related to cutaneous blood flow. [57,58]

The merits with this method were non-contact and painless. Vasomotor tone is regulated by sympathetic nerve fibers, and thus its dysfunction could be associated with varying temperature patterns. [59,60] Generally the AV shunts were maintained in the constricted state by sympathetic tone. The loss of this tone in patients with

diabetic neuropathy leads to an increase in the AV shunt in the feet of patients, opening of the shunt and increased blood flow to the skin. The small fibres are more vulnerable to the metabolic change associated with hyperglycemia, and their injuries may be presented earlier and these changes are less marked than sensory-motor neuropathies. [61]

Understanding that NCS was expensive, difficult and time consuming, the use of other screening tests like DNE, SWMF and VPT were documented. The DNE scores are simple, reproducible, fast and easy to perform and showed to be sensitive and specific to screen DPN. [62] Composite scores, where clinical presentation, quantitative sensory testing and electro-physiologic measures, when combined gives better diagnosis. Few examples are the Diabetic Neuropathy Symptom Score, Diabetic Neuropathy Examination score, Michigan Diabetic Score, etc. [63]

FOOT CARE

Proper foot care is the first and foremost step in diabetic peripheral neuropathy. Since the nerves supplying feet have a long course in the body, they are the one most commonly affected by neuropathy. Loss of blood supply also increase the risk of foot ulcers.

- Using warm water and a mild soap cleaning of feet should be done.
- With a soft towel dry carefully between toes.
- Daily inspection of feet and toes for redness, swelling, cuts, blisters, calluses, or other problems.
- Moisturizing lotion can be used over feet, but avoid between toes.
- Toenails should be trimmed periodically.
- Shoes or slippers should be worn always to protect feet.
- Wear shoes that fit well and allow toes to move.

OFF LOADING IN DIABETIC FOOT [64]

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.

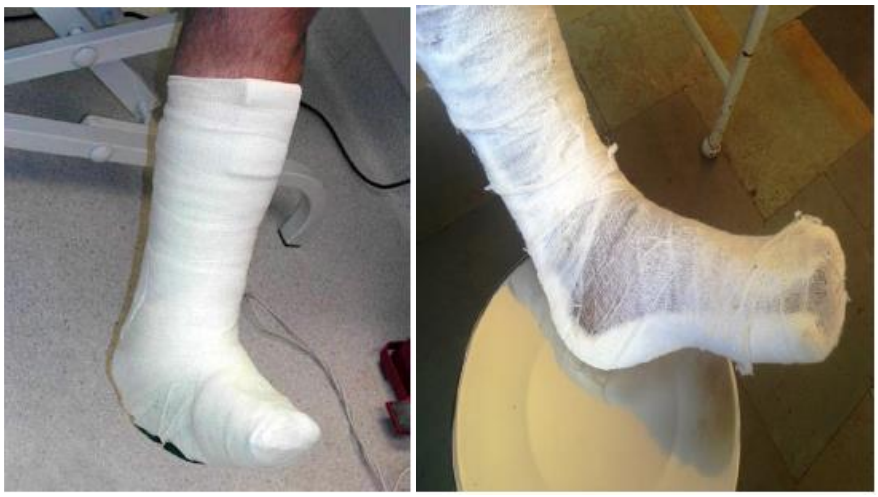


Figure 11. TOTAL CONTACT SLAB.

Figure 12. REMOVABLE CAST WALKER

Figure 13. HALF SHOES.

7. Felt and foam dressing: This is done by applying bilayer of felt and foam to patients' foot. An area of pressure relief is created by removing the foam and felt layers from the vulnerable ulcer area thus offloading the pressure.

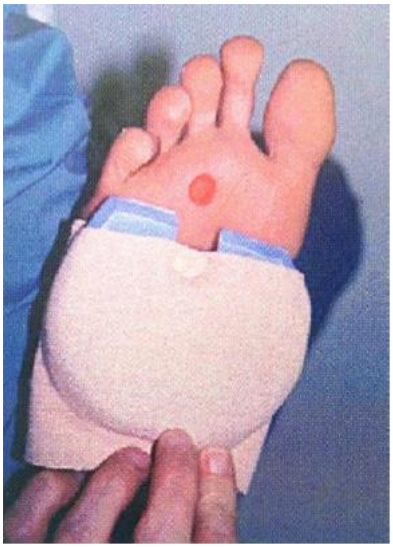


Figure 14. FELT AND FOAM DRESSING

8. Half shoes: also called as weight relief shoes give support to hindfoot and mid foot leaving the forefoot suspended hence used in treatment of forefoot ulcers.
9. Plantar metatarsal pads: they are modified insoles in which area of ulcer in the metatarsal head area is cut so as to suspend the ulcer.
10. Moulded insoles: these are prepared by moulding the insoles over plaster of Paris cast imprint taken from the foot which represent contours of the foot. They are made of microcellular rubber, ethyl vinyl acetate or polyethylene foam.
11. Winged outsole: These are prepared by cutting the wing of outside sole at vulnerable areas hence suspending the ulcer. Compared to insoles these are easy to make can be inspected and last longer.

Vasculopathy in diabetic patients [65]

In patients with diabetes mellitus both microvascular and macrovascular changes are seen.

Microvasulopathy

Observations that diabetic foot ulcerations (DFUs) can develop despite the presence of peripheral pulses have also highlighted the central role of the microcirculation in the pathophysiology of such complications.

Given its status in those with diabetes, the vasoactive role of insulin is important to consider when exploring underlying mechanisms of cutaneous microvascular disease. A key component of insulin's metabolic action is its ability to dilate resistance vessels and precapillary arterioles to increase total blood flow and the microvascular exchange surface perfused within the skeletal muscle, respectively. [34]

Unique to other agonists, insulin achieves its vasodilatory role by synthesizing NO exclusively via a calcium-independent pathway which is altered in diabetic patients due to insulin deficiency. [67] In addition three classical pathways have been described to explain the mechanisms through which hyperglycemia damages the vessels, namely, aldose reductase and the activation of the polyol pathway, advanced glycation end products (AGEs), and protein kinase C activation (PKC). [66] All of these pathways contribute to the production of ROS (reactive oxygen species), such as superoxide, in the vascular wall and are also involved in nerve damage in diabetes, which itself impairs microvascular reactivity, the latter depending on intact sensory nerves. [34]

One of the most notable structural changes of the microvasculature in diabetes involves thickening of the capillary basement membrane. These abnormalities are more pronounced in the leg, likely because of the higher hydrostatic pressure and the inability of the skin microvasculature of diabetic patients to respond adequately to postural changes. [67]

Methods to Explore the Cutaneous Microcirculation in the Diabetic Foot:

1. Laser Doppler :The laser Doppler principle is based upon the phenomenon that when a laser beam emitted by the imaging device hits moving red blood cells in the cutaneous vessels, the light undergoes a change in wavelength (Doppler shift) and the backscatter is detected by the device.[68] Laser Doppler imaging (LDI) is an alternative laser Doppler-based imaging technology that scans a tissue bed of interest (e.g., the volar surface of the forearm) to produce a 2D image and map cutaneous blood flux within that region, with each pixel representing a separate perfusion value.[69]
2. Capillaroscopy: used for assessment of the density, recruitment, and blood flow velocity of the capillaries.[69] Using a microscope with epi-illumination and imaging systems, capillaroscopy is often performed at the periungual region where nail fold capillary loops are oriented parallel to the skin, imaging the width of a few millimeters. For a nail fold capillary pattern to be considered normal, capillary loops ranging from 6 to 15μm in diameter should be homogenously distributed.[70]
3. Transcutaneous Oxygen Tension: Assessing the oxygenation in the cutaneous microcirculation may be considered as an important index of skin blood perfusion. Transcutaneous oxygen tension (TcPO2) is an established technique that allows for noninvasive evaluation of the partial pressure of oxygen in cutaneous tissue. TcPO2 may also have value in predicting healing rates in those suffering from DFU and amputation rates in those with peripheral arterial disease or ischemic ulcers.[71] TcPO2 measures the transfer of oxygen molecules from the blood vessels to the skin surface with a decreased TcPO2 reading indicating decreased oxygenation.[71]

4. Near-Infrared Spectroscopy: Near-infrared spectroscopy, which may also provide an indirect method of evaluating mitochondrial function[72]uses near-infrared light emitted from a probe placed on the skin and is based on the principles that specific wavelengths of red and near-infrared light have the ability to penetrate through biological tissue; absorption of these specific red and near-infrared wavelengths are dominated by hemoglobin; and absorption varies between oxygenated and deoxygenated hemoglobin.[73] Light emitted by the probes typically penetrates the tissue to a depth of 2 cm and is detected by photodetectors, which can provide estimations of total hemoglobin, oxyhemoglobin, deoxyhemoglobin, and tissue oxygen saturation.[73]

Macrovasculopathy: Peripheral Artery Disease (PAD) in the Diabetic Patient

Peripheral artery disease (PAD) is the partial or complete obstruction by atherosclerosis of arteries supplying the lower extremities. Diabetes is a well-known risk factor for PAD.[74,75] It increases the risk of developing lower extremity atherosclerosis over two fold, and there is a 28% increase for every 1% increase in HbA1c.[75,76]

Symptoms and signs:

Patients may also present with hip, thigh or calf claudication depending on the level of arterial occlusion. However, patients with isolated tibial artery occlusion may remain asymptomatic until they suffer a minor trauma to the foot.

Physical examination should focus on a description of the ulcer, signs of ischemia, and a thorough pulse exam. Ischemic ulcers are more likely to be present on the most distal parts of the toes whereas those related to neuropathy most often occur on weight-bearing areas such as the plantar surface of the metatarsal heads or over bony deformities. Other suggestions of impaired lower extremity perfusion such as those

described in the non-ulcer patient are also sought including skin fissuring, dystrophic toenails, and pallor with elevation or dependent rubor.

Clinical examination:

Evidence of decreased pedal perfusion may be discerned from various physical findings including absence of hair growth, dry, cool, or fissured skin, thickened nails, elevation pallor, and dependent rubor. Peripheral pulsation examination should be conducted including anterior tibial, posterior tibial, dorsalis pedis, popliteal and femoral artery.

For patients over 50, an American Diabetes Association consensus panel on PAD has recommended baseline assessment of ankle-brachial indices (ABIs), with repeat studies performed every 5 years for those without abnormalities. (ABI) is a frequently used measure of peripheral artery disease. It is calculated as a ratio of pressures in the ankles to the brachial arteries.an ABI between 1.1 and 1.3 is typically considered normal and can be used to exclude patients with significant arterial disease. An ABI between 0.4 and 0.9 suggests moderate ischemia, and when it is <0.4, it generally signifies severe ischemia.

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 15: HAND HELD DOPPLER.

Doppler Waveform Analysis: Normal peripheral arteries have a triphasic waveform with a brisk upstroke of forward flow during systole due to myocardial contraction, followed by a reversal of flow during early diastole, and a small forward component in late diastole.[38] Waveform evaluation at various levels can provide evidence of PAD.

Arterial Duplex Ultrasound: Duplex scanning employs the dual modalities of B-mode (gray scale) imaging and pulsed wave Doppler spectral frequency analysis. The primary advantage of Duplex ultrasound is that it can be used for anatomic assessment of arteries and to determine the distribution of occlusive lesions.

Other diagnostic modalities used for diagnosis of PAD are,

- Pulsed Volume Recordings (PVRs),
- Toe Pressures,
- Transcutaneous Oxygen Tension (TcPO2)
- Laser Doppler Perfusion
- Skin Perfusion Pressure (SPP)

- Noninvasive Axial Imaging by CTA and MRA

IMMUNOPATHY IN DIABETIC FOOT:[65]

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.[77-81]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. [82-87]

Nonhealing ulcer keratinocytes are hyperproliferative in both basal and suprabasal layers of the epidermis giving rise to parakeratosis and hyperkeratosis, indicating impaired differentiation. [88,89]

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. [90-94]

An imbalance between ECM protein synthesis and remodeling by MMPs and the tissue inhibitors of metalloproteinases (TIMPs) is seen in DFUs. Increased MMP production causes ECM degradation.[95] 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.[96]

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. [78, 97-99]

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. [100,101]

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 [102,103]

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.[104] 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.[105]

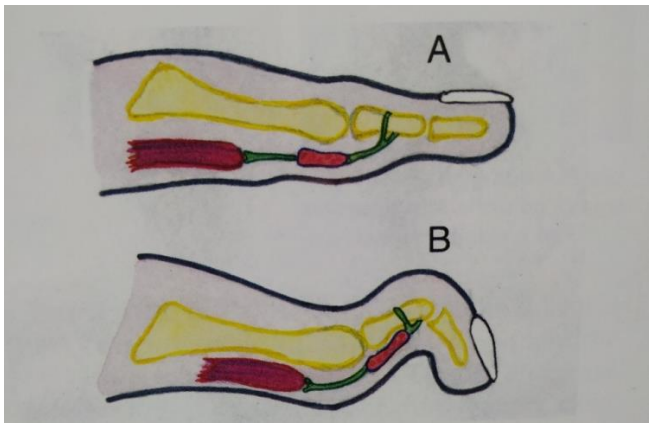


Figure 16.A. Normal position of fibro fatty tissue.

B. Fibrofatty tissue pushed forward in diabetic patients.

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.

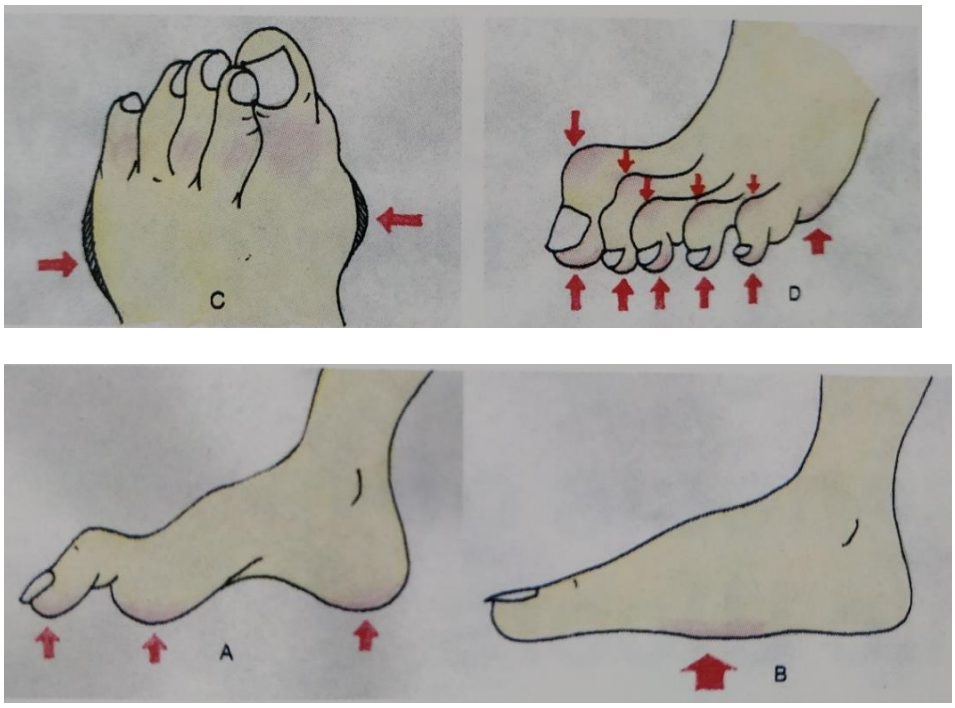


Figure 17. AREAS OF HIGH RISK FOR ULCERATION.

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.

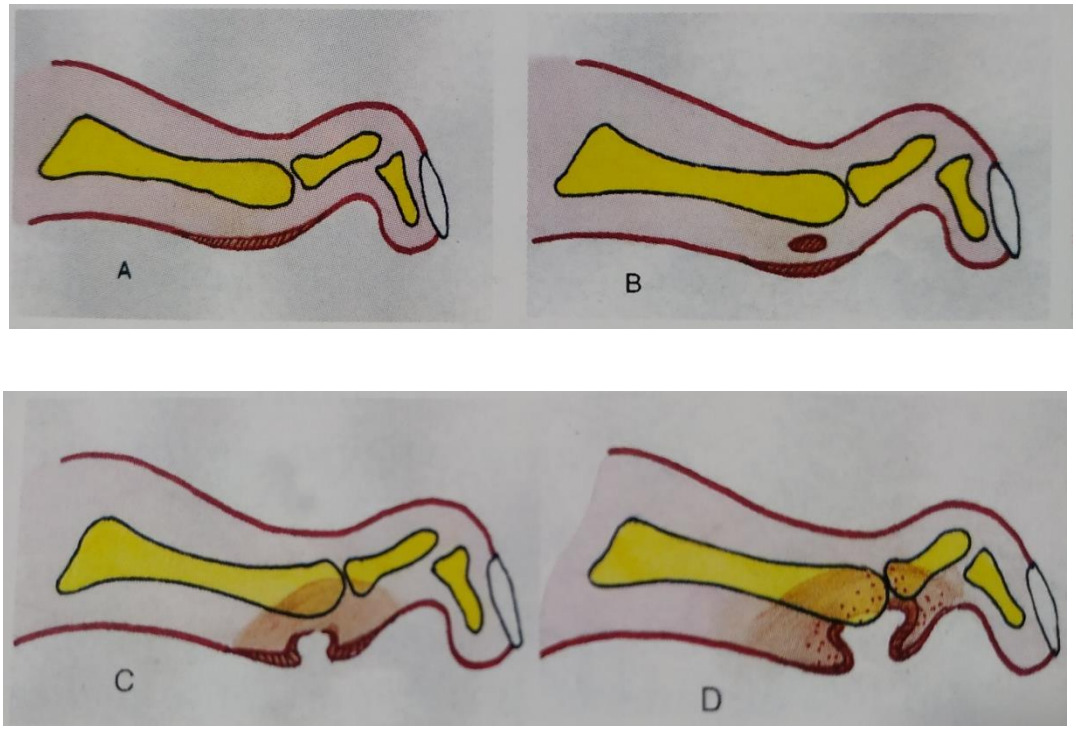


Figure 18. Stages of foot ulcer A. Callus B. Soft tissue damage C. Ulceration D. Infection

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.

CLINICAL IMPLICATIONS OF BIO MECHAMICS

Every attempt should be made to reduce plantar pressure, so as to prevent foot ulceration e.g. MCR foot wears. Plantar pressure analysis identifies the high-pressure point and gives important information regarding appropriate foot wears. Patients with high plantar pressures can be advised to reduce their activity level and walk with short steps and take adequate care of feet.

Figure 19: LONGITUDINAL MEDIAL ARCH OF FOOT

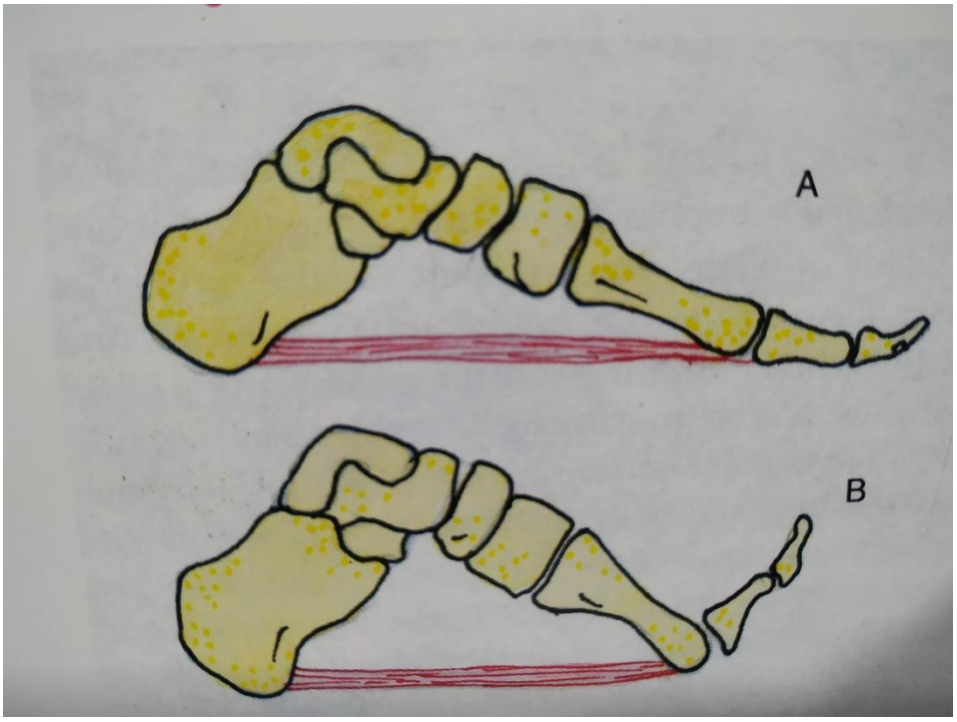
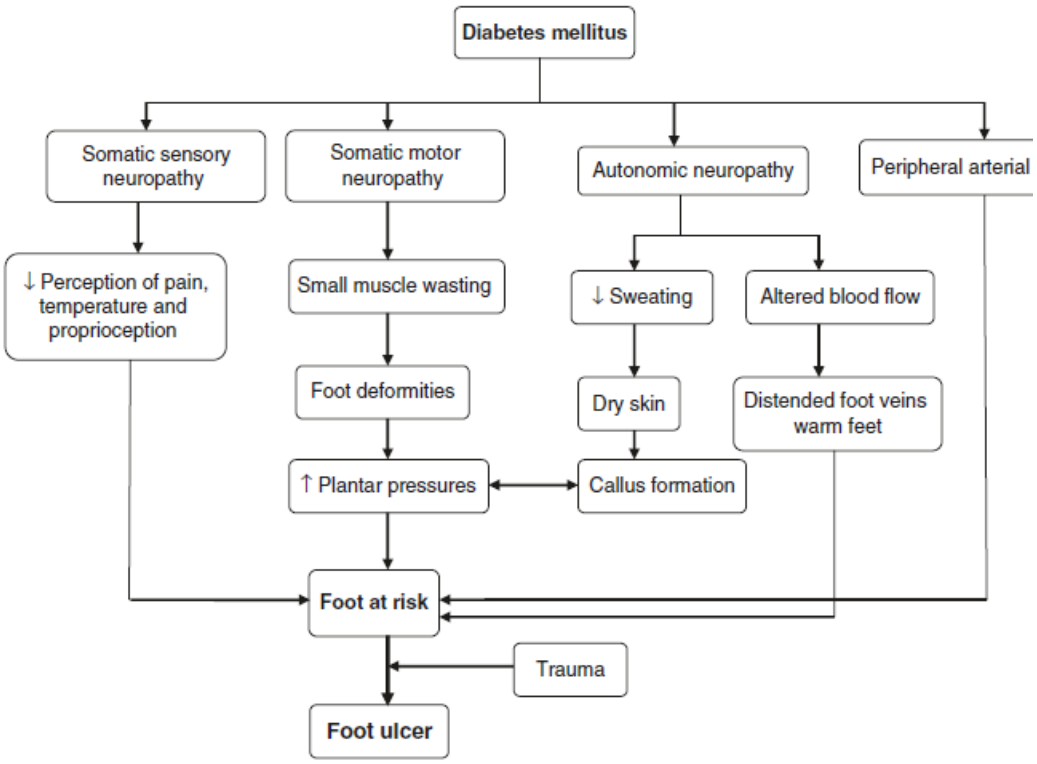


FIGURE 20: A: ARCH FLAT B: CONTRACTION OF PLANTAR APONEUROSIS RESULTING IN ELEVATION OF ARCH

PATHWAY OF FOOT ULCERATION



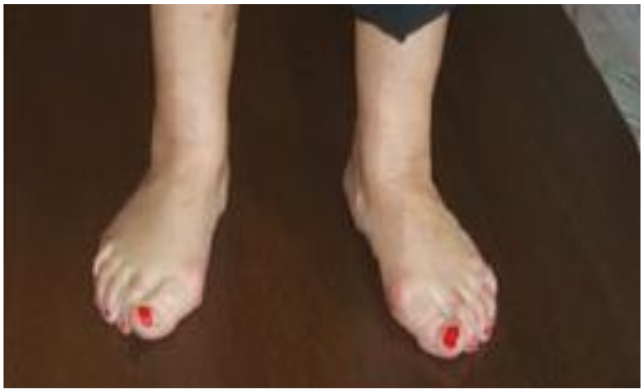


Figure 21. HALLUX VULGUS

PLANTAR PRESSURE MEASUREMENT: 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.

Figure 22**.** HARRIS MAT FOOT IMPRINT.

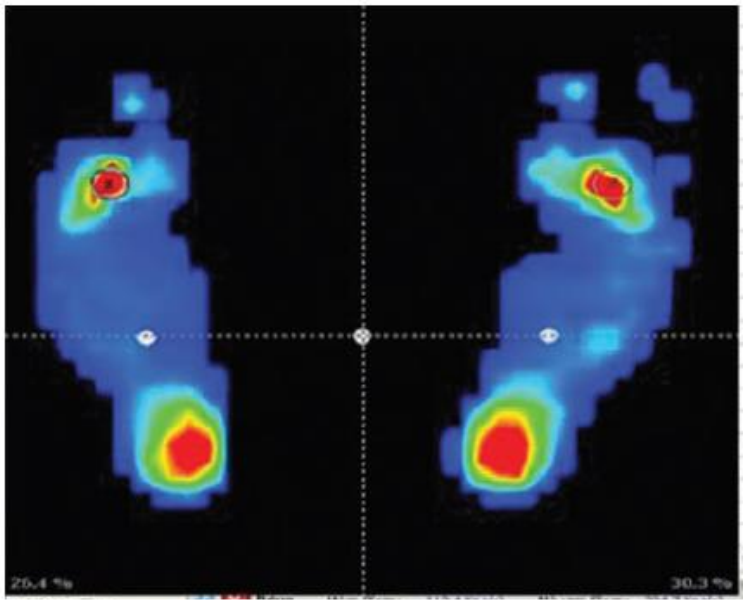


Figure 23: PEDOBAROGRAPH

Relevant studies conducted previously on the same topic:

A meta-analysis conducted YuzheFeng et al identified 764 studies, out of that 30 were selected involving 8365 patients to know the Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy.

This study showed a notable variation in both the reference test and the methodology of Semmes Weinstein monofilament examination. 4 studies which directly compared SWME with NCS and encompassed 1065 patients with DM and 52 patients without DM are identified. SWME had a sensitivity range of 57% (with 95% confidence interval [CI], 44% to 68%) to 93% (with 95% CI, 77% to 99%), specificity range of 75% (with 95% CI, 64% to 84%) to 100% (95% CI, 63% to 100%), negative predictive value (NPV) ranges from 36% (with 95% CI, 29% to 43%) to 94% (95% CI, 91% to 96%) and positive predictive value (PPV) ranges from 84% (with 95% CI, 74% to 90%) to 100% (95% CI, 87% to 100%). [39]

Another meta-analysis conducted by YuzheFeng et al identified 863 studies, out of which 9 articles were selected involving 11007 patients with DM. 6 studies which assessed the prognostic value of SWME regarding diabetic foot ulceration are selected. The relative risk for those patients with SWME positive results versus negative results ranging from 2.5 (95% CI, 2.0 to 3.2) to 7.9 (95% CI, 4.4 to 14.3) in the identified studies with follow up period of 1-4years are selected. 3 these studies assessed the risk of LEA (lower extremity amputation) with a positive SWME result. The relative risk for LEA ranged from 1.7 (95% CI, 1.1 to 2.6) to 15.1 (95% CI, 4.3 to 52.6) with the follow-up between 1.5 and 3.3 years. [106]

A study conducted by Al-Geffari M et al to compare the different screening test for diagnosis of diabetic peripheral neuropathy in primary health care setting found that 45% of the study participants had DPN based on MNSI. The detection rate using the 128-Hz tuning fork and 10g SWM was almost same (32.6% and 31.4% respectively). [107]

A study conducted by Perkins BA et al on the simple screening tests for peripheral neuropathy in the diabetes clinic found that the four-simple screening manoeuvres revealed similar operating characteristics. Cut off point by POC curve analysis revealed that a positive or abnormal test is represented by five incorrect responses out of 8 stimuli applied. Normal or negative test is represented by one or few incorrect responses of 8 stimuli applied. By these criteria, the point estimate of the positive likelihood ratios for vibration testing by the on-off method, vibration testing by the time method, the SWME, and superficial pain sensation test are 26.6, 18.5, 10.2, and 9.2 respectively. The point estimate of the negative likelihood ratios are 0.33, 0.51, 0.34 and 0.50 respectively. These screening tests showed the comparable sensitivity and specificity results. The 10g SMWE, superficial pain test and vibration testing by the on-off method are rapid, required 60s for each administration. The combination of 10g SWME and vibration testing does not add value to each individual screening test. [108]

A multicenter study conducted by MJ Young et al to know the prevalence of DPN in the united kingdom hospital clinic population among 6487 DM patients with median age of 59years (18-90years), 53.9% were males, the prevalence of neuropathy was 28.5%. The prevalence of DPN increased with age from 5% in the age group of 20-29years to 44.2% in the 70 -79 years age group. Neuropathy was associated with duration of DM and was present in 20.8% of patients with diabetes duration less than 5years and in 36.8% of those with diabetes duration greater than 10yeras. The mean vibration perception threshold measured at the greater toe was 21.1 + 13.5 SD volts. [109]

A study conducted by Abhijjet A et al on clinical profile of DPN by nerve conduction revealed that, the incidence of DPN recorded by the clinical

examination was 30% and by nerve conduction study it was 42%. The common complaint by patients was tingling and numbness. Type 2 diabetes is the most common cause of peripheral neuropathy. [110]

A study conducted by Sonalika G et al to know the prevalence and risk factors for peripheral neuropathy among the type 2 DM patients in coastal Karnataka revealed that, according to the DNS instrument 41.4% patients were positive for neuropathy. While 24.5% were positive for neuropathy by DNE score. Males were affected more than the females. Duration of disease was positively correlated to the neuropathy present.[111]

MATERIALS AND METHODS

SOURCE OF DATA:

All eligible patients with Diabetes Mellitus attending Surgery/Medicine OPD or admitted in Surgery/Medicine wards during the study period from October 2017 to May 2019 were considered in the study

STUDY DESIGN

Observational analytical study

METHOD OF COLLECTION OF DATA

Details of cases were recorded as following

- ❖ Pre-tested Questionnaire was filled based on the history elicited.
- ❖ Clinical Examination of the patients was done.
- ❖ Routine investigations were performed along with Specific Investigations like FBS, PPBS and HbA1c.
- ❖ Following tests for peripheral sensory neuropathy were performed.

1. Question verbal neuropathy score.
2. Semmes- Weinstein 10G monofilament wire testing.
3. Vibration perception threshold testing using Biotesiometer.

- ❖ Vascular flow assessment using hand held Doppler.
- ❖ Harris mat foot imprint to detect high pressure points.

INCLUSION CRITERIA

- Diabetic patients with risk of developing peripheral neuropathy with or without foot ulcers (up to Wagner grade 3 ulcers).

EXCLUSION CRITERIA

- Patients who had already undergone amputation of toes for diabetic foot.
- Patients with severe co-morbid conditions.
- Patients with ulcers of Wagner grade 4 or more.
- Patients unwilling to participate in the study

PROCEDURE

Three tests for neuropathy

1. **Semmes-Weinstein monofilament**: This test is done by applying pressure with monofilament at four sites on each foot; 1^{st}, 3^{rd}, and 5^{th} metatarsal heads and plantar surface of distal hallux. The sites over the foot are examined by asking the patient to respond by YES or NO when asked whether the monofilament is being applied to particular site. If the patients does not perceive the sensation, then it is taken as positive.
2. **Vibration perception threshold (VPT):** This test is done using biothesiometer. This device is hand held with a rubber tractor that vibrates at 100Hz.The hand held unit is connected to a base unit by an electric cord. The voltage ranges from 0 to 50 V. the device is held with the tractor balanced

   This is a hand-held device with a rubber tractor that vibrates at 100 Hz. The hand-held unit is connected by an electrical cord to a base unit. This unit contains a linear scale that displays the applied voltage, which ranges from 0 to 50 V. The device is held with the tractor balanced vertically on the pulp of the toe. At this time, the voltage is increased on the base unit until the patient could perceive the vibration. A mean of 3 readings in each foot will be entered for final data analysis. A value of 25 V will be considered as positive.

3. Subjective peripheral neuropathy verbal questionnaire: This includes four queries to identify presence of symptoms of diabetic neuropathy.

- ✓ Do your feet ever feel numb?
- ✓ Do your feet tingle, as is electricity was travelling into your foot?
- ✓ Do your feet feel as if insects were crawling on them?
- ✓ Do your feet ever burn?

A positive answer to any of the above-mentioned questions will be considered as positive

Follow up: Was done for 6 months, at 1st month, 3rd month and 6th month. The results of these tests were compared between diabetic patients with and without foot ulcers and sensitivity and specificity of the tests were calculated.

Sample size calculation

A study conducted by Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG titled 'Choosing a practical neuropathy testing instrument to identify risk for diabetic foot ulceration', published in 1998 is taken as reference for our study. [38]

With 95% confident level and a margin of error of ±15%, a sample size of 40 patients with diabetic foot ulcer and 120 patients without diabetic foot ulcers were involved in the study to compare the Neuropathy among Diabetic patients with and without Foot ulcer with finite population correction.

Sample size was calculated using the formula:

$$n = \frac{z2p\,(1-p)}{d2}$$

Where

z= statistic at 5% level of significance

d= margin of error

p= anticipated prevalence rate

Statistical analysis

After obtaining the data, it was entered using MS Excel (2010) and was analysed using SPSS software version 16. Descriptive analysis of the data was done and presented as frequencies, percentages and means. The association between the DM and neuropathy was tested using Chi-square test and Fisher's exact test. All statistical analysis was carried out at 5% level of significance and p value <0.05 was considered as significant.

Sensitivity, specificity, positive predictive value, negative predictive value, % of false positive, % of false negative and accuracy of the screening test was calculated.

ETHICAL CLEARANCE:

Ethical clearance was obtained before conducting the study from the Institutional Ethical Committee

RESULTS

In the results

Group A: Study subjects with foot ulceration

Group B: Study subjects without foot ulceration.

The mean age of the study participants in Group A was 59.25 ± 12.22years and that of Group B was 61.98 ± 10.65years.

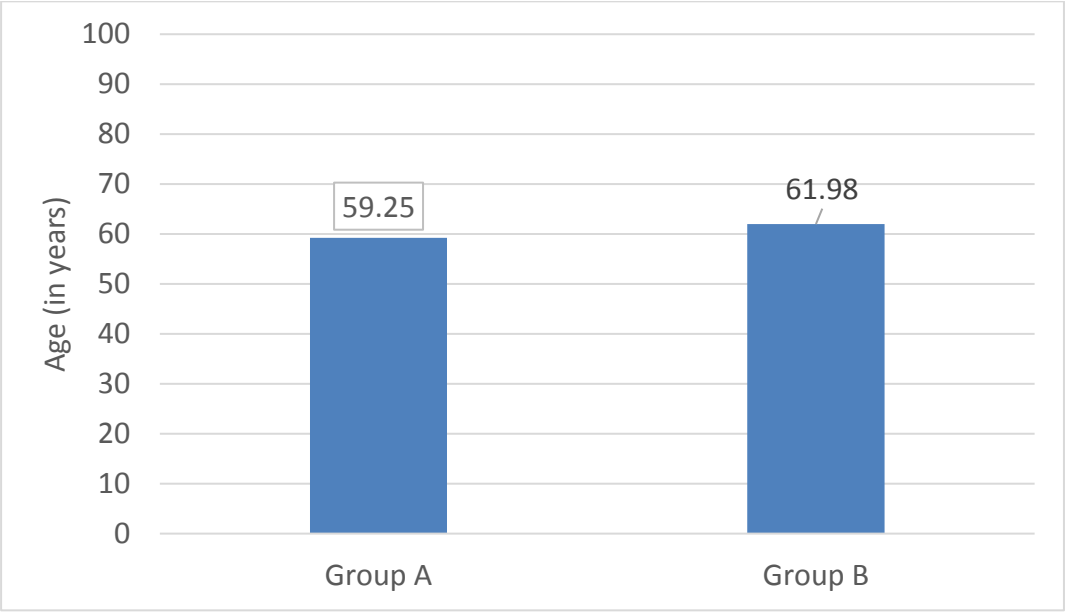


Figure 24: Mean age of study subjects

Table 1: Gender wise distribution of study subjects.

Gender	Group A		Group B		χ^2 Value	P Value
	Frequency	Percentage	Frequency	Percentage		
Male	37	92.5%	82	68.3%	9.193	0.002
Female	3	7.5%	38	31.7%		
Total	40	100%	120	100%		

In Group A, out of 40 study subjects 37 (92.5%) were males and 3 (7.5%) were females. Where as in Group B, out of 120 study subjects 82 (68.3%) were males and 38 (31.7%) were females. This difference was statistically significant (p value = 0.002).

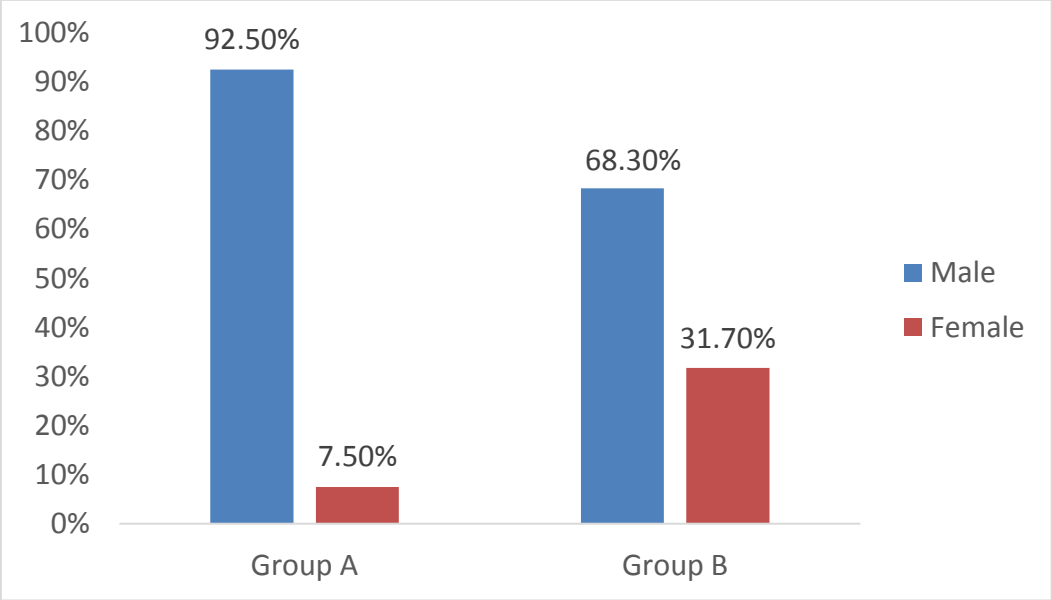


Figure 25: Gender wise distribution of study subjects.

Table 2: Distribution of study subjects based on their literacy.

Literacy	Group A		Group B		χ^2 Value	P Value
	Frequency	Percentage	Frequency	Percentage		
Literate	14	35%	99	82.5%	32.627	<0.001
Illiterate	26	65%	21	17.5%		
Total	40	100%	120	100%		

In Group A, out of 40 study subjects 14 (35%) were literate and 26 (65%) were illiterates. Where as in Group B, out of 120 study subjects 99 (82.5%) were literate and 21 (17.5%) were illiterates. This difference was statistically highly significant (p value < 0.001).

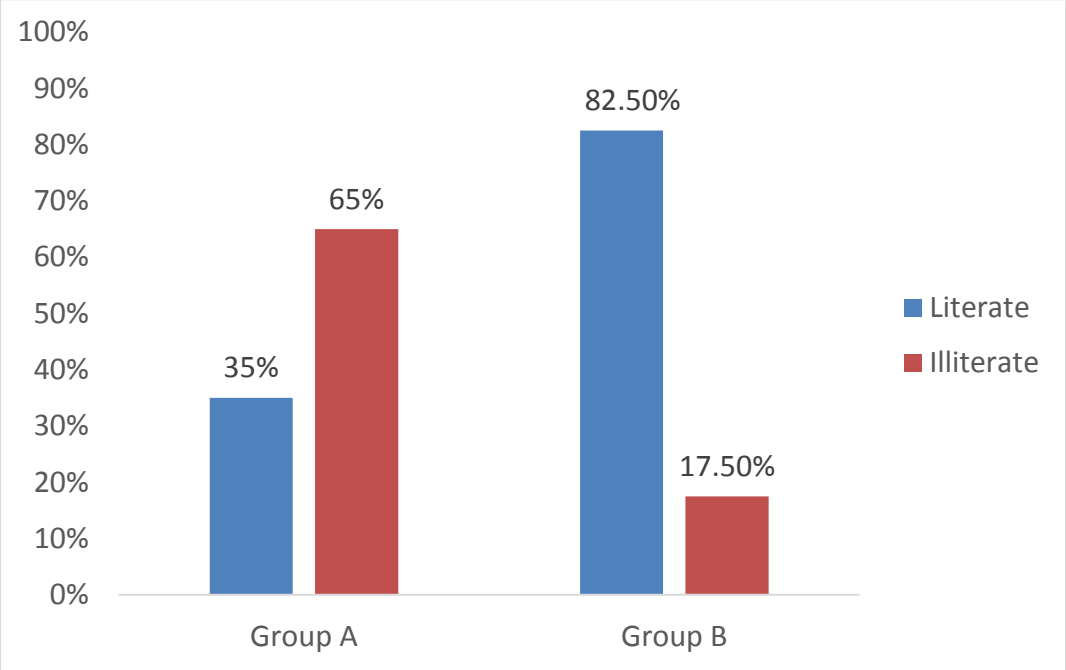


Figure 26: Distribution of study subjects based on their literacy.

Table 3: Association between presence of foot ulcer and Co-morbidities.

Co-morbidities	Group A		Group B		χ^2 Value	P Value*
	Frequency	Percentage	Frequency	Percentage		
Hypertension	9	22.5%	8	6.7%	7.920	0.005
Dyslipidaemia	9	22.5%	8	6.7%	7.920	0.005
Heart disease	5	12.5%	6	5.0%	2.636	0.104
No Co-morbidities	17	42.5%	98	81.6%		
Total	40	100%	120	100%		

Hypertension was more among Group A i.e. 9 (22.5%) and in Group B it was associated in 8 (6.7%) of the study subjects. Dyslipidemia was also more among Group A i.e. 9 (22.5%) and in Group B it was associated in 8 (6.7%) of the study subjects. This difference was statistically significant (p value =0.005). Heart disease was also more among Group A i.e. 5 (12.5%) and in Group B it was associated in 6 (5.0%) of the study subjects. But this difference was not statistically significant (p value =0.104).

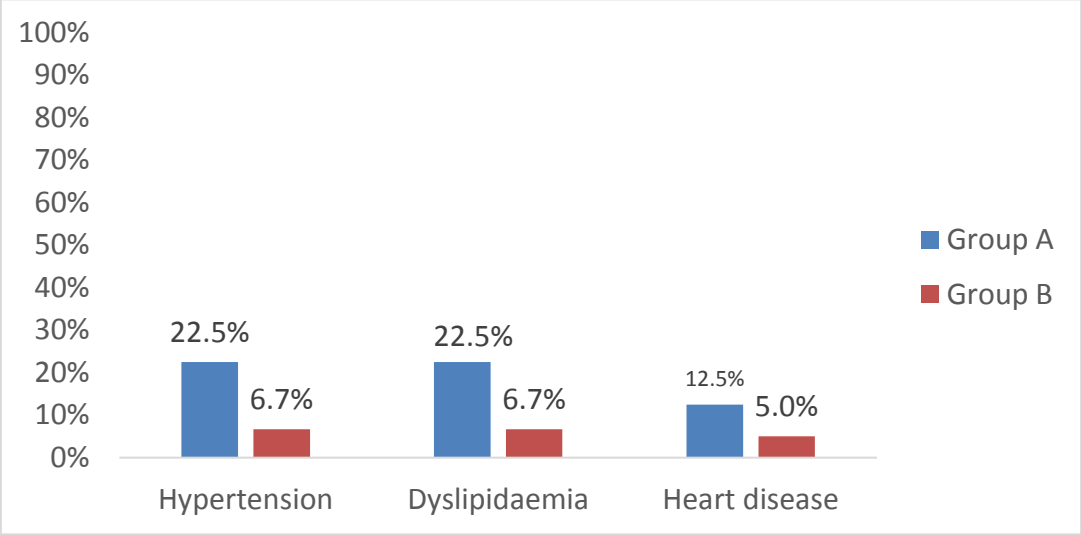


Figure 27: Association between presence of foot ulcer and Co-morbidities.

Table 4: Association between presence of foot ulcer and the duration of diabetes.

Duration of diabetes	Group A		Group B		χ^2 Value	P Value*
	Frequency	Percentage	Frequency	Percentage		
<1year	1	2.5%	1	0.8%	15.648	<0.001
1-5years	11	27.5%	62	51.7%		
6-10years	13	32.5%	43	35.8%		
>10years	15	37.5%	14	11.7%		
Total	40	100%	120	100%		

*Fischer's Exact Test

In Group A, out of 40 study subjects, 1 (2.5%), 11 (27.5%), 13 (32.5%) and 15(37.5%) had the duration of diabetes for less than 1year, 1-5years, 5-10years and more than 10years respectively. Where as in Group B, out of 120 study subjects, 1 (0.8%), 62 (51.7%), 43 (35.8%) and 14(11.7%) had the duration of diabetes for less than 1year, 1-5years, 5-10years and more than 10years respectively. Mean duration of diabetes in Group A was 9.67±5.64 whereas in Group B it was 6.29±3.67. As the duration of diabetes increases the probability of foot ulceration was more. This difference was statistically highly significant (p value <0.001).

Table 5: Association between presence of foot ulcer and the HbA1C level.

HbA1C (%)	Group A		Group B		χ^2 Value	P Value
	Frequency	Percentage	Frequency	Percentage		
≤ 6.5	0	0	48	40%	22.857	<0.001
>6.5	40	100%	72	60%		
Total	40	100%	120	100%		

*Fischer's Exact Test

In Group A, all of the 40 (100%) study subjects had the HbA1C level more than 6.5%. Where as in Group B, out of 120 study subjects, 48 (40%) had the HbA1C level less than 6.5% and 72 (60%) had the HbA1C level more than 6.5%. The mean HbA1c in Group A was 8.52±0.88g and in Group B was 6.75±0.36 Probability of getting foot ulceration was more among patients with uncontrolled diabetes. This difference was statistically highly significant (p value <0.001).

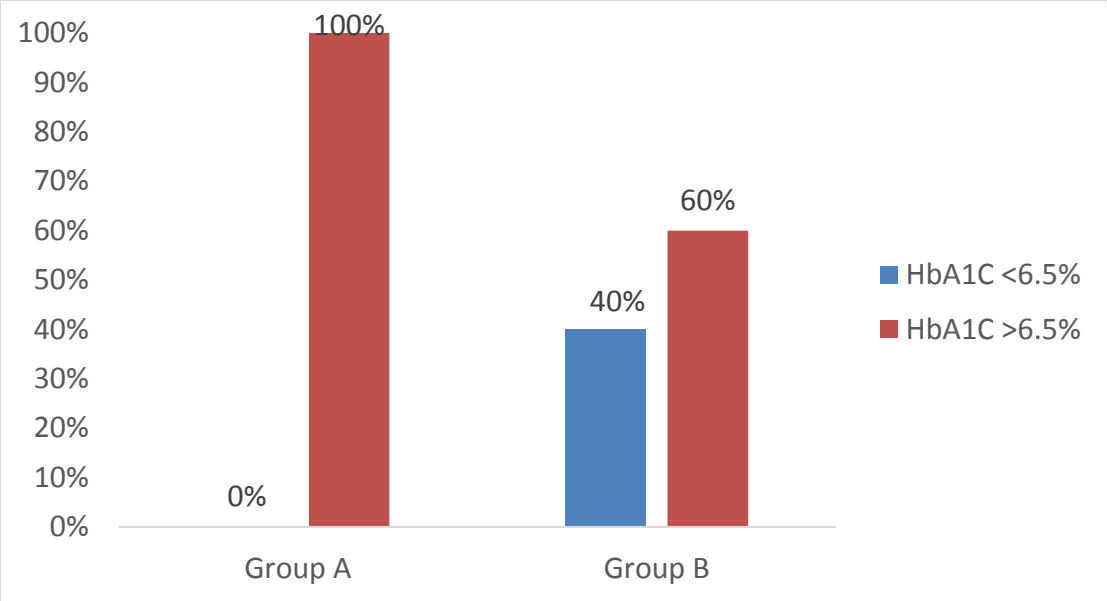


Figure 28: HbA1C levels among the study subjects.

Table 6: Verbal questionnaire method in the diagnosis of Diabetic Peripheral Neuropathy.

Peripheral neuropathy on verbal questionnaire method	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	35	87.5%	10	8.3%
Negative	5	12.5%	110	91.7%
Total	40	100%	120	100%

Peripheral neuropathy on verbal questionnaire method diagnosed diabetic peripheral neuropathy among 35 (87.5%) of the study subjects in Group A and 10 (8.3%) of the study subjects in Group B.

Table 7: Semmes- Weinstein 10G monofilament wire testing in the diagnosis of Diabetic Peripheral Neuropathy.

Semmes-Weinstein 10G monofilament wire testing	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	30	75%	27	22.5%
Negative	10	25%	93	77.5%
Total	40	100%	120	100%

Semmes- Weinstein 10G monofilament wire testing diagnosed diabetic peripheral neuropathy among 30 (75%) of the study subjects in Group A and 27 (22.5%) of the study subjects in Group B.

Table 8: Biothesiometer in the diagnosis of Diabetic Peripheral Neuropathy.

Biothesiometer	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	29	72.5%	16	13.3%
Negative	11	27.5%	104	86.7%
Total	40	100%	120	100%

Biothesiometer diagnosed diabetic peripheral neuropathy among 29 (72.5%) of the study subjects in Group A and 16 (13.3%) of the study subjects in Group B.

Table 9: Tools of screening tests -1

Tools of a screening tests	Verbal questionnaire method	Semmes-Weinstein 10G monofilament wire testing	Biothesiometer
Sensitivity	87.5%	75%	72.5%
Specificity	91.67%	77.5%	86.67%
PPV	77.78%	52.63%	64.44%
NPV	95.65%	90.29%	90.43%
% Of false positive	8.33%	22.5%	13.33%
% Of false negative	12.5%	25%	27.5%
Accuracy	90.63%	76.88%	83.13%

Diabetic peripheral neuropathy diagnosis by verbal questionnaire method showed the sensitivity of 87.5%, specificity of 91.67%, positive predictive value of 77.78%, negative predictive value of 95.65%, percentage of false positive were 8.33%, percentage of false negative were 12.5% and accuracy of diagnosis was 90.63%.By Semmes- Weinstein 10G monofilament wire testing showed the sensitivity of 75%,

specificity of 77.5%, positive predictive value of 52.63%, negative predictive value of 90.29%, percentage of false positive were 22.5%, percentage of false negative were 25% and accuracy of diagnosis was 76.88%. By Biothesiometer showed the sensitivity of 72.5%, specificity of 86.67%, positive predictive value of 64.44%, negative predictive value of 90.43%, percentage of false positive were 13.33%, percentage of false negative were 27.5% and accuracy of diagnosis was 83.13%.

Table 10: Combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method in the diagnosis of Diabetic Peripheral Neuropathy.

Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	35	87.5%	32	26.7%
Negative	5	12.5%	88	73.3%
Total	40	100%	120	100%

Combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 35 (87.5%) of the study subjects in Group A and 32 (26.7%) of the study subjects in Group B.

Table 11: Combination of Biothesiometer and Verbal questionnaire method in the diagnosis of Diabetic Peripheral Neuropathy.

Biothesiometer and Verbal questionnaire method	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	35	87.5%	23	19.2%
Negative	5	12.5%	97	80.8%
Total	40	100%	120	100%

Combination of Biothesiometer and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 35 (87.5%) of the study subjects in Group A and 23 (19.2%) of the study subjects in Group B.

Table 12: Combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer in the diagnosis of Diabetic Peripheral Neuropathy.

Semmes- Weinstein 10G monofilament wire testing and Biothesiometer	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	32	80%	34	28.3%
Negative	8	20%	86	71.7%
Total	40	100%	120	100%

Combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer diagnosed diabetic peripheral neuropathy among 32 (80%) of the study subjects in Group A and 34 (28.3%) of the study subjects in Group B.

Table 13: Combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method in the diagnosis of Diabetic Peripheral Neuropathy.

Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method	Group A		Group B	
	Frequency	Percentage	Frequency	Percentage
Positive	35	87.5%	39	32.5%
Negative	5	12.5%	81	67.5%
Total	40	100%	120	100%

Combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 35 (87.5%) of the study subjects in Group A and 39 (32.5%) of the study subjects in Group B.

Diabetic peripheral neuropathy diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method showed the sensitivity of 82.5%, specificity of 73.33%, positive predictive value of 50.77%, negative predictive value of 92.63%, percentage of false positive were 26.67%, percentage of false negative were 17.5% and accuracy of diagnosis was 75.63%.

Table 14: Tools of screening tests -2

Tools of a screening tests	Semmes-Weinstein 10G monofilament wire testing and Verbal questionnaire method	Biothesiometer and Verbal questionnaire method	Semmes-Weinstein 10G monofilament wire testing and Biothesiometer	Semmes-Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method
Sensitivity	82.5	87.5	80	87.5
Specificity	73.33	80.83	71.67	67.5
PPV	50.77	60.34	48.48	47.3
NPV	92.63	95.1	91.49	94.19
% Of false positive	26.67	19.17	28.33	32.5
% Of false negative	17.5	12.5	20	12.5
Accuracy	75.63	82.5	73.75	72.5

By combination of Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 80.83%, positive predictive value of 60.34%, negative predictive value of 95.1%, percentage of false positive were 19.17%, percentage of false negative were 12.5% and accuracy of diagnosis was 82.5%. By combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer showed the sensitivity of 80%, specificity of 71.67%, positive predictive value of 48.48%, negative predictive value of 91.49%, percentage of false

positive were 28.33%, percentage of false negative were 20% and accuracy of diagnosis was 73.75%.

Diabetic peripheral neuropathy diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 67.5%, positive predictive value of 47.3%, negative predictive value of 94.19%, percentage of false positive were 32.5%, percentage of false negative were 12.5% and accuracy of diagnosis was 72.5%.

Table 15: Distribution of study subjects based on the Harris Mat Foot Imprinting.

Harris Mat Foot Imprinting for high pressure points	Group A		Group B		χ^2 Value	P Value
	Frequency	Percentage	Frequency	Percentage		
Great toe	32	80%	53	44.2%	15.469	<0.001
1st metatarsal	20	50%	28	23.3%	10.159	<0.001
3rd metatarsal	1	2.5%	2	1.7%	0.113	1.000*
5th metatarsal	3	7.5%	5	4.2%	0.702	0.680*
Heel	10	25%	2	1.7%	23.544	<0.001
Total	40	100%	120	100%		

*Fischer's Exact Test

According to Harris Mat Foot Imprinting, out of 40 study subjects in Group A Great toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal and heel was involved in 32 (80%), 20 (50%), 1 (2.5%), 3 (7.5%) and 10 (25%) respectively. Whereas, out of 120 study subjects in Group B Great toe, 1st metatarsal, 3rd metatarsal, 5th metatarsal and heel

were involved in 53 (44.2%), 28 (23.3%), 2 (1.7%), 5 (4.2%) and 2 (1.7%) respectively. This difference was statistically highly significant in the involvement of Great toe, 1st metatarsal and heel (p value <0.001).

Table 16: Distribution of study subjects based on the presence of vasculopathy.

Vasulopathy	Group A		Group B		χ^2 Value	P Value*
	Frequency	Percentage	Frequency	Percentage		
Present	2	5%	4	3.3%	0.231	1.000
Absent	38	95%	116	96.7%		
Total	40	100%	120	100%		

*Fischer's Exact Test

Patients in whom peripheral pulsations of anterior tibial, posterior tibial and dorsalis pedis are absent on palpation and with hand held Doppler are considered as vasulopathy present.

In Group A, out of 40 study subjects 2 (5%) had vasculopathy and 38 (95%) of them did not show any evidence of vasculopathy. Where as in Group B, out of 120 study subjects 4 (3.3%) had vasculopathy and 116 (96.7%) of them did not show any evidence of vasculopathy. This difference was not statistically significant (p value = 1.000).

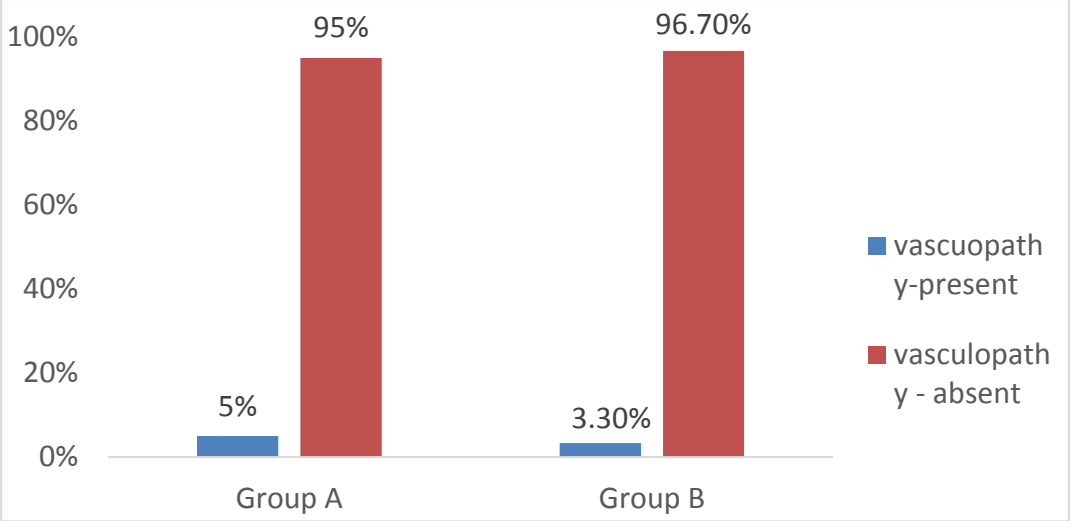


Figure 29: Distribution of study subjects based on the presence of vasculopathy.

DISCUSSION

The present study was the Observational analytical study conducted among the 40 patients with diabetic foot ulcers (Group A) and 120 patients without diabetic foot ulcers (Group B). This study was conducted among the patients attending Surgery/Medicine OPD or admitted in surgery or medicine wards of BLDE(DU)'s Shri B M Patil Medical College, Hospital and Research Centre, Vijayapur.

Studies	Present study	Perkins BAet al [110]	Armstrong DG et al [38]
Mean age ±Std.dev	60.61±11.43 years	52.02±9.86 years	51.8±10.25 years

Table 17: Mean age comparison of study subjects with other studies

The mean age of the study participants in Group A was 59.25 ± 12.22 years and that of Group B was 61.98 ± 10.65 years and mean age of all subjects was 60.61±11.43 years. A similar study conducted by Perkins BA et al [110] also included the study subjects of similar age group which was 52.02±9.86 years

Table 18: Comparison of gender distribution of study subjects with other studies

	Present study		Armstrong DG et al [38]	
Gender	Male	Female	Male	Female
With ulcer	92.5%	7.5%	63.3%	33.3%
Without ulcer	68.3%	31.7%	31.8%	68.2%

In Group A, majority (92.5%) of them were males and 7.5% were females. Where as in Group B, 68.3% were males and 31.7% were females which is similar to study conducted byArmstrong DG et al. [38]

Table 19: Comparison of literacy rate of study subjects with other studies

Literacy	Present study	Bhamre SD et al[112]
Literates	65%	25%
Illiterates	35%	75%

In Group A, 35% were literate and 65% were illiterates. Where as in Group B, 82.5% were literate and 17.5% were illiterates and most of them were farmers or mannual labourers which is comparable to study conducted by Bhamre SD et al[112]as shown in table ..This difference was statistically highly significant (p value < 0.001). This means that foot uclers were more common among the patients who are illiterate. In India, illiteracy is more common, which is inturn associated with rural population with false beliefs and customs like bare foot walking, religious practices like walking on fire, improper footwear usage and lack of knowledge about foot care. All these factors are ascociated with increased risk of diabetic foot ulcer among the illiterate patients. [113]

Table 20: Comparison of Co-morbidities of study subjects with other studies

Co-morbidities	Present study	Abdulghani HM [114]
Hypertension	22.5%	61.4%
Dyslipidemia	22.5%	58.1%
Heart disease	12.5%	14.4%

In the present study, hypertension, dyslipidemia and heart disease was seen among 22.5%, 22.5% and 12.5% respectively. But these findings were high among

Abdulghani HM [114] i.e. hypertension, dyslipidemia and heart disease was seen among 61.4%, 58.1% and 14.4% respectively.

Table 21: Comparison of duration of diabetes of study subjects with other studies

Group	Present study	Mackson Nongmaithemet al [115]
With ulcer	9.67±5.64yrs	7.08 5± 4.48yrs
Without ulcer	6.29±3.67yrs	4.01 ± 2.34yrs

In Group A, 2.5%, 27.5%, 32.5% and 37.5% had the duration of diabetes for less than 1year, 1-5years, 5-10years and more than 10years respectively. Where as in Group B, 0.8%, 51.7%, 35.8% and 11.7% had the duration of diabetes for less than 1year, 1-5years, 5-10years and more than 10years respectively. Mean duration of diabetes in GroupA was 9.67±5.64years whereas in Group B it was 6.29±3.67years. These findings are similar to study conducted by Mackson Nongmaithemet al[115] in which mean duration in patients with ulcers was 7.08 5± 4.48 years and in patients without ulcers was 4.01 ± 2.34years. As the duration of diabetes increases the probability of foot ulceration was more and it was statistically highly significant.

Table 22: Comparison of HbA1C of study subjects with other studies

Group	Present study	Hajieh Shahbazian et al [116]
With ulcer	8.52±0.88g	9.5±1.8g
Without ulcer	6.75±0.36g	7.9±1.7g

In Group A, 100% of the study subjects had the HbA1C level more than 6.5%. Where as in Group B, 40% had the HbA1C level less than 6.5% and 60% had the HbA1C level more than 6.5%. The mean HbA1c in Group A was 8.52±0.88g and in Group B was 6.75±0.36 which is similar to study conducted by Hajieh Shahbazian et al [116]in

which the mean HbA1c in group of patients with ulcer was 9.5±1.8g and in group without ulcer was 7.9±1.7g. Foot ulcer was more commonly seen among patients with uncontrolled diabetes and this difference was statistically highly significant hence the higher levels of HbA1c levels is also a predictor of risk for developing foot ulcers.

Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 87.5% of the study subjects in Group A and 10 8.3% of the study subjects in Group B.

Semmes- Weinstein 10G monofilament wire testing diagnosed diabetic peripheral neuropathy among 75% of the study subjects in Group A and 22.5% of the study subjects in Group B. But a cross-sectional study conducted by Al-Geffari M et al [109] diagnosed DPN in 31.4% of patients suffering it.

Biothesiometer diagnosed diabetic peripheral neuropathy among 72.5% of the study subjects in Group A and 13.3% of the study subjects in Group B. A similar study conducted by Adgaonkar A A et al[117] diagnosed DPN in 42% of patients suffering it.

Table 23: Comparison of Semmes- Weinstein 10G monofilament wire findings with different studies

Parameter	Present study	Al-Geffari M et al [109]	Yuzhe Feng et al [39]
Sensitivity	75%	69.7%	57% to 93%
Specificity	77.5%	87.9%	75% to 100%
PPV	52.63%	82.6%	84% to 100%
NPV	90.29%	78%	36% to 94%

Diabetic peripheral neuropathy diagnosis by Semmes- Weinstein 10G monofilament wire testing showed the sensitivity of 75%, specificity of 77.5%, positive predictive value of 52.63%, negative predictive value of 90.29%, percentage of false positive were 22.5%, percentage of false negative were 25% and accuracy of diagnosis was

76.88%. A study conducted Al-Geffari M et al [109] showed the sensitivity of 69.7%, specificity of 87.9%, PPV of 82.6%, NPV of 78% and accuracy of diagnosis 79.7%. A meta-analysis study conducted by Yuzhe Feng et al [39] showed the sensitivity of 57% to 93%, specificity of 75% to 100%, PPV of 84% to 100% and NPV of 36% to 94%. These findings were similar to the findings of present study.

Table 24: Comparison of Biothesiometer findings with different studies

Parameter	Our study	Armstrong DG et al [38]	P. Jayaprakash et al [118]
Sensitivity	72.5%	100%	83%
Specificity	86.67%	75.6%	63%

By Biothesiometer showed the sensitivity of 72.5%, specificity of 86.67%, positive predictive value of 64.44%, negative predictive value of 90.43%, percentage of false positive were 13.33%, percentage of false negative were 27.5% and accuracy of diagnosis was 83.13%. By verbal questionnaire method showed the sensitivity of 87.5%, specificity of 91.67%, positive predictive value of 77.78%, negative predictive value of 95.65%, percentage of false positive were 8.33%, percentage of false negative were 12.5% and accuracy of diagnosis was 90.63%, these results are similar to the results of study conducted by Armstrong DG et al[38] and P. Jayaprakash et al [118] as discussed in the above table.

Table 25: Comparison of Combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method findings with different studies

Parameter	Present study	Armstrong DG et al [38]
Sensitivity	82.5%	96.7%
Specificity	73.33%	85.9%

Combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 87.5% of the

study subjects in Group A and 26.7% of the study subjects in Group B. Sensitivity and specificity of this combination were 82.5% and 73.33% respectively which are comparable to study conducted by Armstrong DG et al[38]in which sensitivity and specificity were 96.7% and 85.9% respectively.

Combination of Biothesiometer and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 87.5% of the study subjects in Group A and 19.2% of the study subjects in Group B. Combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer diagnosed diabetic peripheral neuropathy among 80% of the study subjects in Group A and 28.3% of the study subjects in Group B. Combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 87.5% of the study subjects in Group A and 32.5% of the study subjects in Group B.

Diabetic peripheral neuropathy diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method showed the sensitivity of 82.5%, specificity of 73.33%, positive predictive value of 50.77%, negative predictive value of 92.63%, percentage of false positive were 26.67%, percentage of false negative were 17.5% and accuracy of diagnosis was 75.63%.

Table 26: Comparison of Combination of Biothesiometer and Verbal questionnaire method findings with different studies

Parameter	Our study	Armstrong DG et al [38]
Sensitivity	87.5%	90.0%
Specificity	80.3%	83.5%

By combination of Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 80.83%, positive predictive value of 60.34%, negative predictive value of 95.1%, percentage of false positive were 19.17%, percentage of false negative were 12.5% and accuracy of diagnosis was 82.5% which are comparable to study conducted by Armstrong DG et al [38].

Table 27: Comparison of Combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer findings with different studies

Parameter	Present study	Armstrong DG et al [38]
Sensitivity	80%	88.2%
Specificity	71.67%	88.2%

By combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer showed the sensitivity of 80%, specificity of 71.67%, positive predictive value of 48.48%, negative predictive value of 91.49%, percentage of false positive were 28.33%, percentage of false negative were 20% and accuracy of diagnosis was 73.75% which are similar to study conducted by Armstrong DG et al [38]. But in the studies conducted by Perkin's et al[77] they have not found any significant improvement in diagnostic value when the screening tests are combined.

Table 28: Comparison of Combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method findings with different studies

Parameter	Present study	Armstrong DG et al [38]
Sensitivity	87.5%	86.7%
Specificity	67.5%	89.4%

Diabetic peripheral neuropathy diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 67.5%, positive predictive value of 47.3%, negative predictive value of 94.19%, percentage of false positive were 32.5%, percentage of false negative were 12.5% and accuracy of diagnosis was 72.5% but in study conducted by Armstrong DG et al[38] sensitivity is similar to our study specificity in their study is increased to89.4%

According to Harris Mat Foot Imprinting, in Group A and Group B the maximum of the study participants got involvement of the Great toe, 80% and 44.2% and this difference was statistically highly significant. Reason for high pressure points at these sites may be because of motor neuropathy causing muscle weakness leading to imbalance and toe deformities.[87] and atrophy of muscles leads to loss of cushion over these sites. Patients are likely to develop ulcers over these sites and should be advised to wear footwears with soft soles like microcellular rubber foot wears.

In Group A, 5% had vasculopathy and 95% of them did not show any evidence of vasculopathy. Where as in Group B, 3.3% had vasculopathy and 96.7% of them did not show any evidence of vasculopathy. All these differences were not statistically significant.

CONCLUSION

- Annual screening of diabetic patients for diabetic neuropathy would be conducted with Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and verbal questionnaire method.
- As screening tool verbal questionnaire method had the higher sensitivity and specificity, followed by Semmes- Weinstein 10G monofilament wire testing and Biothesiometer.
- Combination of Biothesiometer or Semmes- Weinstein 10G monofilament wire testing with Verbal questionnaire method increased the sensitivity and specificity.
- When all the three tests are combined then the sensitivity increased but the specificity to detect DPN decreased.

SUMMARY

The present study was conducted to identify the neuropathy screening tool in diabetic patients with "foot at risk". Three tests used for diabetic neuropathy were Semmes-Weinstein 10 G monofilament wire testing, Vibration perception threshold testing by Biothesiometer and Question verbal neuropathy score.

It was an observational analytical study conducted among the patients attending Surgery/Medicine OPD or wards. We included 40 patients with diabetic foot ulcers (Group A) and 120 patients without diabetic foot ulcers (Group B). Following were the observations in this study.

1. The mean age of the study participants in Group A was 59.25 ± 12.22years and that of Group B was 61.98 ± 10.65years. Majority of them were males in both the groups.
2. Maximum of the study participants in Group A were illiterates, whereas maximum of them in Group B were literates and this difference was statistically highly significant.
3. As the duration of diabetes increases the probability of foot ulceration was more and it was statistically highly significant. Foot ulceration was more commonly seen among patients with uncontrolled diabetes and this difference was statistically highly significant.
4. Semmes-Weinstein 10G monofilament wire testing, Biothesiometer and Peripheral neuropathy on verbal questionnaire method diagnosed DPN among 75%, 72.5% and 87.5% of the study subjects with diabetic foot ulcer respectively.
5. Diabetic peripheral neuropathy diagnosis by verbal questionnaire method showed the sensitivity of 87.5%, specificity of 91.67%, positive predictive value of 77.78%, negative predictive value of 95.65%, percentage of false positive were

8.33%, percentage of false negative were 12.5% and accuracy of diagnosis was 90.63%.

6. Semmes- Weinstein 10G monofilament wire testing showed the sensitivity of 75%, specificity of 77.5%, PPV of 52.63%, NPV of 90.29%, percentage of false positive were 22.5%, percentage of false negative were 25% and accuracy of diagnosis was 76.88%.
7. Biothesiometer showed the sensitivity of 72.5%, specificity of 86.67%, PPV of 64.44%, NPV of 90.43%, percentage of false positive were 13.33%, percentage of false negative were 27.5% and accuracy of diagnosis was 83.13%.
8. Combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method, Combination of Biothesiometer and Verbal questionnaire method and Combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer diagnosed DPN among 87.5%, 87.5% and 80% of the study subjects with diabetic foot ulcer respectively.
9. Combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method diagnosed diabetic peripheral neuropathy among 87.5% of the study subjects with diabetic foot ulcer respectively.
10. DPN diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing and Verbal questionnaire method showed the sensitivity of 82.5%, specificity of 73.33%, PPV of 50.77%, NPV of 92.63%, percentage of false positive were 26.67%, percentage of false negative were 17.5% and accuracy of diagnosis was 75.63%.
11. By combination of Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 80.83%, PPV of 60.34%, NPV of 95.1%,

percentage of false positive were 19.17%, percentage of false negative were 12.5% and accuracy of diagnosis was 82.5%.

12. By combination of Semmes- Weinstein 10G monofilament wire testing and Biothesiometer showed the sensitivity of 80%, specificity of 71.67%, PPV of 48.48%, NPV of 91.49%, percentage of false positive were 28.33%, percentage of false negative were 20% and accuracy of diagnosis was 73.75%.
13. DPN diagnosis by combination of Semmes- Weinstein 10G monofilament wire testing, Biothesiometer and Verbal questionnaire method showed the sensitivity of 87.5%, specificity of 67.5%, PPV of 47.3%, NPV of 94.19%, percentage of false positive were 32.5%, percentage of false negative were 12.5% and accuracy of diagnosis was 72.5%.
14. As screening tool verbal questionnaire method had the higher sensitivity and specificity, followed by Semmes- Weinstein 10G monofilament wire testing and Biothesiometer.
15. Combination of Biothesiometer or Semmes- Weinstein 10G monofilament wire testing with Verbal questionnaire method increased the sensitivity and specificity. If all the three tests are combined then the sensitivity increases but the specificity to detect DPN decreases.
16. Vasculopathy was slightly higher in patients with diabetic foot ulcers. According to Harris Mat Foot Imprinting, in Group A and Group B the maximum of the study participants got involvement of the Great toe, 80% and 44.2% and this difference was statistically highly significant.

BIBLIOGRAPHY

1. King H, Rewers M. Diabetes in adults is now a Third World problem. The WHO Ad Hoc Diabetes Reporting Group. Bull World Health Organ 1991; 69(6): 643-8.
2. Bjork S, Kapur A, King H, Nair J, Ramachandran A. Global policy: aspects of diabetes in India. Health Policy 2003; 66(1): 61-7
3. IDF South- East Asia. [Online]. 2019 [cited 2019 Sep 10];[4screens]. Available from: URL: https://idf.org/our-network/regions-members/south-east-asia/welcome.html
4. Richard JL, Schuldiner S. Epidemiology of diabetic foot problems. La Revue de medecine interne. 2008 Sep;29:S222-30.
5. Joshi R. Metabolic syndrome – Emerging clusters of the Indian Phenotype. The Journal of the Association of Physicians of India 2003; 51: 445-6.
6. Nather A, Bee CS, Huak CY, Chew JL, Lin CB, Neo S, Sim EY. Epidemiology of diabetic foot problems and predictive factors for limb loss. Journal of Diabetes and its Complications. 2008 Mar 1;22(2):77-82.
7. Bakri FG, Allan AH, Khader YS, Younes NA, Ajlouni KM. Prevalence of Diabetic Foot Ulcer and its Associated Risk Factors among Diabetic Patients in Jordan. J Med J 2012; 46: 118-125
8. Waaijman R, Arts ML, Haspels R, Busch-Westbroek TE, Nollet F, Bus SA. Pressure-reduction and preservation in custom-made footwear of patients with diabetes and a history of plantar ulceration. Diabetic Medicine. 2012 Dec;29(12):1542-9.
9. Leone S, Pascale R, Vitale M, Esposito S. Epidemiology of diabetic foot. Infez Med. 2012;20(Suppl 1):8-13.

10. Gray H, Pick TP, Howden R. Anatomy, descriptive and surgical. New York: Bounty Books; 1901

11. Pendsey S. Diabetic foot: a clinical atlas. CRC Press; 2013 Apr 8.

12. Tesfaye S, Vileikyte L, Rayman G, Sindrup S, Perkins B, Baconja M, Vinik A, Boulton A, on behalf of the Toronto Expert Panel on Diabetic Neuropathy. Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management. Diabetes Metab Res Rev. 2011;27:629–38.

13. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res ClinPract 2000; 47(2):123-8.

14. Dyck PJ, O'Brien PC. Quantitative sensation testing in epidemiological and therapeutic studies of peripheral neuropathy. Muscle Nerve 1999; 22(6):659- 62.

15. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH.A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia1993; 36(2):150-4.

16. Tavakkoly-Bazzaz J, Amoli MM, Pravica V, Chandrasecaran R, Boulton AJ, Larijani B, et al. VEGF gene polymorphism association with diabetic neuropathy. MolBiol Rep2010; 37(7):3625-30.

17. Dorsey RR, Eberhardt MS, Gregg EW, Geiss LS. Control of risk factors among people with diagnosed diabetes, by lower extremity disease status. Prev Chronic Dis2009; 6(4):A114.

18. Harati Y. Diabetes and the nervous system. EndocrinolMetabClin North Am1996; 25(2):325-59.

19. Rutkove SB. A 52-year-old woman with disabling peripheral neuropathy: review of diabetic polyneuropathy. JAMA 2009; 302(13):1451-8.

20. Bromberg MB. Peripheral neurotoxic disorders. Neurol Clin2000; 18(3):681- 94.

21. Sugimoto K, Murakawa Y, Sima AAF. Diabetic neuropathy- a continuing enigma. Diabetes Metab Res Rev 2000; 16(6):408-33.

22. Malik RA. Pathology and pathogenesis of diabetic neuropathy. Diabetes Reviews1999; 7:253-60.

23. Ryle C, Donaghy M. Non-enzymatic glycation of peripheral nerve proteins in human diabetics. J Neurol Sci1995; 129(1):62-8.

24. Ziegler D, Ametov A, Barinov A, Dyck PJ, Gurieva I, Low PA. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care2006; 29(11):2365-70.

25. Figueroa-Romero C, Sadidi M, Feldman EL. Mechanisms of disease: the oxidative stress theory of diabetic neuropathy. Rev EndocrMetab Disord2008; 9(4):301-14.

26. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993; 329(27):2002–12.

27. Kleinbongard P, Keymel S, Kelm M. New functional aspects of the L-arginine-nitric oxide metabolism within the circulating blood. Thromb Haemost 2007; 98(5):970–4.

28. Vincent MA, Montagnani M, Quon MJ. Molecular and physiologic actions of insulin related to production of nitric oxide in vascular endothelium. CurrDiab Rep 2003;3(4):279-88.

29. Chu S, Bohlen HG. High concentration of glucose inhibits glomerular endothelial eNOS through a PKC mechanism. Am JPhysiol Renal Physiol 2004; 287(3):F384–92.

30. Cohen RA, Tong X. Vascular oxidative stress: the common link in hypertensive and diabetic vascular disease. J CardiovascPharmacol 2010; 55(4):308–16.

31. Apfel SC, Kessler JA, Adornato BT, LitchyWJ,Sanders S, Rask CA.Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. NGF Study Group. Neurology1998; 51(3):695-702.

32. Krendel DA, Zacharias A, Younger DS. Autoimmune diabetic neuropathy. NeurolClin1997; 15(4):959-71.

33. Carrington AL, Litchfield JE. The aldose reductase pathway and non-enzymatic glycation in the pathogenesis of diabetic neuropathy: a critical review for the end of the 20th century. Diabetes Reviews 1999; 7(4): 275-99.

34. N. Katsilambros, E. Dounis, P. Tsapogas and N. Tentolouris. Atlas of the Diabetic Foot. Italy: British Library Cataloguing in Publication Data; 2003

35. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospec- tive study. Diabetologia. 1992;35:660–3.

36. Tesfaye S, Watt J, Benbow SJ, Pang KA, Miles J, MacFarlane IA. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. Lancet 1996; 348(9043): 1698-701.

37. Barber MA, Conolley J, Spaulding CM, Dellon AL. Evaluation of pressure threshold prior to foot ulceration. J Am Podiatr Med Assoc2001; 91:508–14.

38. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG: Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. Arch Intern Med 1998; 158(3):289–92

39. Feng Y, Schlosser FJ, SumpioBE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. J VascSurg 2009; 50(3):675-82.

40. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes JAMA 2005; 293(2):217–28.

41. Mayfield JA, Sugarman JR. The use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in persons with diabetes. J FamPract 2000; 49(Suppl. 11):S17–29.

42. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diabetes Care 2006; 29(6):1202–7.

43. Ziegler D, Mayer P, Wiefels K, Gries FA. Assessment of small and large fiber function in long-term type1 (insulin-dependent) diabetic patients with and without painful neuropathy. Pain 1988; 34(1):1–10.

44. Krumova EK, Geber C, Westermann A, Maier C. Neuropathic pain: is quantitative sensory testing helpful? CurrDiab Rep 2012; 12(4):393–402.

45. Liniger C, Albeanu A, Bloise D, Assal JP. The tuning fork revisited. Diabet Med 1990; 7(10):859–64.

46. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at high risk for foot ulceration: a prospective multicenter trial. Diabetes Care 2000; 23(5):606–11.

47. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care 1998; 21(7):1071–5.

48. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. Diabetes care. 1994 Jun 1;17(6):557-60.

49. Mirsky IA, Futterman P, Brohkahn RH. The quantitative measurement of vibratory perception in subjects with and without diabetes mellitus. J Lab Clin Med 1953; 41(2):221-35.

50. Bloom S, Till S, Sonksen P, Smith S. Use of a biothesiometer to measure individual vibration thresholds and their variation in 519 non-diabetic subjects. Br Med J 1984; 288 (6433):1793-5.

51. Rheeder P, Van Wyk JT, Hokken JW, Hueting HM. Monofilament assessment of neuropathy in a community diabetes clinic. South African Medical Journal. 2002;92(9):715-9.

52. Dyck PJ, MeltonLJ, O'Brien PC, Service FJ. Approaches to improve epidemiological studies of diabetic neuropathy: insights from the Rochester Diabetic Neuropathy Study. Diabetes 1997; 46:S5–8.

53. Veves A, Manes C, Murray HJ, Young MJ, Boulton AJ. Painful neuropathy and foot ulceration in diabetic patients. Diabetes Care 1993; 16(8):1187–9.

54. Young RJ, Zhou YQ, Rodriguez E, Prescott RJ, Ewing DJ, Clarke BF. Variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetic polyneuropathy. Diabetes 1986; 35(2):192–7.

55. Feldman EL, Stevens MJ, Thomas PK, Brown MB, Canal N, Greene DA: A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1993; 16(8):1187-9.

56. BrilV, TomiokaS, BuchananRA, Perkins BA, mTCNS Study Group. Reliability and validity of the modified Toronto Clinical Neuropathy Score in diabetic sensorimotor polyneuropathy. Diabet Med 2009; 26(3): 240–6.

57. Papanas N, Papatheodorou K, Christakidis D, Papazoglou D, Giassakis G, Piperidou H, et al. Evaluation of a new indicator test for sudomotor function (Neuropad) in the diagnosis of peripheral neuropathy in type 2 diabetic patients. ExpClinEndocrinol Diabetes 2005;113(4):195–8.

58. Papanas N, Giassakis G, Papatheodorou K, Papaoglou D, Monastiriotis C, ChristakidisD,et al. Use of the new indicator test (Neuropad) for the assessment of the staged severity of neuropathy in type 2 diabetic patients. ExpClinEndocrinol Diabetes 2007;115:58–61.

59. Anbar M. Clinical thermal imaging today. IEEE Eng Med Biol 1998; 17(4):25–33.

60. VargasJVC, Brioschi ML, Dias FG, Parolin MB, Mulinari-Brener FA, Ordonez JC, etal.Normalized methodology for medical infrared imaging. Infrared Physics & Technology 2009; 52(1):42–7.

61. Flynn MD, Tooke JE. Microcirculation and the diabetic foot. Vasc Med Rev.1990; 1:121–38.

62. Vinik AI, Erbas T, Park TS, Stansberry KB, Scanelli JA, Pittenger GL. Dermal neurovascular dysfunction in type 2 diabetes. Diabetes Care 2001; 24(8):1468–75.

63. Ewing DJ, Burt AA, Campbell IW, Clarke BF. Vascular reflexes in diabetic autonomic neuropathy. The Lancet 1973; 302(7842):1354–6.

64. Pendsey S. Diabetic foot: a clinical atlas. CRC Press; 2013 Apr 8.

65. Veves A. The diabetic foot. Springer; 2018.

66. Lekkala J. Plantar shear stress measurements—A review. Clinical Biomechanics. 2014 May 1;29(5):475-83.

67. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. Diabetologia. 1992;35:660–3.

68. D'Ambrogi E, Giurato L, D'Agostino MA, Giacomozzi C, Macellari V, Caselli A, Uccioli L. Contribution of plantar fascia to the increased forefoot pressures in diabetic patients. Diabetes Care. 2003;26:1525–9.

69. Kida Y, Kashiwagi A, Nishio Y, Kodama M, Abe N, Shigeta Y. Is difference of arterial and venous oxygen content a possible marker for diabetic foot? Diabetes Care. 1988;11:515–6.

70. Fleckenstein JL, Watumull D, Conner KE, Ezaki M, Greenlee RG Jr, Bryan WW, Chason DP, Parkey RW, Peshock RM, Purdy PD. Denervated human skeletal muscle: MR imaging evaluation. Radiology. 1993;187:213–8.

71. Suzuki E, Kashiwagi A, Hidaka H, Maegawa H, Nishio Y, Kojima H, Haneda M, Yasuda H, Morikawa S, Inubushi T, Kikkawa R. 1H- and 31P-magnetic resonance spectroscopy and imaging as a new diagnostic tool to evaluate neuropathic foot ulcers in type II diabetic patients. Diabetologia. 2000;43:165–72.

72. Reiber GE, Vileikyte LO, Boyko ED, Del Aguila M, Smith DG, Lavery LA, Boulton AJ. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes care. 1999 Jan 1;22(1):157-62.

73. Myerson MS, Shereff MJ. The pathological anatomy of claw and hammer toes. J Bone Joint Surg. 1989;71-A:45–9.

74. Garbalosa JC, Cavanagh PR, Wu G, et al. Foot function in diabeticpatients after partial amputation. Foot Ankle Int. 1996;17:43–8.

75. Lavery LA, Lavery DC, Quebedaux-Farnham TL. Increased foot pressures after great toe amputation in diabetes. Diabetes Care. 1995;18:1460–2.

76. Nester CJ. Review of literature on the axis of rotation at the subtalar joint. Foot. 1998;8:111–8.

77. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. SciTransl Med. 2014;6(265):265sr6.

78. Stojadinovic O, Pastar I, Nusbaum AG, Vukelic S, Krzyzanowska A, Tomic-Canic M. Deregulation of epidermal stem cell niche contributes to pathogenesis of nonhealing venous ulcers. Wound Repair Regen. 2014;22(2):220–7.

79. Stojadinovic O, Yin N, Lehmann J, Pastar I, Kirsner RS, Tomic- Canic M. Increased number of Langerhans cells in the epidermis of diabetic foot ulcers correlates with healing outcome. Immunol Res. 2013;57(1–3):222–8.

80. Yager DR, Zhang LY, Liang HX, Diegelmann RF, Cohen IK. Wound fluids from human pressure ulcers contain elevated matrix metalloproteinase levels and activity compared to surgical wound fluids. J Invest Dermatol. 1996;107(5):743–8.

81. Liang L, Stone RC, Stojadinovic O, Ramirez H, Pastar I, Maione AG, Smith A, Yanez V, Veves A, Kirsner RS, Garlick JA, Tomic- Canic M. Integrative analysis of miRNA and mRNA paired expression profiling of primary fibroblast derived from diabetic foot ulcers reveals multiple impaired cellular functions. Wound Repair Regen. 2016;24(6):943–53

82. Lindley LE, Stojadinovic O, Pastar I, Tomic-Canic M. Biology and biomarkers for wound healing. PlastReconstr Surg. 2016;138(3Suppl):18S–28S.

83. Pilcher BK, Wang M, Qin XJ, Parks WC, Senior RM, Welgus HG. Role of matrix metalloproteinases and their inhibition in cutaneous wound healing and allergic contact hypersensitivity. Ann N Y Acad Sci. 1999;878:12–24.

84. Nagaoka T, Kaburagi Y, Hamaguchi Y, Hasegawa M, Takehara K, Steeber DA, et al. Delayed wound healing in the absence of intercellular adhesion molecule-1 or L-selectin expression. Am J Pathol. 2000;157(1):237–47.

85. Madlener M, Parks WC, Werner S. Matrix metalloproteinases (MMPs) and their physiological inhibitors (TIMPs) are differentially expressed during excisional skin wound repair. Exp Cell Res. 1998;242(1):201–10.

86. Parks WC. Matrix metalloproteinases in repair. Wound Repair.Regen. 1999;7(6):423–32.

87. Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. Wound Repair Regen. 1996;4(4):411–20.

88. Stojadinovic O, Landon JN, Gordon KA, Pastar I, Escandon J, Vivas A, et al. Quality assessment of tissue specimens for studies of diabetic foot ulcers. ExpDermatol. 2013;22(3):216–8.

89. Stojadinovic O, Pastar I, Vukelic S, Mahoney MG, Brennan D, Krzyzanowska A, et al. Deregulation of keratinocyte differentiation and activation: a hallmark of venous ulcers. J Cell Mol Med. 2008;12(6B):2675–90.

90. Maione AG, Smith A, Kashpur O, Yanez V, Knight E, Mooney DJ, et al. Altered ECM deposition by diabetic foot ulcer-derived fibroblasts implicates fibronectin in chronic wound repair. Wound Repair Regen. 2016;24(4):630–43.

91. Liang L, Stone RC, Stojadinovic O, Ramirez H, Pastar I, Maione AG, Smith A, Yanez V, Veves A, Kirsner RS, Garlick JA, Tomic- Canic M. Integrative analysis of miRNA and mRNA paired expression profiling of primary fibroblast derived

from diabetic foot ulcers reveals multiple impaired cellular functions. Wound Repair Regen. 2016;24(6):943–53.

92. Velander P, Theopold C, Bleiziffer O, Bergmann J, Svensson H, Feng Y, et al. Cell suspensions of autologous keratinocytes or autologous fibroblasts accelerate the healing of full thickness skin wounds in a diabetic porcine wound healing model. J Surg Res. 2009;157(1):14–20.

93. Maione AG, Brudno Y, Stojadinovic O, Park LK, Smith A, Tellechea A, et al. Three-dimensional human tissue models that incorporate diabetic foot ulcer-derived fibroblasts mimic in vivo features of chronic wounds. Tissue Eng Part C Methods. 2015;21(5):499–508.

94. Berlanga-Acosta J, Mendoza-Mari Y, Martinez MD, Valdes-Perez C, Ojalvo AG, Armstrong DG. Expression of cell proliferation cycle negative regulators in fibroblasts of an ischemic diabetic foot ulcer. A clinical case report. Int Wound J. 2013;10(2): 232–6.

95. Yang M, Sheng L, Zhang TR, Li Q. Stem cell therapy for lower extremity diabetic ulcers: where do we stand? Biomed Res Int. 2013;2013:462179.

96. Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S, Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia. 2002;45(7):1011–6.

97. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. Wound Repair Regen. 2014;22(5):569–78.

98. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen. 2008;16(5):585–601.

99. Pastar I, Stojadinovic O, Krzyzanowska A, Barrientos S, Stuelten C, Zimmerman K, et al. Attenuation of the transforming growth factor beta-signaling pathway in chronic venous ulcers. Mol Med. 2010;16(3–4):92–101.

100. Costa PZ, Soares R. Neovascularization in diabetes and its complications. Unraveling the angiogenic paradox. Life Sci. 2013;92(22):1037–45.

101. Lauer G, Sollberg S, Cole M, Flamme I, Sturzebecher J, Mann K, et al. Expression and proteolysis of vascular endothelial growth factor is increased in chronic wounds. J Invest Dermatol.2000;115(1):12–8.

102. Aljada A, Friedman J, Ghanim H, Mohanty P, Hofmeyer D, Chaudhuri A, et al. Glucose ingestion induces an increase in intranuclear nuclear factor kappaB, a fall in cellular inhibitor kappaB, and an increase in tumor necrosis factor alpha messenger RNA by mononuclear cells in healthy human subjects. Metabolism.2006;55(9):1177–85.

103. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. J ClinEndocrinolMetab. 2000;85(8):2970–3.

104. Sarrafian SK. Biomechanics of the subtalar joint complex. ClinOrthop Res. 1993;290:17–26.

105. Hutton WC, Dhanendran M. The mechanics of normal and hallux valgus feet—a quantitative study. ClinOrthopRelat Res. 1981;157:7–13.

106. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination is asignificant predictor of the risk of foot ulceration and amputation in patients with diabetesmellitus. Journal of vascular surgery. 2011 Jan 1;53(1):220-6.

107. Meijer JW, van Sonderen E, Blaauwwiekel EE, Smit AJ, Groothoff JW,Eisma WH, et al. Diabetic neuropathy examination: a hierarchical scoring system to diagnose distal polyneuropathy in diabetes. Diabetes Care2000; 23(6):750-3.

108. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination is a significant predictor of the risk of foot ulceration and amputation in patients with diabetes mellitus. Journal of vascular surgery. 2011 Jan 1;53(1):220-6.

109. Al-Geffari M. Comparison of different screening tests for diagnosis of diabetic peripheral neuropathy in Primary Health Care setting. International journal of health sciences. 2012 Jun;6(2):127.

110. Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. Diabetes care. 2001 Feb 1;24(2):250-6.

111. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993 Feb 1;36(2):150-4.

112. Bhamre SD, Kailash KM, Sadiwala CA. A Clinical Profile of Diabetic Foot Patients at Tertiary Health Care Institute, Nashik. MVP Journal of Medical Science. 2015 Jun 1;2(1):49-52.

113. Viswanathan V, Madhavan S, Rajasekar S, Chamukuttan S, Ambady R. Urban-rural differences in the prevalence of foot complications in South-Indian diabetic patients. Diabetes care. 2006 Mar 1;29(3):701-3.

114. Abdulghani HM, AlRajeh AS, AlSalman BH, AlTurki LS, AlNajashi NS, Irshad M, Alharbi KH, AlBalawi YE, AlSuliman YA, Ahmad T. Prevalence of diabetic comorbidities and knowledge and practices of foot care among diabetic patients: a

cross-sectional study. Diabetes, metabolic syndrome and obesity: targets and therapy. 2018;11:417.

115. Nongmaithem M, Bawa AP, Pithwa AK, Bhatia SK, Singh G, Gooptu S. A study of risk factors and foot care behavior among diabetics. Journal of family medicine and primary care. 2016 Apr;5(2):399.

116. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). Pakistan journal of medical sciences. 2013 May;29(3):730.

117. Adgaonkar AA, Dawange AA, Adgaonkar SA, Kale V, Shekokar P. Clinical profile of peripheral neuropathy in diabetes mellitus by nerve conduction study. Sch J App Med Sci. 2014;2(6A):1973-7.

118. Jayaprakash P, Bhansali A, Bhansali S, Dutta P, Anantharaman R, Shanmugasundar G, Ravikiran M. Validation of bedside methods in evaluation of diabetic peripheral neuropathy. The Indian journal of medical research. 2011 Jun;133(6):645.

ANNEXURES

ANNEXURE I

SAMPLE INFORMED CONSENT FORM:

TITLE OF THE PROJECT	**SCREENING TESTS FOR NEUROPATHY IN DIABETIC PATIENTS WITH "FOOT AT RISK"**

PURPOSE OF RESEARCH:

I have been informed that this study is conducted to identify proper tools for screening of neuropathy in diabetic patients with "foot at risk".

PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomforts during the examination or during my treatment. This is mainly the result of my condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in the study will help to identify proper tools for screening of neuropathy in diabetic patients with "foot at risk".

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study to **DR. …….** in the Department of General Surgery who will be available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that **DR…….** may terminate my participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me. But no further compensation

would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Date

(Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that **DR. …….** has explained to me the purpose of research, the study procedure, that I will undergo and the possible discomforts as well as benefits that I may experience in my own language. I have been explained all the above in detail in my own language and I understand the same. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to signature) Date

ANNEXURE II

PROFORMA FOR CASE TAKING

SL NO

Name

Age IP NO

Sex UNIT

Religion DOA

Occupation DOD

Address:

Mobile No:

Chief Complaints:

History of Presenting Illness:

A. Duration:

B. Onset

Past History:

Treatment History

Personal History:

A. Diet

B. Smoking

C. Alcohol / Tobacco chewing

D. Bowel and Bladder

E. Menstrual history:

Family History:

GENERAL PHYSICAL EXAMINATION:

Built: Well/Moderate/Poor

Nourishment: Well/Moderate/Poor

Facial expression:

Temperature: Pulse:

B.P: Respiratory Rate:

Eye Signs:

LOCAL EXAMINATION:

Inspection:

B) **Palpation**:

TESTS FOR NEUROPATHY

1. Question Verbal neuropathy score

- Do your feet feel numb?
- Do your feet tingle, as is electricity was travelling into your foot?
- Do your feet feel as if insects were crawling on them?
- Do your feet ever burn?

2. Semmes- Weinstein 10 g monofilament wire system

3. Vibration perception threshold testing using biothesiometer

Other tests

- Hand held Doppler for vasculopathy.
- **Harris mat foot imprint** for pressure points.

SYSTEMIC EXAMINATION:

Per Abdomen

Respiratory System

Cardio Vascular System

Central Nervous System

LABORATORY TESTS

Haemoglobin% :

Total Count :

Platelets :

Differential Count

Neutrophil :

Lymphocytes :

Eosinophils :

Basophils :

Blood Urea :

Serum Creatinine :

FBS :

PPBS :

HBA1C :

SPECIAL TESTS:

FINAL DIAGNOSIS

Follow up

ANNEXURE III – MASTER CHART

SL NO	IP/ OPD NO	h/o foot ulcer	AGE (in years)	Gender	Literacy	Co-morbidities	Duration of DM (in years)	HBA1C	VQ method	S-W TEST	BIOTHESIOMETER	HMFI	Vasulopathy
1	O-396636	1	67	F	1	1	20	8.1	2	1	1	G	2
2	I-14731	1	80	M	2	3	15	8.4	1	1	1	G, M-1,M-5	2
3	I-14712	1	40	M	1	0	3	7.8	1	1	1	G	2
4	I-14711	1	50	M	2	1,2	10	8.4	1	1	1	G	2
5	I-42711	1	65	M	2	0	10	9	1	1	1	H	2
6	I-14464	1	49	M	1	0	7	8.8	1	1	1	M-1	2
7	I-15578	1	51	M	1	0	8	9.5	1	1	1	H	2
8	I-33148	1	40	M	1	1	3	7.2	2	2	2	H	2
9	I-33393	1	45	M	2	0	5	7.8	2	2	2	M-1	2
10	O-396635	1	53	F	2	1,2	20	8.6	1	1	1	G,M-1	2
11	I-38892	1	67	M	2	0	5	6.8	2	2	2	G	2
12	O-391494	1	62	M	1	0	3	7.4	1	1	2	G	2
13	O-392183	1	65	M	2	0	3	6.9	2	2	2	M-1	2
14	O-392117	1	63	M	2	1	15	8	1	1	2	G,H	2
15	O-392524	1	62	F	2	2	10	10	1	1	1	G	2
16	I-7946	1	73	M	2	0	12	9.4	1	1	1	G,M1	2
17	I-8002	1	34	M	1	0	8	8.8	1	1	1	G,M-5	2
18	I-7945	1	76	M	2	0	15	9.4	1	1	1	G,M-1	2
19	I-7992	1	65	M	2	0	10	8	1	1	1	G	2
20	I-6833	1	54	M	1	2	4	8.2	1	1	1	G	2
21	O-394548	1	61	M	2	0	8	9	1	1	1	G,H	2
22	I-38589	1	57	M	1	0	4	7.2	2	2	2	G,M-1,H	2
23	I-10633	1	65	M	2	0	15	10	1	1	1	G,M1	2
24	I-10626	1	70	M	2	0	20	9.2	1	1	1	G,M-1	2
25	I-10660	1	50	M	2	2	7	9.4	1	1	1	G,M-5	2
26	I-8085	1	53	M	1	1,3	6	8.8	1	2	1	G,H	2
27	I-7682	1	70	M	2	0	20	7.8	1	2	2	G,M-1	2
28	I-7108	1	85	M	2	1,2	20	9.5	1	1	1	G,M1	2
29	I-17646	1	65	M	2	3	6	8.8	1	1	1	G,M-1	2
30	O-240707	1	63	M	1	0	15	8.6	1	1	1	G,M-1	1
31	I-20371	1	70	M	2	1	1	11	1	1	1	G,M-1	2
32	I-20943	1	66	M	1	2,3	12	8.5	1	1	1	G,M-1	2
33	O-233536	1	65	M	2	0	3	8.1	1	1	1	G,M-1	2
34	I-17663	1	58	M	2	0	15	8.2	1	1	1	G,M-1	2

35	I-15991	1	70	M	2	0	8	7.8	1	1	1	G,M-3,H	2
36	I-21663	1	60	M	2	0	12	8.4	1	2	1	M-1	1
37	I-22935	1	53	M	2	1,2	5	8.3	1	1	2	G	2
38	I-22957	1	45	M	1	3	4	7.8	1	2	2	G,M-1	2
39	I-24070	1	57	M	2	0	12	8.5	1	2	1	G,H	2
40	I-27627	1	26	M	1	0	8	10	1	1	2	H	2
41	I-3537	2	50	M	1	0	6	7.6	2	2	2	G,M-1,M-5	2
42	0-395891	2	70	F	2	0	5	7.4	2	2	2	G	2
43	O-395844	2	73	M	1	0	12	7.2	2	2	1	G,,M-5	2
44	O-396452	2	68	F	1	0	8	7	2	2	2	0	2
45	O-396758	2	50	M	1	0	7	6.5	2	2	2	0	2
46	O-396785	2	66	M	1	0	12	6.8	2	2	2	0	2
47	O-392219	2	81	M	1	0	20	7.2	2	2	2	G,M-1	2
48	O-391477	2	55	F	1	0	20	7.2	2	2	2	G,M-1	2
49	O-392181	2	57	M	1	0	10	7.6	1	1	1	G,M-3	2
50	O-392088	2	65	M	1	0	6	7.2	2	2	2	0	2
51	0-392577	2	62	M	1	2	6	7.5	2	1	1	G,M-1	2
52	O-392572	2	60	M	1	0	10	6.5	1	2	2	0	2
53	O-392520	2	72	M	1	0	15	7.2	2	1	1	G,M1	2
54	O-392411	2	62	M	1	0	10	6.5	2	2	2	0	2
55	O-392458	2	55	M	1	2	5	6.8	1	2	2	0	2
56	O-392581	2	70	M	1	0	6	6.8	2	2	2	0	2
57	O-401410	2	60	M	2	0	20	8.2	1	1	1	G,M-1	2
58	O-392429	2	47	M	1	0	11	6.8	2	2	2	G	2
59	O-390745	2	70	M	2	0	3	7.2	2	2	2	0	2
60	O-392459	2	70	M	1	2	20	6.8	1	1	2	G,M-3	2
61	O-392639	2	65	M	1	0	1	7	2	2	1	G,M-1	2
62	O-392232	2	52	M	1	0	8	7.1	2	2	2	0	2
63	O-178419	2	59	F	2	0	8	6.8	2	2	2	G,M-1	2
64	O-178426	2	48	F	2	0	4	6.5	2	2	2	G	2
65	O-403378	2	46	M	1	0	4	6.8	2	1	2	G	2
66	O-403371	2	70	M	2	2	6	6.5	2	2	2	G,M-1	2
67	O-403381	2	53	M	1	3	3	6.2	2	2	2	G	2
68	O-403383	2	66	F	2	0	10	6.5	2	2	2	G,M-1	2
69	O-403384	2	72	M	1	0	4	6.3	2	2	2	0	2
70	O-403376	2	48	F	1	1	7	6.5	2	2	2	0	2
71	O-403399	2	76	M	1	3	8	6.8	2	2	2	G,M-1	2
72	O-403395	2	70	M	1	0	9	6.3	2	1	1	G,M-1	2
73	O-403396	2	65	F	1	0	5	6.2	2	2	2	0	2
74	O-403397	2	60	F	1	2	6	6.7	2	2	2	0	2
75	O-403400	2	64	F	1	1	6	6.5	2	2	2	0	2
76	O-403401	2	68	M	1	0	4	7	2	2	1	0	2
77	O-403405	2	42	F	1	3	3	6.4	2	2	2	0	2
78	O-403408	2	65	F	1	0	5	6.6	2	2	2	0	2

79	O-403416	2	69	M	2	0	9	6.4	2	2	2	G	2
80	O-403424	2	67	M	1	0	7	7.2	2	1	1	G	2
81	O-403427	2	60	M	1	2	6	6.5	2	2	2	0	2
82	O-403419	2	74	M	1	0	12	6.5	2	1	2	G,M-1,M-5	2
83	O-403423	2	70	F	1	3	10	6.9	1	2	2	G,M-5	2
84	O-403534	2	66	M	1	0	5	6.7	2	2	2	0	2
85	O-403544	2	63	F	1	3	3	6.4	2	2	2	0	2
86	O-403385	2	60	F	1	0	8	6.5	2	2	2	G	2
87	O-403612	2	76	F	2	1	6	6.6	2	2	2	0	2
88	O-403728	2	70	F	1	0	7	6.9	2	2	2	G	2
89	O-403863	2	80	M	1	0	4	7.4	2	1	2	0	2
90	O-403872	2	38	M	2	2,3	3	7.2	2	1	2	G,M-1,M-5	2
91	O-403877	2	57	M	1	0	5	6.6	2	2	2	0	2
92	O-403891	2	75	M	1	1	6	6.6	2	2	1	G,M-1	2
93	O-403914	2	54	F	1	0	4	6.2	2	2	2	0	2
94	0-403909	2	54	F	1	0	4	6.3	2	2	2	0	2
95	0-403192	2	55	F	1	2	5	6.4	2	2	2	0	2
96	0-403917	2	54	F	1	1	3	7	2	1	2	0	2
97	0-336599	2	49	F	1	0	3	7.1	2	1	1	G,M-1	2
98	0-336583	2	68	M	1	0	4	6.4	2	2	2	G	2
99	0-336585	2	45	F	1	0	3	6.5	2	2	2	0	2
100	0-336607	2	68	F	2	1	4	6.4	2	2	2	0	2
101	0-336605	2	66	F	1	0	4	6.7	2	2	2	G	2
102	0-336610	2	58	F	1	0	6	6.6	2	2	2	G,M-1	2
103	0-336611	2	54	F	1	0	4	7.2	2	1	2	G	2
104	0-336581	2	68	M	1	1	3	7.2	2	2	1	G	2
105	0-336680	2	54	M	1	0	5	6.9	2	2	2	G,M-1	2
106	0-336669	2	73	M	1	0	5	6.8	2	2	2	0	2
107	0-336678	2	60	F	1	0	5	6.8	2	1	2	0	2
108	0-336737	2	55	F	1	0	4	6.5	2	2	2	G,H	1
109	0-336639	2	75	M	1	0	7	6.7	2	2	1	0	2
110	0-336839	2	75	M	2	0	5	6.5	2	2	2	0	2
111	0-327529	2	66	M	2	0	7	6.8	2	2	2	G,M-1	2
112	0-327520	2	43	M	2	1	4	6.8	2	1	1	0	2
113	0-327535	2	68	M	1	0	5	6.5	2	2	2	0	2
114	0-327528	2	75	F	1	0	6	6.5	2	2	2	G	2
115	0-327546	2	45	F	1	0	3	6.5	2	1	2	G,M-1	2
116	0-327706	2	62	M	1	0	4	6.4	2	2	2	0	2
117	0-327759	2	60	M	1	0	6	6.5	2	2	2	M-1	2
118	0-327754	2	33	M	1	0	3	6.7	2	2	2	0	2
119	0-327879	2	38	M	1	0	4	7.3	2	1	2	G,H	2
120	0-327937	2	55	M	1	0	3	7.4	2	2	2	0	2
121	0-327957	2	66	F	1	0	4	6.5	2	2	2	0	2
122	0-328015	2	70	M	2	0	6	6.8	2	2	2	0	2

123	0-3280016	2	76	M	1	0	12	7.2	1	1	2	G,M-1	2
124	0-328028	2	75	M	1	0	12	7	1	2	2	0	2
125	0-327521	2	68	M	2	0	8	6.8	1	2	2	G,M-1	2
126	0-327536	2	58	F	1	0	3	6.9	2	2	2	0	2
127	0-327540	2	65	M	1	0	6	6.5	2	2	1	0	2
128	0-327549	2	54	M	1	0	3	7	2	1	2	G,M-1	2
129	0-327706	2	62	M	1	0	5	6.4	2	2	2	0	2
130	0-328015	2	79	M	1	0	11	6.2	2	2	2	G,M-1	1
131	0-328038	2	74	M	1	0	8	6.4	2	2	2	0	2
132	0-327557	2	65	M	2	0	7	6.5	2	2	2	0	2
133	0-291149	2	66	M	1	0	4	6.8	2	1	2	G	2
134	0-291148	2	67	M	1	0	4	6.6	2	2	2	0	2
135	0-291165	2	68	M	2	0	5	6.5	2	2	2	0	2
136	0-291169	2	65	M	1	0	3	6.5	2	2	2	0	2
137	0-291168	2	69	F	1	0	5	6.5	2	1	2	G	2
138	0-291171	2	83	M	2	0	11	7.8	1	1	1	G,M-1	1
139	0-291466	2	69	M	2	0	7	6.5	2	2	2	0	2
140	0-291148	2	62	M	2	0	6	6.4	2	2	2	0	2
141	0-291156	2	73	M	1	0	6	6.7	2	2	2	0	2
142	0-291146	2	49	F	1	0	3	6.5	2	1	2	G	2
143	0-291540	2	55	F	1	0	5	6.6	2	2	2	0	2
144	0-291811	2	52	F	1	0	4	6.5	2	2	2	0	2
145	0-291826	2	64	M	1	0	5	7	2	1	2	G	2
146	0-266029	2	47	M	1	0	5	7.3	2	2	2	0	2
147	0-266037	2	74	M	1	0	6	6.7	2	2	2	0	2
148	0-266053	2	70	M	1	0	5	7	2	1	2	G	2
149	0-266056	2	42	M	1	0	3	6.1	2	2	2	G	2
150	0-266062	2	72	M	1	0	12	6.5	2	2	2	0	1
151	0-266061	2	53	M	1	0	4	6.4	2	2	2	0	2
152	0-266078	2	52	M	1	0	3	6.5	2	2	2	0	2
153	0-266077	2	74	M	1	0	7	6.7	2	2	2	G,M-1	2
154	0-266083	2	68	M	1	0	6	6.7	2	2	2	0	2
155	0-266066	2	79	M	1	0	7	6.6	2	2	2	0	2
156	0-265721	2	42	M	1	0	4	6.8	2	2	2	0	2
157	0-266105	2	53	F	1	0	3	6.9	2	2	2	0	2
158	0-266-84	2	55	M	1	0	3	7.4	2	1	2	G.M-1	2
159	0-266184	2	55	M	1	0	4	6.6	2	2	2	0	2
160	0-265919	2	40	M	1	0	3	6.7	2	2	2	0	2

KEY TO MASTER CHART

- **Gender**: M= Male, F= Female
- **Literacy**: 1= Literate, 2= Illiterate

  Literate: Those who have studied at least up to 10^{th} standard.

  Illiterate: Those who have not studied at least up to 10^{th} standard.
- **h/o foot ulcer:** 1= Present (Group A), 2= Absent (Group B)
- **Co-morbidities** :0= Absent, 1= hypertension, 2= Dyslipidemia, 3= heart diseases
- **VQ method: Verbal questionnaire method:** 1= Positive, 2= Negative
- **S-W monofilament test:** 1= Positive, 2= Negative
- **Biothesiometer**:1= Positive, 2= Negative
- **HMFI**: Harris Mat Foot Imprinting for high pressure points

  0 = Not involved, G= Great toe, M1= 1st metatarsal, M3= 3rd metatarsal, M5= 5th metatarsal, H= Heel
- **Vasulopathy :** 1= Present, 2= Absent

ANNEXURE IV: PHOTOGRAPHS

Figure 30: Biothesiometer in use

Figure 31: Semmes-Weinstein monofilament in use.

Figure 32: Harris mat foot imprint being taken.