"A COMPARATIVE STUDY OF TOPICAL HUMAN PLACENTAL EXTRACT WITH TOPICAL SUCRALFATE IN THE MANAGEMENT OF DIABETIC FOOT ULCERS"

By

Dr. AKARSH Y G

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY

IN

GENERAL SURGERY

Under the Guidance of

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Signature of the candidate

Dr.AKARSH Y G

ABSTRACT

INTRODUCTION:

Diabetes mellitus is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.Diabetic foot is one of the major complications of diabetes mellitus. One in every six people with diabetes will have a foot ulcer during his /her life time.

Diabetic foot ulcers require an integrated, multidisciplinary management which include wound care and diabetic control. Ideally dressings should reduce the symptoms, provide wound protection and encourage healing.Some of them are collagen, alginates and hydro fibers, hydrogels, hydrocolloids, foam dressings. A few new techniques were also introduced to aid in healing like offloading, topical negative Pressure therapies.

Sucralfate is a commonly used antacid .It is a basic aluminum salt of sucrose octasulfate. It acts as a mechanical barrier by strong electrostatic interaction with proteins at the ulcer site. Sucralfate has also been shown to have anti bacterial activity .Recent studies have also shown that it is structurally similar to heparin, and hence has angiogenic properties.

Placental extract is prepared from fresh term healthy human placenta, after delivery.It increases the synthesis of collagen, tissue protein, accelerates neoangiogenesis, and epithelialization. It also has immunotropic effect, EGF and Fibroblastic growth factor, which supports ossification and reduces surrounding tissue inflammation.

OBJECTIVES OF THE STUDY:

1. To evaluate the efficacy of topical sucralfate in the management of diabetic foot ulcers.
2. To evaluate the efficacy of topical human Placental extract in the management of diabetic foot ulcers.
3. To compare the efficacy of both topical sucralfate and human placental extract in the management of diabetic foot ulcers.

METHODOLOGY:

SOURCE OF DATA:

Study will be conducted on minimum of 100 patients divided into two groups - group I and group II each containing 50 patients , presenting to the department of surgery in R.L.Jalappa Hospital & Research Centre, SDUMC ,Kolar, during the period from January 2014 to May 2015 .

Patients presenting with Ulcers due to diabetes (wagners grade 1 & 2) are included in the study after considering other co-morbid conditions After clinical examination patients are grouped into two groups and after debridement they undergo the treatment and the wound is assessed weekly .

GROUP 1: All patients with odd numbers will be categorized into group 1 who will receive topical sucralfate dressing.

GROUP 2: All patients with even numbers will be categorized into group 2 who will receive topical human placental extract dressing.

INCLUSION CRITERIA:

1. All patients with type 2 diabetes mellitus with diabetic foot ulcers of Wagner's grade 1 and 2.

EXCLUSION CRITERIA:

1. Patients with chronic venous insufficiency of lower limbs with dermal changes and lymphedema.
2. Patients with uncontrolled diabetes with severe co morbid medical conditions.

RESULTS:

In our study we found that the mean reduction of wound area in patients treated with topical human placental extract was 14 sq cm and in patients treated with topical sucralfate was 8 sq cm which was statistically significant ($p<0.001$). The mean percentage reduction of wound area in human placental extract group was 39.04% and in sucralfate group was 29.04% , which showed statistical significance ($p< 0.001$).In terms of granulation tissue which was assessed at 4 weeks ,48 patients in human placental extract group had 100-75% granulation tissue where as in sucralfate group only 36 patients had 100-75% granulation tissue ($p=0.002$).

CONCLUSION: Human placental extract dressing therapy in the treatment of diabetic foot ulcers was found to be more effective, safe, promoter of wound healing, and hence can be recommended for the treatment of diabetic foot ulcers.

Keywords:Daibetic foot ulcers , human placental extract , sucralfate.

LIST OF ABBREVATIONS:

EGF	Epidermal Growth Factor
PGF2	Prostaglandins 2
TNF	Tumor Necrosis Factor
FGF	Fibroblast Growth Factor
VEGF	Vascular Endothelialcell Growth Factor
ECM	Extra Cellular Matrix
MMP	Matrix Metallo Proteinases
Hb	Haemoglobulin
PVR	Pulse Volume Recording
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
COX	Cyclo-oxygenase

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1.INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. It is the leading cause of end stage renal disease, a major cause of non traumatic amputations, responsible for 30% of the preventable blindness and a leading cause of cardiovascular mortality.The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. According to the world health organization, at least 171 million people worldwide have diabetes. The figure is likely to double by 2030.[1] Diabetic foot is one of the major complications of diabetes mellitus. One in every six people with diabetes will have a foot ulcer during his /her life time.[2]Currently there is a wound care revolution and a wide variety of dressings are available yet there is no ideal dressing .During the last two decades a wide variety of innovative dressings have been introduced in wound healing ,such as Benzoyl peroxide, collagen, insulin , oxygen therapy, sucralfate, honey and vinegar.

Sucralfate is a commonly used antacid .It is a basic aluminium salt of sucrose octasulfate. It acts as a mechanical barrier because of a strong electrostatic interaction with proteins at the ulcer site.[3]Sucralfate has also been shown to have anti bacterial activity.[4]Recent studies have also shown that it is structurally similar to heparin, and hence has angiogenic properties[5].Recently a peptide fraction isolated from the placental extract,exhibited distinct collagenase activity and helps in achieving faster and better healing.[6]

Placental extract is prepared from fresh term healthy human placenta, after delivery.It increases the synthesis of collagen, tissue protein, accelerates neo-angiogenesis, and epithelialization. It also has immunotropic effect, EGF and Fibroblastic growth factor, which supports ossification and reduces surrounding tissue inflammation and oedema.[7]

This study compare topical sucralfate with human placental extract in diabetic foot ulcers .They are highly efficacious in achieving faster and better healing. There is a need to optimize the ideal type of dressings in diabetic foot ulcers and thus the study is being taken up.

2. AIMS AND OBJECTIVES

1. To evaluate the efficacy of topical sucralfate in the management of diabetic foot ulcers.
2. To evaluate the efficacy of topical human Placental extract in the management of diabetic foot ulcers.
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3. REVIEW OF LITERATURE

ANATOMY OF FOOT

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

The foot and ankle contain:[8]

• 26 bones (one-quarter of the bones in the human body);

• 33 joints;

• More than 100 muscles, tendons, and ligaments.

• A network of blood vessels, nerves, skin and soft tissue.

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

Skin :[9,10,11]

The skin of dorsum of the foot is thin and highly flexible, containing hair follicles, sweat glands and scanty sebaceous gland. Hairs are sparse and thick. It is less then 2mm thick and few fibrous septa penetrate to deeper facial structures. The plantar skin is 5mm thick especially over those points which bear weight viz. heel, ball of big toe and lateral margins of the sole. It has no hair follicles or sebaceous glands but sweat glands are numerous .

Hypodermis is composed of loose areolar connective tissue, most of this is collagenous and elastic fibre's running parallel to the surface of the skin but some are continuous with the fibre's of dermis. Hypodermis is well supplied with blood vessels and nerve endings. Tactile sensation is exceptionally good in the sole. The subcutaneous tissue in the sole as in the palm differs from that of the rest of body in being more fibrous, tough and stingy. Fibrous septa divide the tissue into small loculi which are filled with fluid fat under tension. This makes a shock absorbing pad especially over the heel and over the tips of toes.

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

Plantar aponeurosis: Cover the whole length of the sole. It arises posteriorly from the medial and lateral tubercles of the calcaneus and 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. A very dense and strong intermediate part is known as plantar aponeurosis.

Parts of the Foot:

Structurally, the foot has three main parts:

The forefoot: Is composed of the five toes (called phalanges) and their connecting long bones (metatarsals). Each toe (phalanx) is made up of several small bones. The big toe (hallux) has two phalanges, two joints (interphalangeal joints) and two tiny, round sesamoid bones that enable it to move up and down. The other four toes each have three bones and two joints. The phalanges

are connected to the metatarsals by five metatarsal phalangeal joints at the ball of the foot. The forefoot bears half the body's weight and balances pressure on the ball of the foot.

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

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

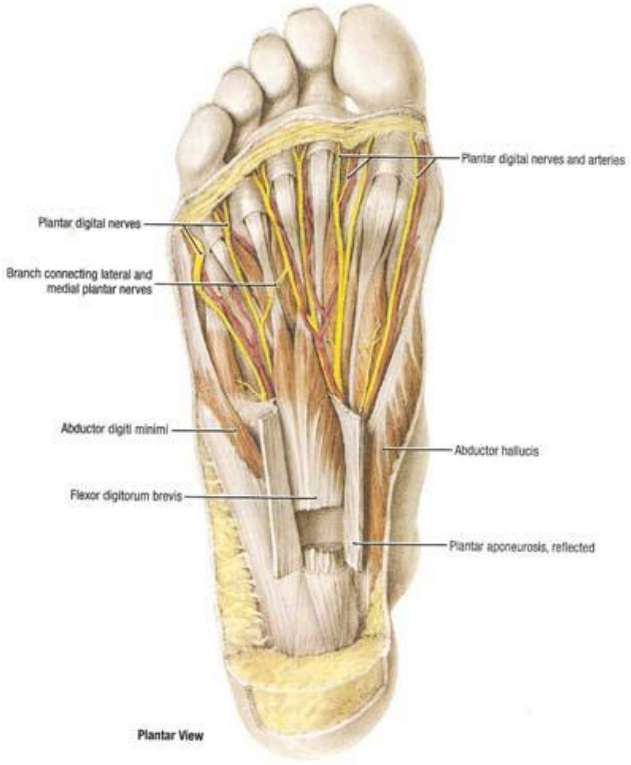
The Arches: The foot has three arches. The medial longitudinal arch is composed of the calcaneus, talus, navicular, cuneiforms, and the first three metatarsals. The lateral longitudinal arch is composed of the cuneiforms, cuboid and the fourth and fifth metatarsals. The transverse arch is composed of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

Muscles, Tendons, and Ligaments: There are 20 muscles in the foot that give the foot its shape by holding the bones in position and expand and contract to impart movement.

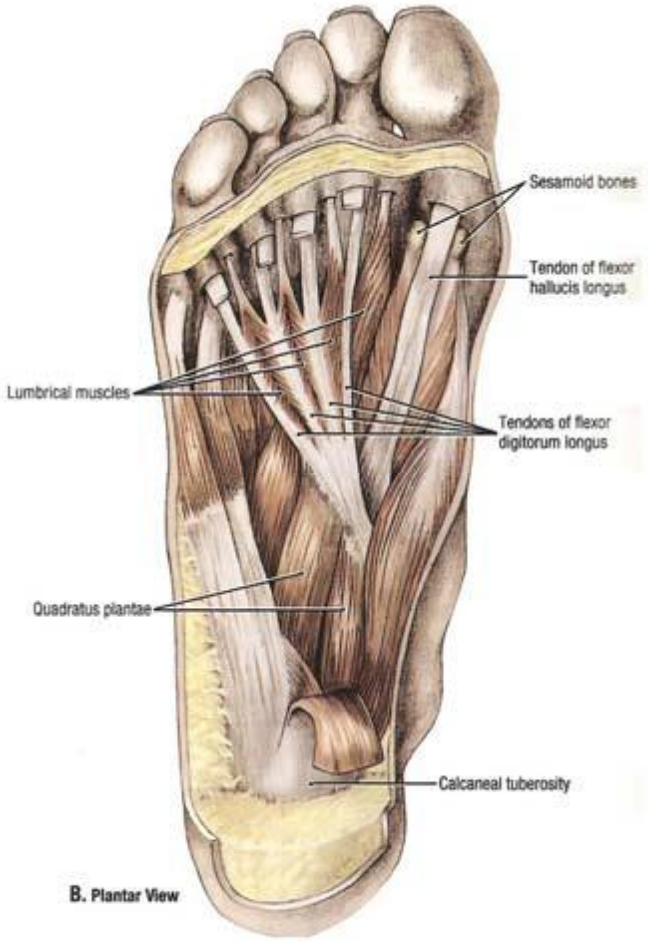
The muscles in the sole of the foot are categorized into four layers:

Muscles in the first layer include Flexor digitorum brevis, Abductor hallucis and Abductor digiti minimi. In the second layer are tendon of Flexor hallucis longus,Flexor digitorum accessorius

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.



First layer



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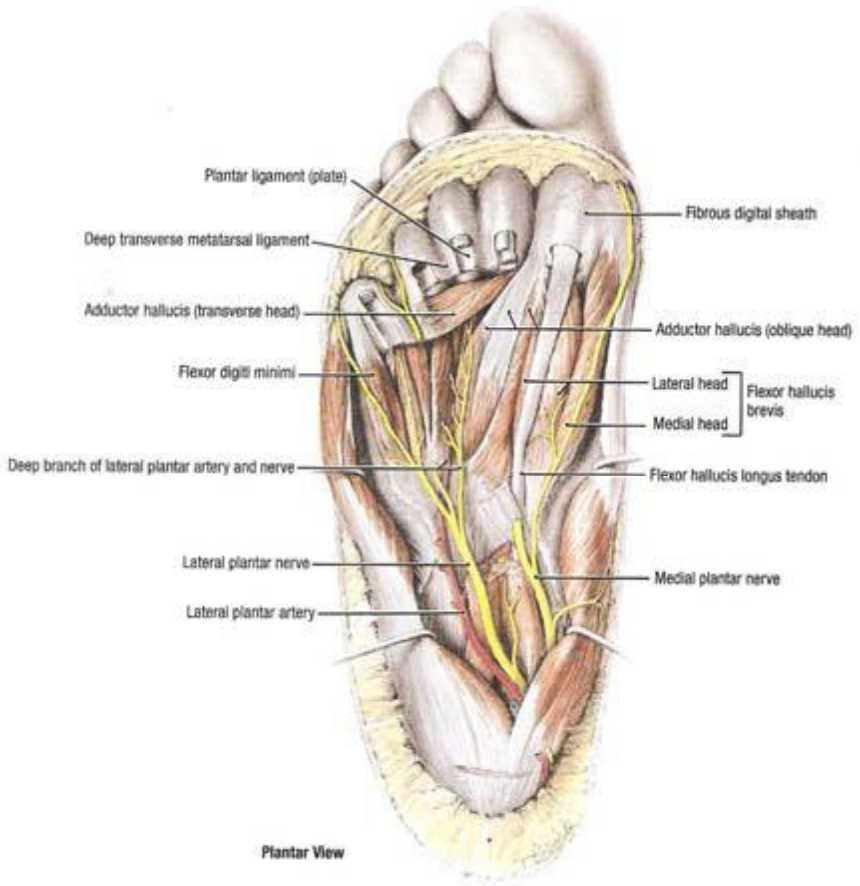
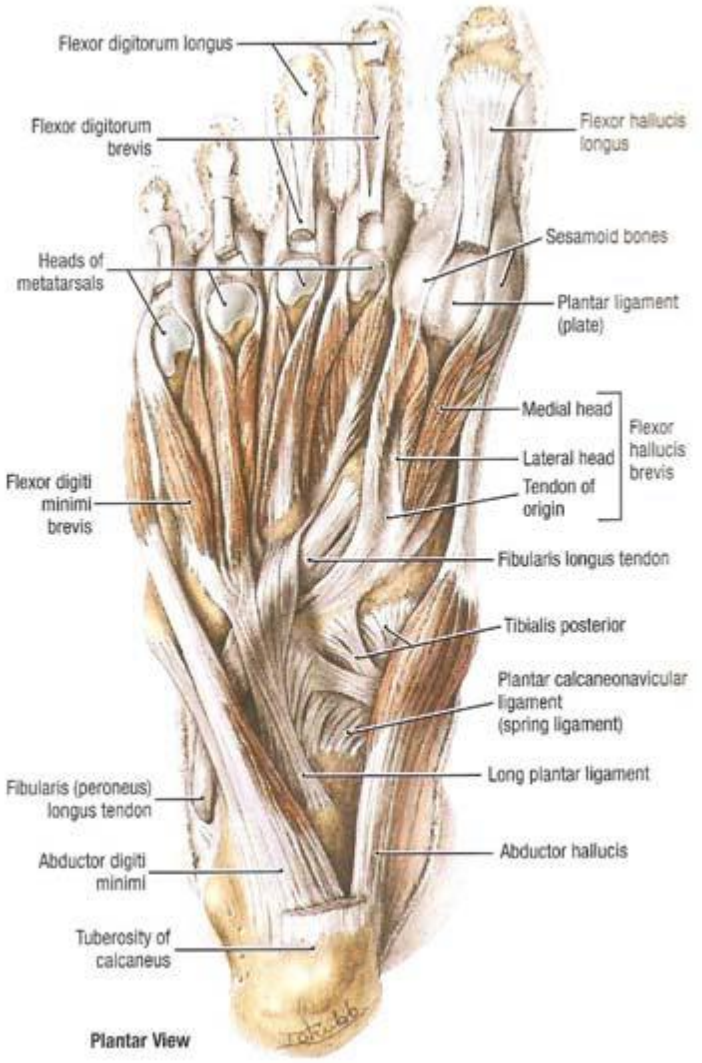

Plantar ligament (plate)
Deep transverse metatarsal ligament
Adductor hallucis (transverse head)
Flexor digiti minimi
Deep branch of lateral plantar artery and nerve
Lateral plantar nerve
Lateral plantar artery
Fibrous digital sheath
Adductor hallucis (oblique head)
Lateral head
Medial head
Flexor hallucis brevis
Flexor hallucis longus tendon
Medial plantar nerve
Plantar View

Third layer



Fourth layer

Figure 1 : Four layers of muscles of foot

Vasculature of sole:

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

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

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

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

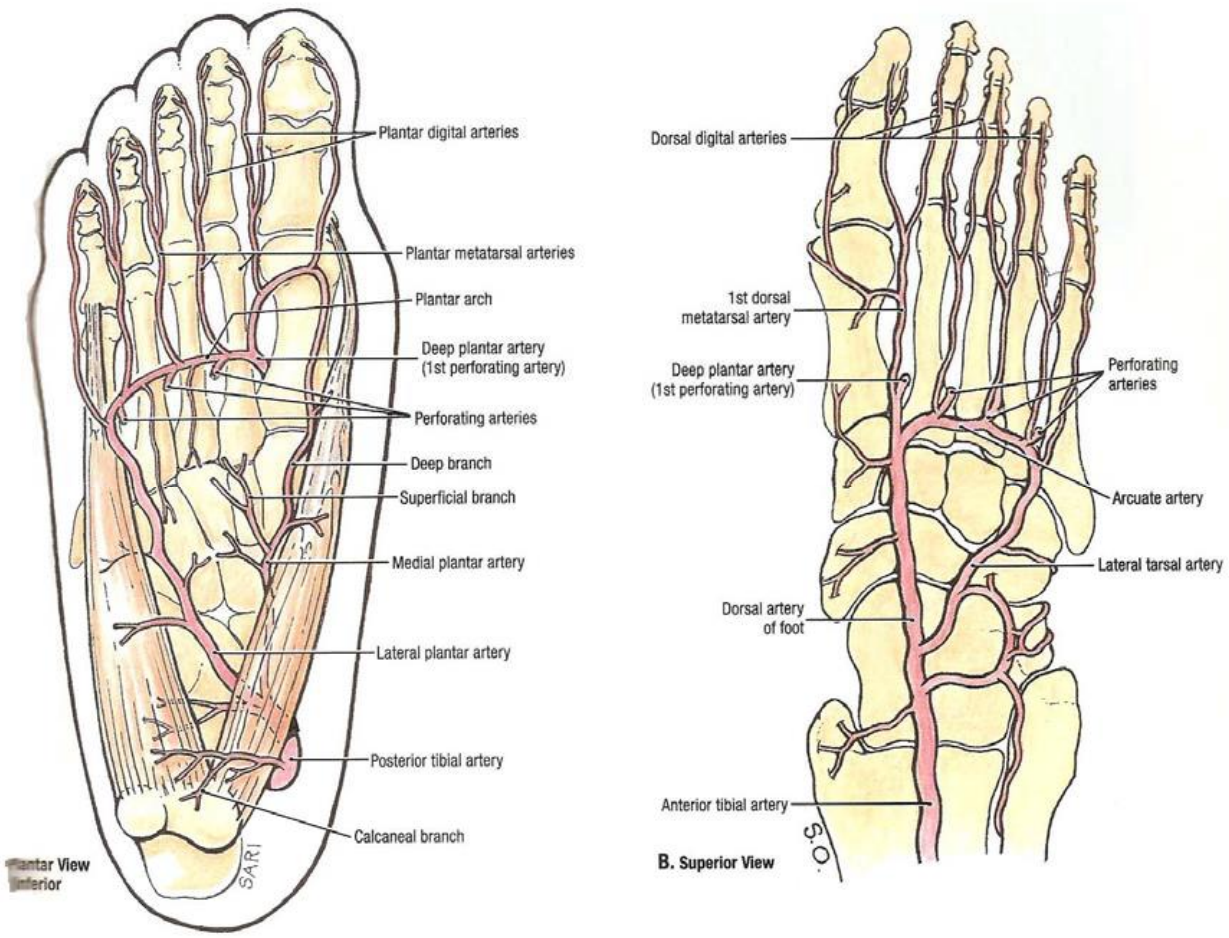


Figure -2: Arteries of the sole.

Nerve supply of the sole of the foot:

Medial Plantar Nerve: The medial plantar nerve is a terminal branch of the tibial nerve. It gives,

1. Muscular branches to the abductor hallucis, flexor digitorum brevis, flexor Hallucis brevis, and the first lumbrical muscle.

2. Cutaneous branches: Plantar digital nerves run to the sides of the medial three and one-half toes.

Lateral Plantar Nerve: The lateral plantar nerve is a terminal branch of the tibial nerve.

Branches:

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

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

3. From the deep terminal branch supplies the adductor hallucis, the second, third and fourth lumbrical, and all the interossei, except those in the fourth intermetatarsal space.

Vasculature of the dorsum:

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

1.Lateral tarsal artery.

2. Arcuate artery.

3. First dorsal metatarsal artery.

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

Nerve supply of the dorsum of the foot:

Deep Peroneal Nerve: It divides into terminal, medial and lateral branches. The medial branch supplies the skin of the adjacent sides of the big and second toes.

The lateral branch supplies the extensor digitorum brevis muscle.

Spaces of the Foot:

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

Four median Plantar Spaces:

1. The first space is located between the plantar aponeurosis and the flexor Digitorum brevis.
2. The second space is situated between the flexor digitorum brevis and the conjoined long flexor tendons and quadratus plantae.
3. The third space is found between the flexor digitorum longus (with its Associated lumbricals muscles) and the oblique head of the abductor hallucis.

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

These spaces are bound both laterally and medially by dense connective tissue septa hence infection may travel from one space to another. The sheaths of the entire flexor tendon extend from the toes and proximal to the distal head of the metatarsal bones; therefore infection within these sheaths either may remain local or break into one of the four spaces.

The 3rd layer of the sole of the foot is enclosed inferiorly by the plantar fascia and superiorly by the metatarsal and small muscles and ligaments of the foot. It is continuous distally into the toes through the lumbricals and web space along with the long flexor tendons.

WOUND HEALING

A wound is defined as a separation or discontinuity of the skin, mucous membrane or tissue caused by physical, chemical or biological insult.

As noted by John Hunter, "The injury alone has in all cases a tendency to produce the disposition and the means of a cure."

"Wound healing consists of a complex but very orderly array of overlapping phases in which highly specialized cells interact with an extracellular matrix to lay down a new framework for tissue growth and repair".[12]

A surgeon's goal in wound management is to create an environment where the healing process can proceed in an optimal fashion. Wound healing is a fundamental hemostatic process in response to injury. It involves the activation of basic cellular process of inflammation, cell proliferation, and cell growth as well as regeneration of these processes once repair is complete.

TYPES OF WOUND HEALING[13]

HEALING BY PRIMARY INTENTION

The wounds are closed after the surgery with simple suturing, skin graft or flaps.

HEALING BY SECONDARY INTENTION

There is no active intent to seal the wound. This type of repair is associated with a highly contaminated wound and will close by re epithelialization which results in contraction of the wound.

HEALING BY TERTIARY INTENTION

Also referred to as delayed primary closure. A contaminated wound is initially treated by repeated debridement, systemic or topical antibiotics or negative pressure wound therapy for several days to control infection. Once the wound is assessed as being ready for closure, surgical intervention such as suturing skin graft placement or flap is performed.

NORMAL WOUND HEALING

Wound healing is the body's response to injury. Phases of wound healing are presented as separate events, however they do not occur independently and the degree of temporal overlap are significant. Emphasis is on the underlying physiologic process and the pattern of responses with surgical applications. Every tissue in the body undergoes reparative process after injury. Bone has the unique ability to heal without scar.

The PROCESSES OF WOUND HEALING take place in an overlapping and sequential manner

- Coagulation
- Phagocytosis
- Chemotaxis
- Mitogenesis
- Collagen Synthesis
- Extracellular Matrix Synthesis
- Contraction

PHASES OF WOUND HEALING

1. Hemostasis and inflammatory phase

2. Proliferative phase

3. Maturation and remodeling phase.

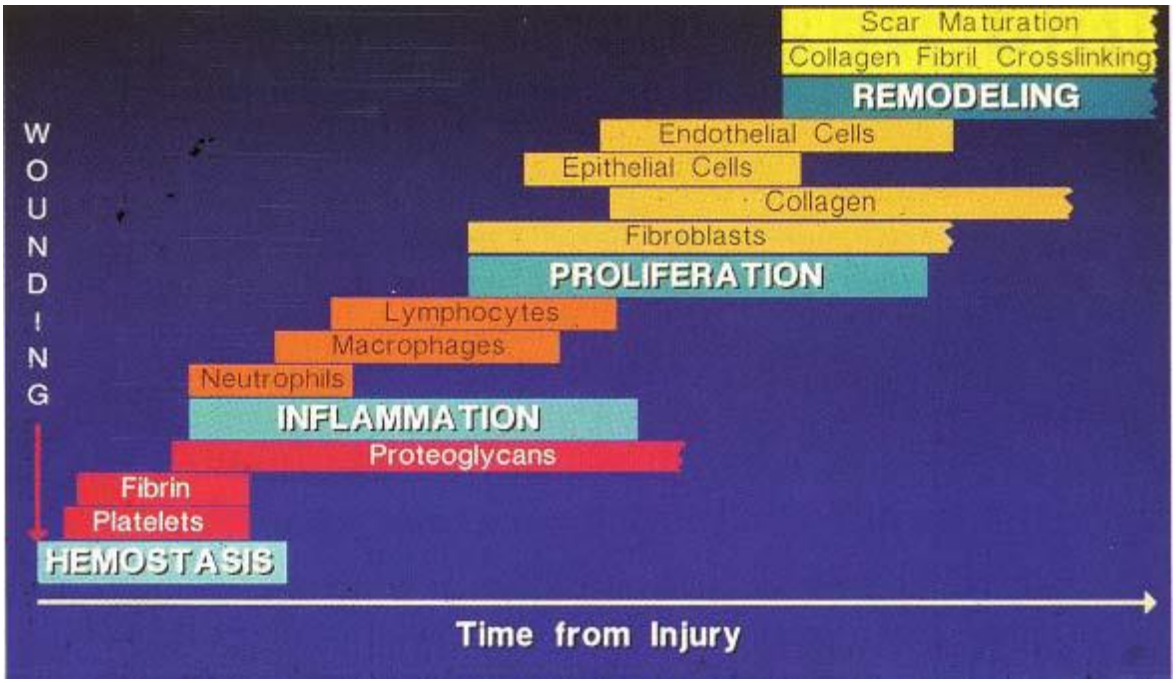


Figure 3: Phases of wound healing.

INFLAMMATORY PHASE

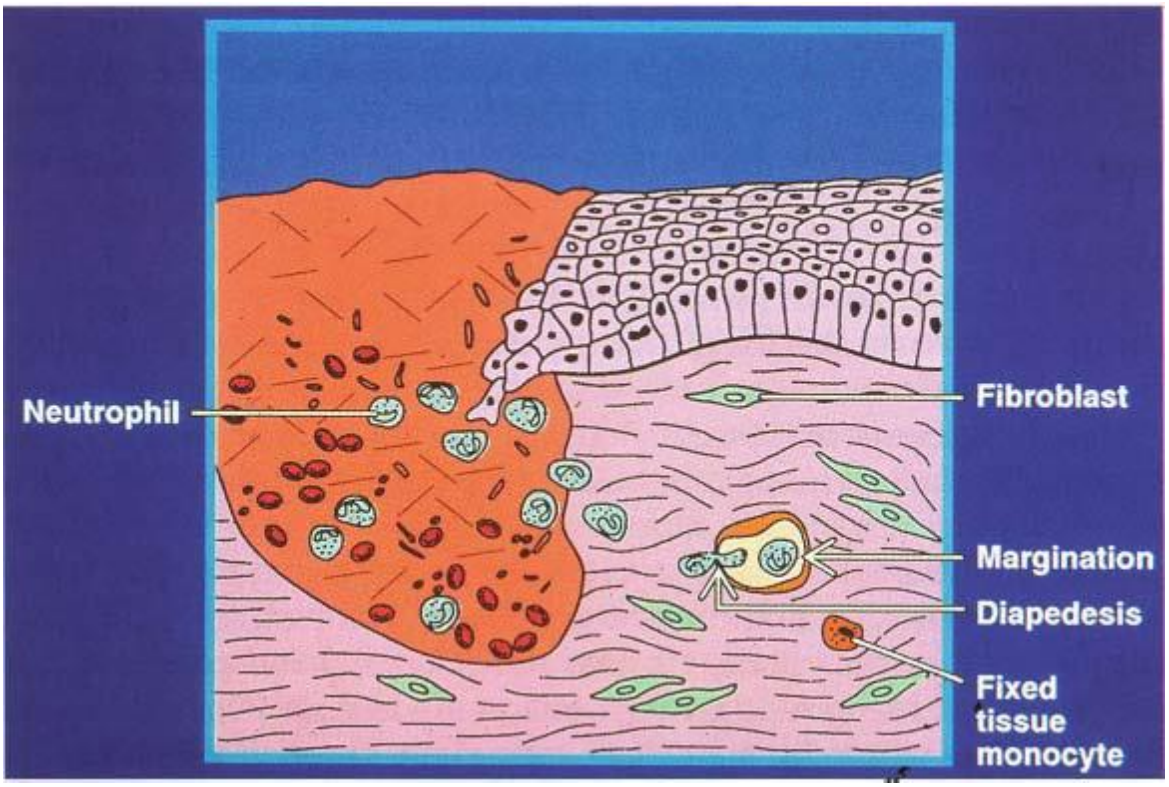


Figure 4:Inflammatory phase

The inflammatory phase of acute wound healing begins immediately after injury. The initial response to the disruption of blood vessel is bleeding. The hemostatic response to this is clot formation to stop hemorrhage. Platelet plug formation initiates the hemostatic process along with clotting factors activated by collagen and basement membrane exposed by the injury.

After injury, transient vasoconstriction is mediated by catecholamines, thromboxane and prostaglandins (PGF2). Platelets degranulation, the emptying of the granules into the extracellular space, provide the contents of alpha granules and dense granules, most notably platelet derived growth factor (PDGF) and transforming growth factor beta (TGF beta). These

substances initiate chemotaxis and proliferation of inflammatory cells, beginning the inflammatory response that will ultimately heal the wound.

Transient vasoconstriction is necessary to decrease blood at the time of the initial wounding and also to allow clot formation. Once a clot has been formed and active bleeding has stopped, vasodilatation increases local blood flow to the wounded area, supplying cells and substrate necessary for further wound repair. The vascular endothelial cells also deform, increasing vascular permeability.

At this stage, the wound is full of debris from the initial injury.

It consists of a mixture of

1. Injured, devitalized tissues (fat, muscle, epithelium)

2. Clot (platelets, erythrocytes, and fibrin)

3. Bacteria (from the skin and the external environment)

4. Extravasated serum proteins

5. Foreign materials.

PROLIFERATIVE PHASE[14]

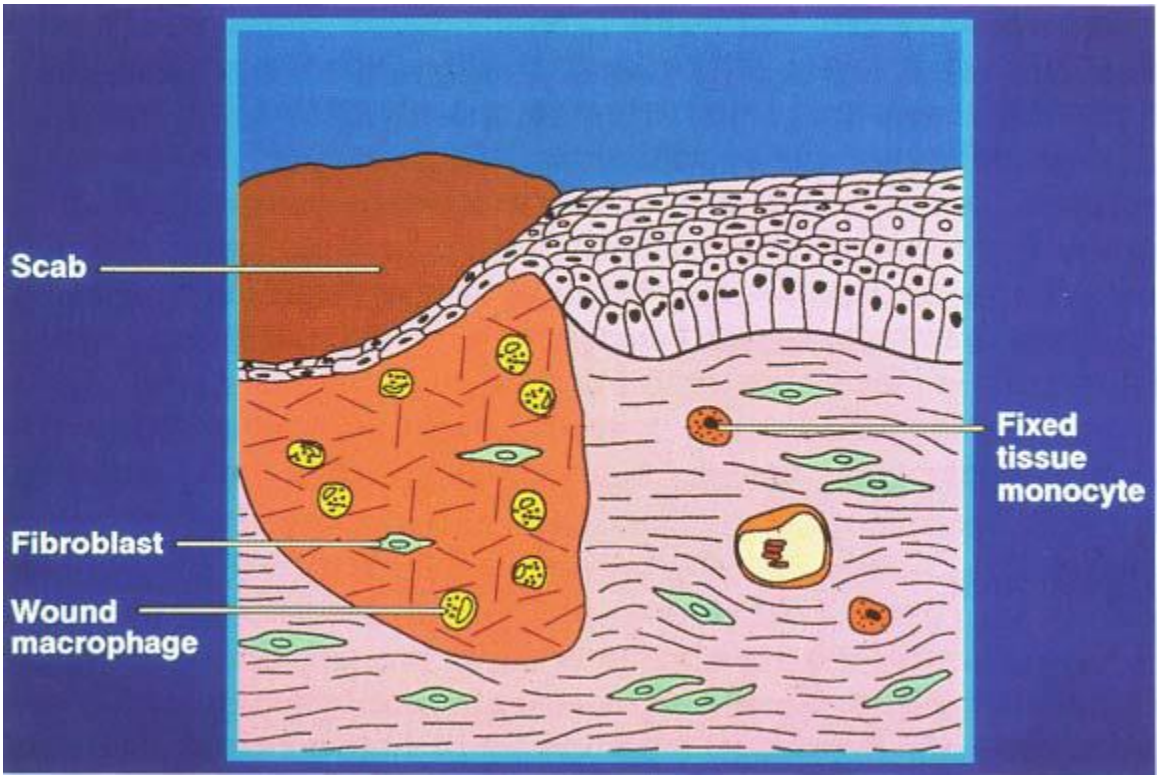


Figure 5 : Proliferative phase

It begins with the formation of a provisional matrix of fibrin and fibronectin as part of initial clot formation.The proliferative phase is characterized by fibroblast proliferation and collagen deposition to replace the provisional fibrin matrix and to provide a stable extracellular matrix at the wound site. The new matrix consists of collagen, proteoglycans and fibronectins. In addition, angiogenesis occurs such that new blood vessels replace the previously damaged capillaries and provide nourishment for the matrix. Granulation tissue formation and the process of epithelization also occur.

Once the fibroblasts have entered the wound they produce collagen, proteoglycans and other components. Fibroblast activity is predominately regulated by PDGF and TGF-Beta. PDGF

secreted by platelets and macrophages stimulates fibroblast proliferation, chemotaxis and collagenase expression.

Endothelial cells are activated by TNF-alpha and basic FGF (bFGF) to initiate angiogenesis such that new blood vessels are initiated to promote blood flow to support the high metabolic activity in the newly deposited tissue. Angiogenesis is regulated by a combination of local stimulatory factors such as vascular endothelialcell growth factor (VEGF) and antiangiogenic factors such as angiostatin, endostatin,thrombospondin and pigment epithelium-derived growth factor. As the wound continues to heal, the granulation tissue forms to provide the transitional replacement for normal dermis and ultimately evolves into a scar.

REMODELING PHASE

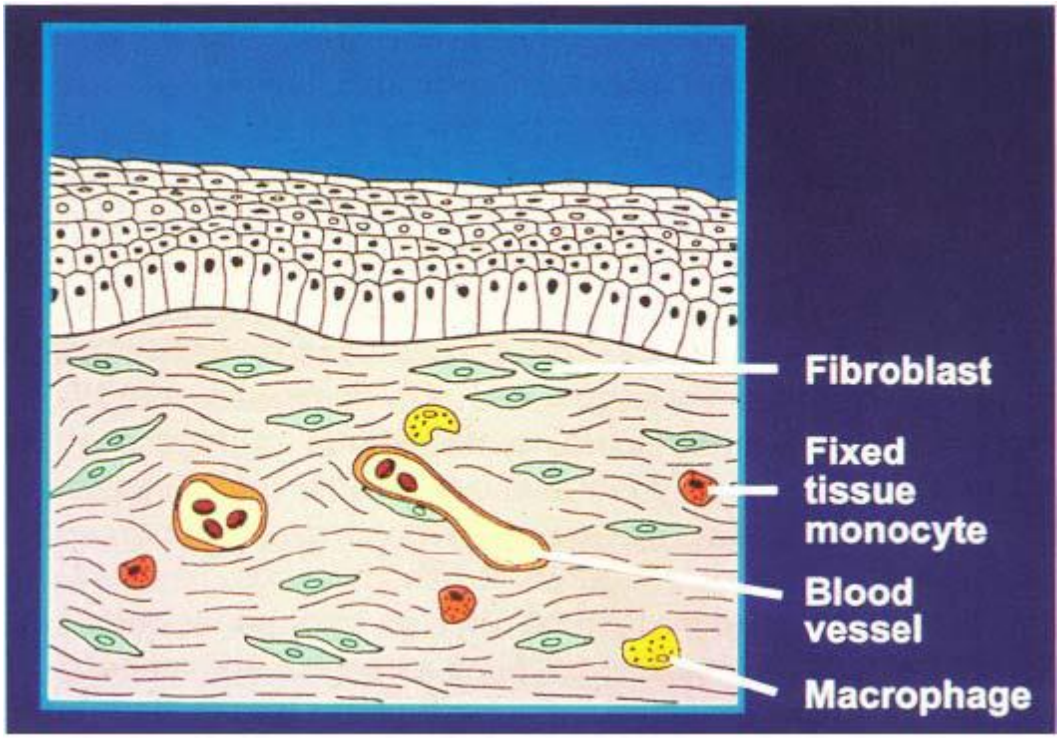


Figure 6:Remodeling phase

The ECM is dynamic and is constantly undergoing remodeling. The last phase of wound healing is the remodeling phase in which granulation tissue matures into a scar. Small capillaries aggregate into larger blood vessels and there is an overall decrease in the water content of the wound. Similarly cell density and overall metabolic activity of the wound decrease. Initially there is increased deposition of type III collagen also referred to as reticular collagen that is gradually replaced by type I collagen, the dominant fibrilar collagen in skin.[15] As the wound continues to remodel, changes in collagen organization increases the tensile strength to a maximum of about 80% of normal tissue. Matrix metalloproteinases(MMPs) control the degradation of extra cellular matrix components to facilitate epithelial cell migration into the wound, angiogenesis and overall tissue remodeling.

FACTORS AFFECTING WOUND HEALING

Local factors:-

- Surgical technique
- Tissue vascularity
- Mechanical stress
- Movement
- Extent of wound surface
- Haemorrhages
- Foreign bodies
- Oedema and Dehydration
- Local irradiation
- Suture material and techniques
- Wound infection

Systemic factors:-

- Age
- Obesity
- Malnutrition
- Vitamin deficiency
- Anaemia and hypoxia
- Systemic disease
- Temperature

PATHOPHYSIOLOGY OF DIABETIC FOOT

Knowledge of the pathophysiologic changes caused by diabetes Mellitus is essential for proper understanding and treatment of foot problems in diabetics.

There are 4 main causes for development of foot lesion in a diabetic

1. Peripheral Neuropathy.
2. Peripheral vasculopathy.
3. Charcot foot.
4. Infection.

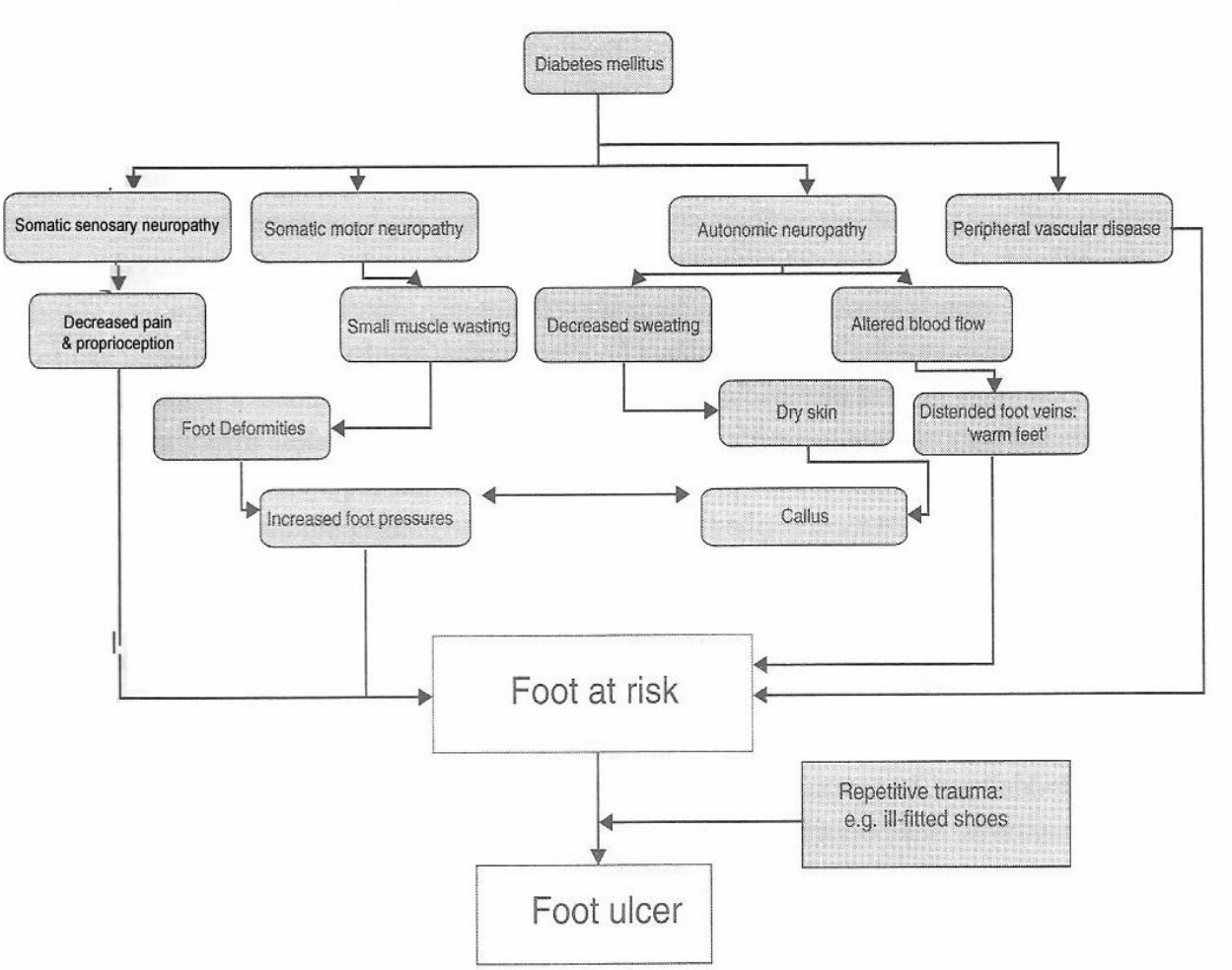


Figure 7 : Pathophysiology of Diabetic foot ulcer

1) **Neuropathy**[16]

The commonest Diabetic polyneuropathy is distal symmetrical neuropathy, the main initiating factor for foot ulceration, affecting about 30% of all diabetic people.[17,18] About one-fourth (nearly 28%) of type I diabetic patients develop distal symmetrical neuropathy. Its incidence parallels the duration and severity of hyperglycemia in both type I and type II diabetes. Age, duration of diabetes, and poor glycemic control being major determinants; also retinopathy and albuminuria. Less well-established correlates of diabetic neuropathy include increasing age,

hypertension, and cardiovascular risk factors.[19,20] Vascular and metabolic factors are both implicated in the pathogenesis of diabetic neuropathy. The neuropathic foot is characteristically healthy. It is well nourished, has hair, maintains good dorsalis pedis pulses and posterior tibial pulses, has a high arch. Callus formation is common on pressure points on the soles or toes, and there may be sweating. This indicates lumbar sympathetic activity. On the soles, thick calluses can act as foreign bodies and cause bruising of the subcutaneous tissues with extravasation of blood and serum from the capillaries. This leaves a culture medium pool for local bacteria to grow and cause an abscess. The condition may be unsuspected because of anesthesia conferred by the neuropathy and can expand without being detected until the patient develops generalized infection or the process is detected by it's foul odour. At times the overlying callus is so hard that the infection can more easily involve the underlying joint capsule and the metatarsal head than the callus itself. Thus osteomyelitis associated with calluses can be explained and easily understood. The same disease process may occur on the top of hammer toes or in relation to the deformed and collapsed bones and joints associated with Neuro-osteoarthropathy / Charcot's foot. Proposed hypothesis for the development of neuropathy in patients with diabetes are chronic hyperglycemic state, activation of protein kinase C , oxidative stress, Increased Polyol Pathway Flux and non-enzymatic glycation .

Vasculopathy:[21,22]

Both the Microvascular and Macrovascular disease is seen in diabetics. The vascular lesions are:

I. Macro vascular disease.

a) Atherosclerosis b) Medial calcification c) Diffuse initimal fibrosis.

II. Micro vascular disease.

a) Arteriosclerosis b) Specific Diabetic microangiopathy c) Diabetic Fibrosis.

Macro vascular disease:

1. Deranged metabolism of glucose producing sorbitol through polyol pathway.

2. Hyperglycemia, Keen et al conclude that not only are borderline diabetics more liable to arterial disease than normal but also that this increased risk can probably be significantly reduced by treatment.

3. The risk of atherosclerosis in a diabetic is seen particularly in patients with early onset requiring high insulin doses. The work of Peters and Hales 1965, has led to the postulate that raised plasma insulin is Possibly atherogenic.

4. Fibrinocoagulopathy: Large deposits of fibrin in the vascular lesions of maturity onset diabetes and atherosclerosis have been demonstrated by earlier workers.

5. Atherosclerosis: Degenerative Vascular disease affecting principally the tunica intima of arteries and composed of fibrosis and or fatty change. Ulceration and secondary thrombosis commonly occur. This is found more frequently and with greatest severity in diabetics.

Occlusion of the femoral artery is the most common lesion and characteristically starts at the region of hiatus in the adductor magnus. Atheroma of the profunda femoris artery, the major source of blood for thigh muscles, causes stenosis at its origin. Diffuse disease of any combination of stenosis or occlusion of the arteries between the aorta and ankle occurs. The diabetics more frequently have multiple occlusions of the Popliteal and its branches which limits

the application of reconstructive arterial surgery. Hence this pattern of atherosclerosis affecting the leg arteries carries serious threat to the survival of the limbs.

Calcification of the arteries: Calcification of the tunica media of muscular arteries is a common feature of long-standing diabetes which is the commonest cause of these changes. The distinguishable feature is its relatively regular, tiny, speckled appearance and commonly affects the vessels of the foot. Tunica intima may be relatively unaffected despite major deposits of calcium in the media. Hyperglycemia has a direct role in the development of this condition.

Microangiopathy:

Haemodynamic hypothesis

Increased microvascular blood flow

↓

Endothelial injury response

↓

Microvascular sclerosis

↓

Limitation of maximum hyperaemia

+/-

↓

Impaired autoregulation

The clinical association between retinopathy, neuropathy and nephropathy suggest a common factor between them, the disease of the small blood vessels.

The typical changes in diabetes are:

I. Thickening of capillary basement membranes

II. Proliferative changes in arterioles arteries:

Cause of micro Angiopathy:

These morbid anatomical changes are the end result of metabolic disturbances which continued for long period.

The two major initial changes are:

a. Venular dilatation.

b. Increased capillary permeability.

Charcot foot[23,24]

Charcot's polyneuropathy is a progressive condition affecting the bones and joints of the foot and is characterized by joint dislocation, subluxation, and pathological fractures of the foot of neuropathic patients, often resulting in a debilitating deformity. Bone and joint damage in the tarso-metatarsal joints and mid tarsal joints leads to two classical deformities: the rocker bottom deformity, in which there is displacement and subluxation of the tarsus downwards, and the medial convexity, which results from displacement of the talo-navicular joint or from tarso-metatarsal dislocation. Both are often associated with a bony prominence which is very prone to ulceration and healing is notoriously difficult. When the ankle and subtalar joints are involved, instability of the hindfoot can result.

Infection[25]

Foot infection occur frequently in persons with diabetes and the occurrence of infection is an event that most often leads to more serious sequelae particularly hospitalization and amputation .Foot infections usually occur at the site of trauma / ulceration. Thus patients with peripheral neuropathy / foot deformity are at increased risk for ulceration .Infection of the plantar space accounts majority of diabetic foot infections .Majority of infections start with infected ulcers on the plantar aspect of the foot interdigital infections and nail bed infections. In the initial stage there is usually an area of localized cellulitis, then infection progresses and once deep space infection is established ascending cellulitis, lymphangitis and lymphadenopathy also develop. Because of the anatomical tight compartment in foot, infection ascends along the tendon sheaths into posterior compartment of the leg, flexor canal, subsoleal compartment.

INVESTIGATIONS:[26]

The following investigations are done for the diagnosis, and treatment of the diabetic foot:

I. Routine investigations

1. Blood investigations : Hb, TLC, DLC, ESR

2. Renal profile: Blood urea, serum creatinine

3. Urine – Albumin, Sugar, ketone bodies & microscopy

II. Special investigations

a) Glycosuria:

Results from hyperglycemia, when blood glucose level reaches 180 mg% (Renal threshold).

Renal threshold increases with increase in age and in diabetic nephropathy no glycosuria will be present with serum level of 200mg% glucose.

b) Ketonuria: If glucose is present in urine, ketone bodies should also be determined which can be detected by Rothera's acetone test. It is the first sign to be recognized in ketosis.

c) Fasting blood sugar: Hyperglycemia is most decisive indicator of diabetes. Fasting blood sugar more than 120mg/dl is indicative of diabetes.

d) Post prandial blood sugar: After overnight fast, the patient is given breakfast of 100gms of carbohydrates or 100gms of glucose load. Then venous blood is checked for glucose levels every half hour for two hours. If it exceeds 180mg% it is indicative of diabetes mellitus.

e) Glucose tolerance test: The ability of the body to dispose of an additional load of glucose is known as glucose tolerance test (G.T.T). It can distinguish normal subject who should have good glucose tolerance from diabetic who does not.

Metabolic profile and Glycohemoglobin: Assessment of serum glucose, glycohemoglobin.

Culture and sensitivity test:

Pus from infected area is cultured for micro organisms and their sensitivity to various antibiotics is tested so that appropriate antibiotic can be administered to control the infection.

Radiology of the foot:

X-ray of the foot should be taken if there is any suspicious infection deep to the foot, e.g. abscess or osteomyelitis. The signs which suggest the presence of osteomyelitis are destruction of bone commonly seen at metatarso phalangeal joint or in the interphalangeal joint of the great toe. Sequestrum and subperiosteal new bones formations are common. A small amount of gas in the tissues or in the abscess cavity may be seen. Large amounts of subcutaneous gas especially if it extends to the leg, indicates the presence of a serious anaerobic infection.

Noninvasive vascular laboratory study:

Pulse-volume recording (PVR) or plethysmography: uses pneumatic cuffs encircling the thighs, calves, ankles, feet and occasionally, toes to sense segmental volume changes with each pulse beat. The resulting tracings provide useful information about the haemodynamic effects of the arterial disease at each level. In severe disease, tracings at the transmetatarsal level may become nearly flat. PVR is noninvasive and rapid and, therefore, may be repeated frequently to help assess the overall hemodynamic response to medical or surgical treatment. The ankle-brachial blood pressure index is potentially unreliable because of arterial calcification.

Imaging Studies:

Duplex scanning can provide images of arterial segments that help localize the extent of disease, and simultaneous Doppler measurement of flow velocity can help estimate the degree of stenosis. Duplex scanning is quite useful in visualizing aneurysms, particularly of the aorta or popliteal segments. Unfortunately, Doppler techniques are not accurate in assessing the hemodynamic consequences of atherosclerotic peripheral arterial disease involving the extremities. Use of this technique probably is best left to the discretion of the vascular specialist.

Plain x-ray studies of the diabetic foot may demonstrate demineralization and Charcot joint and occasionally may suggest the presence of osteomyelitis.

CT scan and MRI: Although an experienced clinician usually can diagnose a plantar abscess by physical examination alone, CT scan or MRI is indicated if a plantar abscess is suspected but not clears on physical examination. Contrast angiography is indicated if haemodynamically significant vascular disease precludes healing of the ulcer or is causing intractable pain at rest.

Angiography is best ordered by the vascular or endovascular surgeon to ensure that the study performed actually visualizes the entire segment of the arterial tree to facilitate the potential vascular procedure. Magnetic resonance angiography (MRA) is an alternative for patients with renal compromise and patients who are allergic to contrast materials.

Other Tests:

A hand-held Doppler scanner may be used to assess arterial signals, to localize arteries to facilitate palpation of pulses, or to determine the loss of Doppler signal as a proximal blood pressure cuff is inflated. The latter pressure divided by the upper extremity systolic pressure is called the ankle-brachial index (ABI) and is an indication of severity of arterial compromise. Normal ABI averages 1.0. An ABI less than 0.9 suggest atherosclerotic disease, with a sensitivity of approximately 95%. In general, an ABI below 0.3 suggests a poor chance for healing of distal ischemic ulcerations. Unfortunately, ABI often is falsely elevated if the underlying arteries are heavily calcified, a finding common in diabetic persons.

TREATMENT

Classification and Staging[27,28,29]

After completing the basic assessment, it will now be possible to classify the diabetic foot. For practical purposes, the diabetic foot can be divided into distinct entities:

1. The Neuropathic foot.
2. The Neuro ischaemic foot.

Neuropathy is nearly always found in association with ischaemia, so the ischaemic foot is best called the neuro ischaemic foot. In rare cases the foot may clinically be ischemic without

signs of neuropathy, but in practice, the diabetic ischemic foot is treated in the same way as the neuro ischaemic foot, and thus, we have continued with the two main divisions. It is essential to classify the diabetic foot by differentiating between the neuropathic and the neuro ischaemic foot as their management will differ in many respects.

Neuropathic foot

The neuropathic foot is a warm, well-perfused foot with bounding pulses and distended dorsal veins due to arteriovenous shunting. Sweating is diminished so skin and any callus tend to be hard and dry and prone to fissuring Toes are flexed and the arch of the foot may be raised Ulceration commonly develops on the sole of the foot, associated with neglected callus and high plantar pressures. Despite the good circulation, necrosis can develop secondary to severe infection. The neuropathic foot is also prone to bone and joint problems which we refer to as Charcot's osteoarthropathy.

Neuroischaemic foot

The neuroischaemic foot is a cool, pulseless foot with poor perfusion and almost invariably also has neuropathy. The colour of the severely ischaemic foot can be a deceptively healthy pink or red caused by dilatation of capillaries in an attempt to improve perfusion. The neuro ischaemic foot may be complicated by swelling, often secondary to cardiac failure or renal impairment. Ischaemic ulcers are commonly seen around the edges of the foot, including the apices of the toes and the back of the heel, and are associated with trauma or wearing unsuitable shoes. The neuro ischaemic foot develops necrosis in the presence of infection or if tissue perfusion is critically diminished.

WAGNER CLASSIFICATION OF DIABETIC FOOT LESIONS:

Grade 0	At risk foot no obvious ulcer, thick callus prominent metatarsal heads, claw toes or any bony abnormality.
Grade I	Superficial ulcer not clinically infected.
Grade II	Deeper ulcer often infected but no bone involvement.
Grade III	Deep ulcer, abscess formation, bony involvement.
Grade IV	Localized Gangrene.
Grade V:	Gangrene of the whole foot.

PRINCIPLES OF SURGICAL MANAGEMENT

1. Early recognition and prompt intervention.

2. Control of blood glucose

3. Complete rest of injured area.

4. Careful but complete debridement and drainage of all area involved

5. Appropriate antibiotic coverage

6. Wound care and dressings

7. Appropriate vascular reconstructions

8. Careful follow up including podiatric appliances and modified footwear.

9. More experienced consultation as necessary.

SURGICAL MANAGEMENT

DEBRIDEMENT AND CLEANSING

Debridement is removal of all dead (devascularised, necrotic, infected tissue or foreign material) from the wound. Many ulcers present with a clean base but some may require debridement when there is adherent slough and tissue that impairs epithelization, granulation and wound contraction.

TYPES OF DEBRIDEMENT INCLUDE

1. SURGICAL DEBRIDEMENT: The removal of nonviable, contaminated and infected tissue using surgical technique under anaesthesia. Surgical debridement converts indolent wounds into acute wounds and restores circulation and allows oxygen delivery to the wounds. Used in wounds with large amount of necrotic or infected tissue. It is performed by skilled medical personal.

2. ENZYMATIC DEBRIDEMENT Specific proteolytic enzymes are applied to the wound to remove and digest necrotic tissue and dissolve the devitalized tissue. It can be used in patients receiving anticoagulants and contraindicated for surgery. Advantage is it can be done as outpatient dressing. Most common types are: Collagenase (Santyl) and Papain Urea. Collagenases are enzymes that are isolated from *Clostridium histolyticum*. These have high predisposition for the major collagen types (I and II), but they not active against keratin, fat or fibrin.[30-32] Papain, obtained from the papaya plant, is effective in the breakdown of fibrinous material and necrotic tissue. When combined with urea, it denatures nonviable protein matter.

3. MECHANICAL DEBRIDEMENT It is a nonselective, physical method of removing necrotic tissue. It includes wet-to-dry dressings and high- pressure irrigation or pulsed lavage and hydrotherapy. [33,34] Wet-to-dry is one of the most commonly prescribed and over used methods of debridement in acute care settings. Hydrotherapy in the form of whirlpool may remove surface skin, bacteria, wound exudates and debris. This modality is good for larger wounds with a significant amount of devitalized tissue. Used when the local bacterial burden is more of a concern than stimulation of healing in a non-healing wounds. Disadvantage: Painful and non-selective (removes both healthy and necrotic tissue).

4. AUTOLYTIC DEBRIDEMENT Seen with the use of dressings such as hydro colloids and hydrogels. Occurs naturally in a healthy, moist wound environment when arterial perfusion and venous drainage are maintained.

5. CHEMICAL DEBRIDEMENT Specific chemicals are used to remove necrotic tissue

• Povidone iodine-Broad spectrum antimicrobial activity.

• Acetic acid(O.5%-5%)- Effective against Pseudomonas species.

• Chlorhexidine- Active against gram-positive and gram-negative organisms.

• Hydrogen peroxide- De-sloughing agent with some bactericidal effect.

• Sodium hypochlorite solution-High pH causes irritation to skin.

6. BIOLOGICAL (LARVAL) THERAPY

Larval therapy utilizes the sterile form of the *Lucilia sericata* blowfly for the debridement of necrotic and infected wounds. Maggots secrete a powerful proteolytic enzyme that liquefies

necrotic tissue.[35,36] It has been noted that wound odor and bacterial count, including methicillin-resistant Staphylococcus aureus, diminish significantly with larval therapy. Larval therapy seems to be beneficial, but there is paucity of controlled studies to support its routine use in the diabetic foot wounds.

WOUND DRESSINGS AND WOUND CARE PRODUCTS

For centuries, wound healing was considered as a series of mysterious mechanisms and numerous topical treatments have been applied to wounds like honey, diluted wine, flowers etc. Till many years commonly used dressings were pads or strips of linen. In 1962, Winter's work on moist wound healing was the major achievement in wound care dressings. Wound dressings are categorized into two :

1) **Primary dressings:** Also known as contact layer dressings. These directly interact with the wound surface and promote healing.
2) **Secondary dressings(Passive dressings):**Dressings covering the primary dressing. Today many wound care products are present in the market which need to be tailored for our use.

The principal characteristics of modern dressings:

1) Maintain moist environment at the wound surface and improve cell migration.
2) Absorb excess exudates
3) Allow painless removals
4) Being impermeable to bacteria.

SELECTION OF WOUND DRESSINGS

Before choosing a wound dressing a thorough wound assessment should be

done and it should be tailored to the patients wound to influence wound healing.

The main criteria before choosing a wound dressing are:

1) Clinical appearance of the wound, healing phase, etiology and size of wound.

2) Amount of exudates.

3) Presence of infection.

4) Depth of wound

5) Condition of surrounding skin

6) Dressing availability and cost

7) Patient acceptability.

WOUND CARE DRESSINGS

Based on the type of material used for the preparation of dressing they may be classified as conventional, synthetic and biological dressings.

A. CONVENTIONAL DRESSINGS:

These dressing materials are made up of fabric material such as gauze, but allow evaporation of moisture resulting in a dry desiccated wound bed and allow entry of exogenous bacteria into the wound. This led to the origin of compound dressings such as Tulle grass which is a wide mesh gauze impregnated with medical grade paraffin. This results in a relatively non-adherent dressing. Further developments in 1980 involved incorporation of antibacterial agents such as carbolic acid and mercuric chloride, penicillin and polymyxin creams in combination with absorbent dressings. Recent innovation uses silicone polymer in place of paraffin. These dressings are less adherent to the wounds making dressing changes less traumatic. The concept of moist wound dressings gained importance during the mid 1980's. Based on a study by Atiyeh

BS, El-Musa KA, Dham R, full and partial thickness cutaneous wounds, when exposed to wet and moist environment showed improved healing. It has been found that moist environment prevents dessication of denuded dermis or deeper tissues and allows faster and unimpeded migration of keratinocytes over the wound surface and also facilitates the cytokines to exert their effects on wound contracture and re epithelization.

Since the conventional dressings had limitations for application on full thickness wounds, research into the development of more advanced wound dressings for the treatment of wounds has resulted in the development of synthetic and biological dressings.

B. SYNTHETIC DRESSINGS:

These dressings can be classified into

1. **Films :** They are homogeneous dressings composed of a polymer sheet coated on one side with an adhesive. The most commonly used Polymers include polyurethane, polyethylene, Polycaprolactone, polytetra- fluoroethylene, dimethyl aminoethyl methacrylate. Film dressings are well suited for superficial wounds, but lack of absorbing capacity and impermeablity to water vapour and gases cause accumulation wound fluid beneath the dressing and hence leakage of exudate and entry of exogenous bacteria to the wound surface. Therefore, they are not convenient for larger wounds.
2. **Foams and sprays :** Foam dressings are sheets of foamed solutions of polymers such as polyvinyl-alcohol and polyurethane which are superior to film dressings in that they provide thermal insulation and help to maintain a moist environment at the surface of the wound. Furthermore, they are gas permeable, non-adherent, light and comfortable. Examples are silastic foam and lyo foam, which have the advantage of being formable in situ to treat

irregular cavity wounds. However, these dressings are difficult to use in certain anatomical areas. Spray dressings are more comfortable to the wounds surface and they are totally portable. Most sprays are copolymers e.g., Aeroplast is a copolymer of hydroxy vinyl chloride acetate modified maleic resin ester. Further studies have resulted in the development of dressings composed of spray and foam combinations e.g., gelatin based sprayable foam.

3. COMPOSITE DRESSINGS : These are composed of laminates of two or more layers. The outer layer is designed for durability and elasticity and may serve as a rate controller for water evaporation, while the inner layer is designed for maximum adherence and elasticity. Composite dressings may be classified as follows:

a. Hydrocolloid dressings : These dressings are compound formulations containing a cocktail of elastomeric adhesive and gelling agents. Carboxy methyl cellulose is the most common absorptive ingredient acting as absorbent for wound fluid.

1. Granuflex : This material consists of an outer protective layer of polyurethane foam and an inner layer consisting hydrocolloid/ polymer complex.

2. Epigard: This is a composite of an layer of reticulated polyurethane laminated to an outer sheet of microporous polytetra fluoroethylene (PTFE) Adherence, availability, sterility, long shelf life and low cost are its major advantages.

3. Biobrane: This is a composite of an ultra thin porous membrane of polydimethyl siloxane bonded to an inner nylon mesh. Roberts et al and Stein successfully used these for both superficial and deep donor sites. Lin et al, opines that bacterial infection was a common problem to this dressing.

b. Hydrogel sheets: These are sheets of 3-D networks of cross linked hydrophilic polymers. They interact with aqueous solutions. The most commonly used polymers are polyethylene

oxide, polyacrylamide and polyvinyl pyrrolidine. Owing to their unique cooling ability, they may be of great benefit for use as a first aid measure for thermal burns. An example is Vigilon which is reinforced polyethylene oxide hydrogel sandwiched between 2 polyethylene films. They are however slippery to use and difficult to keep in place in a high sheer stress.

c. Hydrogel Amorphous : These are similar in composition to sheet hydrogels except that the polymer has not been cross linked to form a sheet. They contain small quantities of collagen, alginate or complex carbohydrates. They are unique in their ability to donate moisture to a dry wound eschar and facilitate autolytic debridement in wounds. But owing to the viscosity of the amorphous hydrogel, it may be difficult to retain it in the wound bed. However, hydrogel dressings exhibit more rapid rate of closure and re-epithelialization as compared with the hydrocolloid wound dressing.

d. Gels : Several types of gel based dressings have been developed. For example Wichterlie and Lim produced hydroxyethyl methacrylate (HEMA) based hydrogel which was biocompatible and non toxic. Subsequently Nathan et al, developed PHEMA PEG (Hydran) hydrogel which is directly formed on the wound surface. Later, in 1977 a new type of wound covering Geliperm was developed by Wokalek et al, which is formed by polymerization of agarose and acrylamide. Further modification resulted in the development of a cross linked polyethylene oxide hydrogel.

e. Super Absorbents : This dressing has an island configuration consisting of an extra thin hydrocolloid as the adhesive portion with a central area of non woven absorbent covering the superabsorbent particles encased inside, e**.g.,** Combiderm, Conva Tec., etc. All the above dressings act only, as temporary dressings and do not help in massive burn injuries with very limited skin donor sites and are usually combined with alternative wound closure techniques.

C. Biological Dressings:

These are derived from natural tissues usually consisting of various formulations and combinations of collagen, elastin and lipid. They are far superior to synthetic dressings in that they :

1. Restore a water vapour barrier and prevent dehydration of the wound

2. Decrease evaporational heat loss

3. Decrease protein and electrolyte losses in wound exudate

4. Prevent bacterial contamination of the wound and hence protect the wound and patient from sepsis

5. Permit less painful dressing changes

6. Permit painless movement over joints

7. Facilitate debridement of wounds

8. Create good granulation tissue bed for autografting of deep wounds

9. Can be used to test for successful subsequent autograft

10. Decrease healing time of partial thickness burns and donor sites and

11. Improve quality of healing, inhibit excessive fibroblasts and decrease contraction.

Biological dressings range from allograft, heterografts from pigs, dogs and other species, to embryonic membranes, embryo foetus and neonatal skins, films of reconstituted collagen from bovine and other sources, fibrin, cultured epidermal grafts, dermal matrix grafts and cultured dermal matrix composite grafts.

Allograft:

Allograft skin normally can be obtained from a family member but is most commonly harvested from cadavers. The use of fresh frozen lyophyillized allograft is most effective for thermal injuries especially for extensive full thickness burns. Amniotic membranes have also been used as allograft, but are ineffective in the prevention of evaporative water loss leading to wound dehydration.

Xenograft:

These are grafts from animal sources and porcine skin is the most commonly used xenograft owing to structural similarity to human skin with respect to its texture, adherence and collagen content although dissimilar at the microscopic level. The major disadvantages of xenograft and allograft are that they become vascularized and unless immunosuppressive drugs are employed to prevent rejection have to be removed. Further, the excessive use of immunosuppressive drugs increases the risk of wound infection.

Thus, the major disadvantages of using allografts / xenografts may be described as

1. Non-uniform
2. Troublesome and costly to obtain
3. Difficult to sterilize and store aseptically
4. Have a short shelf-life
5. Potentially antigenic
6. Carry a risk of unusual contaminants and
7. May provide hypersensitivity to one or more complex constituents.

Collagen Dressings:

The development of collagen dressings is logical in view, of its unique structural and functional characteristics. The most highly characterized form of collagen aggregate is the fibril or fiber. The packing arrangement for molecules within collagen fibrils imposes several structural requirements on the molecule participating in the construction of such aggregates. In addition to providing mechanical support to the connective tissue, the collagens also form an essential substrate for cellular adhesion and migration. Therefore, collagen is considered to be an important morphogenetic factor in embryonic development and in the regenerative process.

The hydrophilic nature of the collagen attributed by its molecular structure characterized by high content of diamino dicarboxylic amino acids and carbohydrates provides a surface geometry very suitable for cell adhesion.

Engineered Skin Substitutes:

Bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers.[37,38] Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers Apligraf™ and Dermagraft™ Both have demonstrated efficacy in randomized controlled trials. Tissue-engineered skin substitutes can provide the cellular substrate and molecular components necessary to accelerate wound healing and angiogenesis. They function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components .[39,40]

Extracellular matrices (nonliving) are generally derived from devitalized tissue to produce an immunologically inert acellular dermal matrix.

1) Dermal regeneration template (IntegraTM)

2) Allogenic dermal matrix (AlloDerm™)

3) Matrix of human dermal fibroblasts (TransCyte™)

4) Porcine small intestine submucosa (Oasis™)

They are composed of structural cellular components and growth factors utilized to promote natural tissue remodeling .[41,42] Integra™ dermal regeneration template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds

HUMAN PLACENTAL EXTRACT:

It is known from traditional folk knowledge that the placenta, contains a wide range of biologically active components. Indeed, it is claimed that the placenta is capable of producing just about any substance found in any organ of the body. Use of human placenta as a therapeutic agent, therefore, in no way hampers ecological balance rather promotes resource recovery from a designated biomedical waste. Placenta serves as a natural store house of many biologically active components with significant healing attributes.[43] Various extracts of placenta have been described, however, only an aqueous extract of fresh full term human placenta acts as a potent biogenous stimulator.[44] Clinical efficacy of an aqueous extract of human placenta in wound healing is already established.[45] Wound healing is a complicated interrelated process wherein the injured dermal and epidermal tissue is naturally regenerated. Placental extract, ever since its usage has been shown to be clinically effective in healing normal as well as infected wounds

It is involved in almost every stage of healing. It is also used in wound dressings to speed up the process of recovery. Though clinically well-tested, emphasis is now being laid in understanding the bioactive components involved in the process of healing.

PREPARATION: Placental extracts can be classified into two different types: aqueous extract and hydroalcoholic extract. The components present in the extract depend on the method of its preparation and are based on solubility of the components in respective solvent of extraction. Thus, an aqueous extract is likely to contain more polar molecules such as peptides/proteins, small organic components like amino acids, nucleotides, polydeoxyribonucleotides (PDRNs), carbohydrates and trace amount of lipids mostly bound to proteins which are comparatively soluble in aqueous medium. Likewise, various types of lipids may be present in hydroalcoholic extract (less polar and hydrophobic). Modern indigenous aqueous placental extract is prepared employing Filatov's procedure.

MOA: Clinical evaluation of the aqueous extract revealed that it has anti-inflammatory and antiplatelet aggregation activity. The extract exhibits anti-inflammatory response probably either through inhibition/inactivation of chemical mediators or by directly modulating prostaglandin (PG) production by suppression of cyclooxygenase (COX). Kinins, chemical mediators of nonimmunological type of inflammation, have two membrane receptor B1 and B2, for their activities. It also helps in activation of the clotting cascade by trauma which results in platelet activation, followed by aggregation.

In addition, an aqueous extract of human placenta has also shown to stimulate collagen synthesis *in vivo* in rats. Human and animal models show that placental extract has an immunostimulating action both at cellular and humoral levels. It probably increases IgG and IgM at the humoral level and total lymphokines at the cellular level. It also reports several advantages over antibiotics and chemotherapeutic agents in terms of antibacterial activity including vascularisation of wound environment and is free from side effects.

SIDE EFFECTS: Stinging sensation, burning sensation and atrophy.

OTHER TOPICAL AGENTS

Collagen: Collagen is critical in the proliferative phase of wound healing. Exogenous sources of collagen primarily purified bovine extracts, are available as gels, particles, and in an alginate dressing. Exogenous collagen provides additional protein for tissue repair.

Hyaluronic Acid: Hyaluronic acid is involved in the structure and organization of the extracellular matrix and is associated with increased mitotic activity. It is a high molecular weight polysaccharide synthesized in the plasma membrane of fibroblasts and other cells. **Beta Glucan:** It is a major cell-wall carbohydrate extracted from grains as oats and barley. Beta glucan is thought to increase macrophage infiltration, speeding the onset of fibroplasias and fibrogenesis, stimulation of increased tissue granulation, and enhanced re epithelialisation. **Silver Arglaes:** Silver compounds are powerful antimicrobials, useful in promoting healing. Arglaes is an inorganic phosphate similar to other compounds such as silver nitrate, silver oxide and silver chloride. It consists of fused sodium and calcium phosphates with small amounts of silver in the presence of water, these materials release free silver ions.

L-lysine hydrochloride[46]

Lysine (abbreviated as Lys or K) is an essential amino acid. L-Lysine Hydrochloride has shown improvement in both the rate and quality of wound healing. Another feature of this molecule is its ability to support healing process in long standing wounds. On histopathology, lysine treated wounds showed a thickening of the dermo-epidermal layer, with increased cell proliferation from the basal keratinocytes.L- lysine monohydrochloride (L-Iysine) has been shown to promote therapeutic angiogenesis in wound healing.

Oxandrolone[47]

Oxandrolone is an anabolic steroid with a high anabolic and low androgenic ratio and has anticatabolic, protein-sparing properties. Exogenous anabolic agents clubbed with nutritional intervention can result in a threefold to fourfold higher rate of protein synthesis than with nutritional interventions alone.[46]

Honey dressings

Medical role of honey were known since ancient past. Dressings promote moist wound healing, autolytic and osmotic debridement and have antimicrobial activity. It is due to the slow release of low levels of hydrogen peroxide

Sucralfate

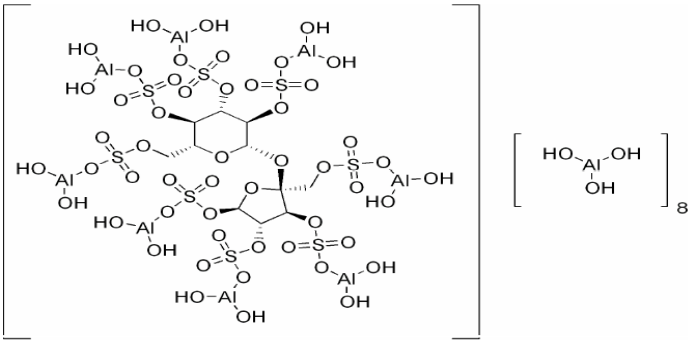
Sucralfate is an oral gastrointestinal medication primarily indicated for the treatment of active duodenal ulcers. Sucralfate is also used for the treatment of gastroesophageal reflux disease (GERD) and stress ulcers. Unlike the other classes of medications used for treatment of peptic ulcers, sucralfate is a sucrose sulfate-aluminium complex that binds to the hydrochloric acid in the stomach and acts like an acid buffer with cytoprotective properties. Sucralfate was approved by the U.S. Food and Drug Administration (FDA) in 1981.

CHEMICAL DATA:

Formula: C12H54Al16O75S8`

Mol. mass: 2086.75 g/mol

STRUCTURE OF SUCRALFATE:



SYSTEMATIC NAME: Hexadeca-μ-hydroxytetracosahydroxy[μ8-[1,3,4,6-tetra-*O*sulfo-β-Dfructofuranosyl-α-D-glucopyranoside tetrakis(hydrogen sulfato)8-)]] hexadecaaluminum

Sucralfate has been investigated as a treatment for leg ulcers, diabetic ulcers, decubitus ulcer, as well as for rapid and efficient healing of skin impairments such as scratches, cuts and other uninfected wounds, burns and skin cracks. In contact with the damaged skin, sucralfate forms a protective barrier covering the damaged area of the skin. It is known that sucralfate, in the form of tablets and suspension, has been administered for decades in the treatment of stomach and duodenal ulcers. In these pharmaceutical forms, sucralfate lines stomach and duodenal mucosa by forming a protective covering epithelium on the surface of damaged tissue. As compared to the stated, traditional forms of sucralfate, has a much greater capacity of adhering to damaged skin epithelium and its action is not dependent on the degree of skin acidity, i.e. pH value of skin. Clinical studies have proved efficient renewal of the damaged skin and efficient healing of uninfected wounds of different origin. The care of venous ulcers often relies on palliative and often unsuccessful therapies . It is clear that wound healing is

dependent on angiogenesis, cell proliferation, extracellular matrix remodeling, tissue inflammation and good re-epithelialization

Thus the ideal drug for the treatment of venous ulcers should possess properties that improve all these biological parameters. Sucralfate is a basic aluminium complex of sucrose sulfate, structurally related to heparin but without anticoagulant activity. Although structurally related to sucrose, sucralfate is not utilized as a sugar in vivo in humans. One of the oldest materials to be used in wound management is honey, the use of which was described by the Egyptians as early as 1600 BC. In recent years there has been an increasing interest in the use of sucrose as a wound dressing. Sugar, either in the form of granulated sugar or pastes composed of caster and icing sugar has been used successfully in the treatment of a variety of wounds, including bedsores and diabetic ulcers.

Recent studies have shown the stimulating effect of sucralfate on EGF expression and on the expression of other factors involved in tissue repair processes . Furthermore, the stimulating effects of sucralfate on the vascular factors, including angiogenesis, which play important roles in tissue repair, have been demonstrated . Topical sucralfate has been successfully studied in peristomal and perineal dermatoses, in moist desquamation during radiotherapy, in erosion and ulceration of the perineal area, in vaginal ulceration, in dystrophic epidermolysis bullosa, in second and third degree burns, and in a pilot trial with non-healing, full-thickness venous stasis ulcers refractory to 8 weeks of conventional therapy . It has been previously suggested that sucralfate can bind basic fibroblast growth factor, thus protecting its degradation and allowing it to act as an angiogenetic molecule .

Furthermore, sucralfate is able to stimulate the synthesis and release of epidermal growth factor which in turn stimulates healing and affects prostaglandin synthesis . It has also been indicated

that sucralfate induces the proliferation of dermal fibroblasts and keratinocytes in vitro, and inhibits the release of interleukin-2 and interferon-γ from damaged skin cells

MOA:

The action of sucralfate can now be defined by the '1 x 1 x 1' mechanism of action--that is, one action of sucralfate is important for acute prevention, one is relevant to both acute and chronic protection, and one is important for chronic ulcer healing. Maintenance of mucosal vascular integrity and of blood flow, which ensures rapid epithelial restitution to repair superficial defects, are the most important acute actions of sucralfate. The enhanced binding by sucralfate of fibroblast growth factor and epidermal growth factor stimulates angiogenesis, granulation tissue, and epithelization for ulcer healing. This 1 x 1 x 1 theory of the mechanism of action of sucralfate concentrates on the relevant effects of this drug (which has more than a dozen actions) and may help to elucidate the molecular mechanism of action.

Sucralfate wound healing mechanisms may include:

- Stimulation of fibroblast proliferation.
- Enhancing the formation of granulation tissue.
- Decreasing collagenase activity, inhibition of glucocorticoid activity
- Direct or indirect antibacterial activity by affecting inflammatory cells
- Neovascularization.

The in-vitro activity of sucralfate (sucrose octa-sulphate) in suspension was examined against 128 strains of Gram-negative bacilli. Inhibitory activity was demonstrated against all isolates and bactericidal activity was demonstrated for 68. Sucralfate has inhibitory and bactericidal antibacterial activity which may contribute to its in-vivo clinical efficacy.

4.MATERIALS AND METHODS

The present study was carried out at Department of Surgery, Sri Devaraj Urs medical college, R.L.Jalappa Hospital and Research centre and teaching hospitals attached to SDUMC. Period of study was from January 2014 to September 2015.

STUDY DESIGN

The prospective randomized clinical trial was conducted on patients with diabetic ulcers of lower extremities.

SOURCE OF DATA

Diabetic patients with ulcers of lower limb extremities admitted at Department of Surgery, Sri Devaraj Urs medical college and R.L.Jalappa Hospital and Research centre, Tamaka, Kolar and teaching hospitals attached to SDUMC.

SAMPLE SIZE

The study comprised of 100 patients. The patients were randomly divided into two groups. Group I comprising 50 patients received topical sucralfate and Group II comprising 50 patients received human placental extract dressings.

SELECTION CRITERIA

INCLUSION CRITERIA.

1. All patients with type 2 diabetes mellitus with diabetic foot ulcers of Wagner's grade 1 and 2.

EXCLUSION CRITERIA

1. Patients with chronic venous insufficiency of lower limbs with dermal changes and lymphedema.

2. Patients with uncontrolled diabetes with severe co morbid medical conditions.

METHODOLOGY

- The study was approved by the Ethical and Research Committee of Sri Devaraj Urs Medical College,Kolar.
- After finding the suitability as per inclusion and exclusion criteria patients were selected for the study and briefed about the nature of the study, the interventions used and written informed consent was obtained.
- The selected patients underwent appropriate treatment for a period of one to two weeks.

This was to stabilize the wound and institute appropriate medical and surgical treatment.

It included diabetic control, control of infection by appropriate antibiotics which were based on culture and sensitivity reports.

- Also surgical debridement and correction of other medical illness were considered.
- After the initial treatment period the eligible patients were divided randomly into test group and controls.
  - ✓ GROUP 1:All patients with odd numbers categorized were into group 1 who received sucralfate dressings.
  - ✓ GROUP 2:All patients with even numbers were categorized into group 2 who received Human placental extract dressings

- The descriptive data of the participants like name, age, sex, detailed history, were obtained by interviewing the participants and clinical examination and necessary investigations like complete blood count, random blood sugar, blood urea and serum creatinine and culture of the ulcer were recorded on predesigned and pretested proforma.

Initial wound measurement was taken in both the groups before starting their respective treatment that is sucralfate in group I and human placental extract dressing dressing in group II.

INITIAL WOUND ASSESSMENT

☐ Ulcer examination was done in all these patients and wound was assessed of its characteristics and photographed.

☐ Ulcer was assessed by the investigator at the beginning of the study and at the end of the study.

☐ The dressing was changed every day or early if mandated.

☐ Wounds were inspected for :

1. Presence of slough as percentage of total ulcer surface area.
2. Progress of granulation tissue as percentage of total ulcer surface area.
3. Ulcer size as change in surface area and reduction percentages.
4. Wound bed preparation for skin grafting.
5. Infection of wounds.

☐ The amount of non viable tissue, degree of wound granulation and overall wound response was evaluated on baseline, one week, two weeks, three weeks and four weeks.

☐ The visual scores for the percentage of wound covered with necrotic tissues are-

1- 76-100% of wound covered by necrotic tissue.

2-51-75% of wound covered by necrotic tissue.

3- 26-50% of wound covered by necrotic tissue.

4- 11-25% of wound covered by necrotic tissue.

5- 0-10% of wound covered by necrotic tissue.

6- No necrotic tissue covering the ulcer.

☐ The visual scores for the percentage of wound filled by granulation tissues are-

1- No granulation tissue covering the ulcer.

2- Pink/dull <25% wound filled.

3- Bright beefy 25-74% wound filled.

4- Bright beefy red 75-100% wound filled.

☐ The reduction of wound size area was measured in sq cm .

☐ We have applied the following formula to calculate % reduction in area of wound after four weeks period in both cases and controls.

$$\textbf{\% Reduction of wound after four weeks} = \frac{\textbf{Initial area – Final area X 100}}{\textbf{Initial area}}$$

☐ The results obtained were statistically evaluated and the main parameters were analyzed by Chi square and student t test, p value of <0.05 was considered significant. SPSS software version 16 and Open Epi info software version 2.3 were used.

5.RESULTS AND OBSERVATIONS

The present study was conducted in Sri Devaraj Urs Medical College, R.L.Jalappa Hospital and Research center and the findings are tabulated as below. During the study period from January 2014 to September 2015, 100 diabetic patients with ulcers of the lower limb were randomized into group one (topical sucralfate dressings) and group two (topical human placental extract dressings). These groups were studied for the effect of topical human placental extract dressings versus topical sucralfate dressings on wound healing of diabetic foot ulcers.

AGE DISTRIBUTION

Out of total of 100 patients, 50 received topical sucralfate dressings and the 50 patients received topical human placental extract dressings. Highest number of patients was observed to be in the 61-70 yrs group indicating diabetic foot ulcers are most common in that age group. The mean age between two groups was statistically not significant (p=0.817). The patients falling into respective age groups are as follows:

TABLE 1: AGE DISTRIBUTION

AGE GROUP	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP
31-40YRS	2	5
41-50YRS	15	12
51-60YRS	14	11
61-70YRS	14	17
71-80YRS	4	2
81 YRS AND ABOVE	1	3

GRAPH 1: AGE DISTRIBUTION

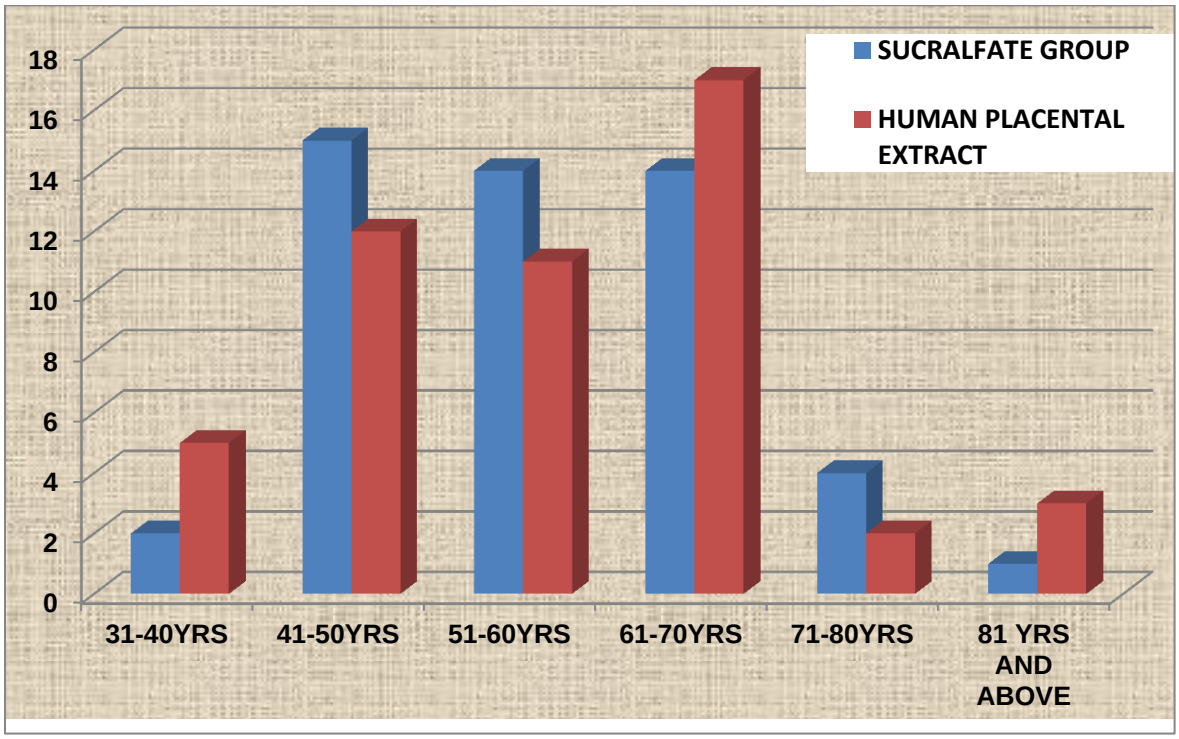


TABLE1A:MEAN AGE BETWEEN TWO GROUPS

AGE	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MEAN ± SD	57.14±11.61	57.7±12.49	0.817

SEX DISTRIBUTION

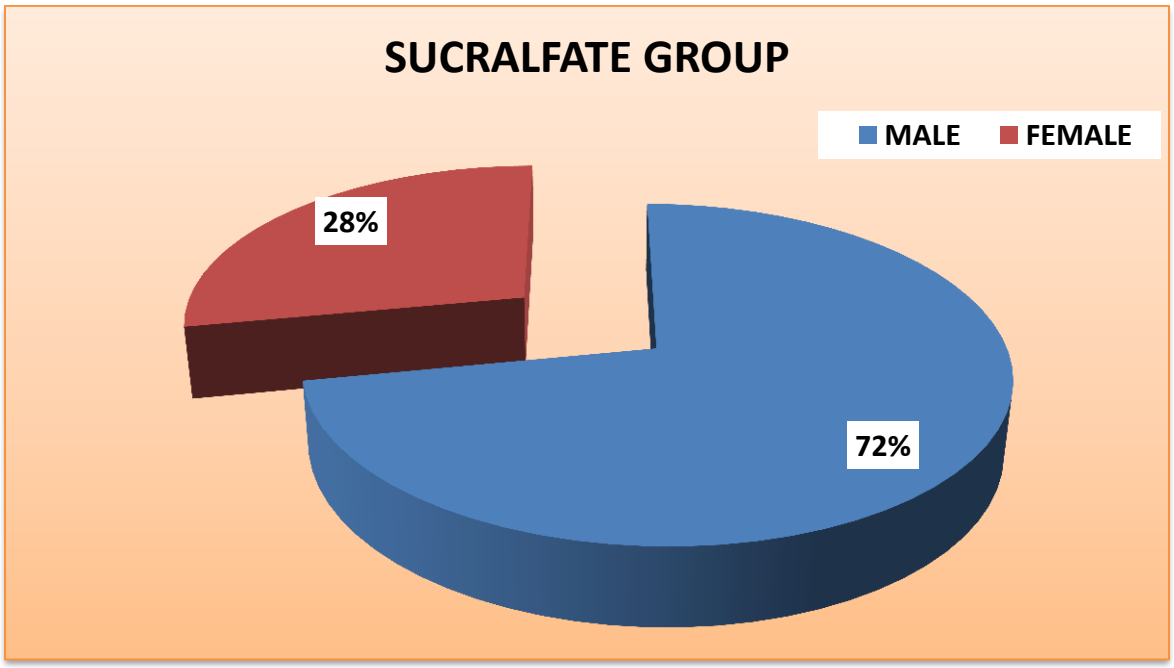
Out of total of 50 patients receiving sucralfate dressings, 36 were male and 14 were female and of the 50 patients receiving human placental extract dressings 38 were male and 12 patients were female. The male to female ratio of the human placental extract dressings group is 3:1 and the sucralfate group is 2:1

TABLE 2 :SEX DISTRIBUTION

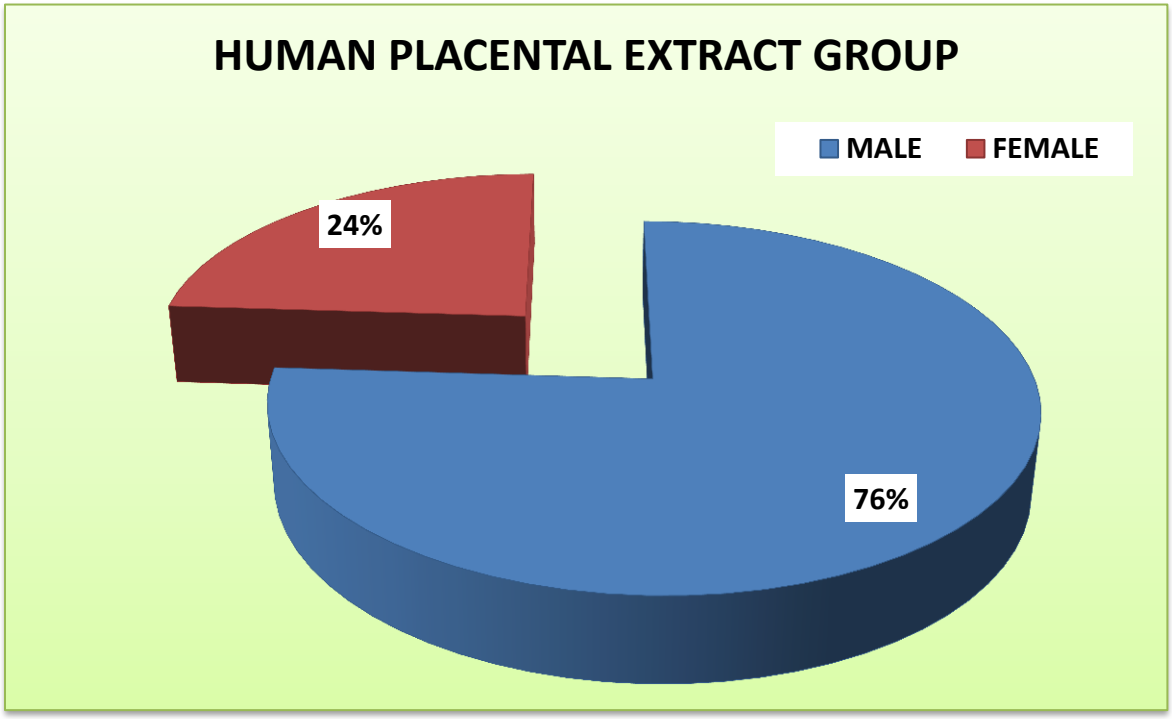
GENDER	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MALE	36	38	0.820
FEMALE	14	12	
TOTAL	50	50	

.

GRAPH 2A: SEX DISTRIBUTION



GRAPH 2B: SEX DISTRIBUTION



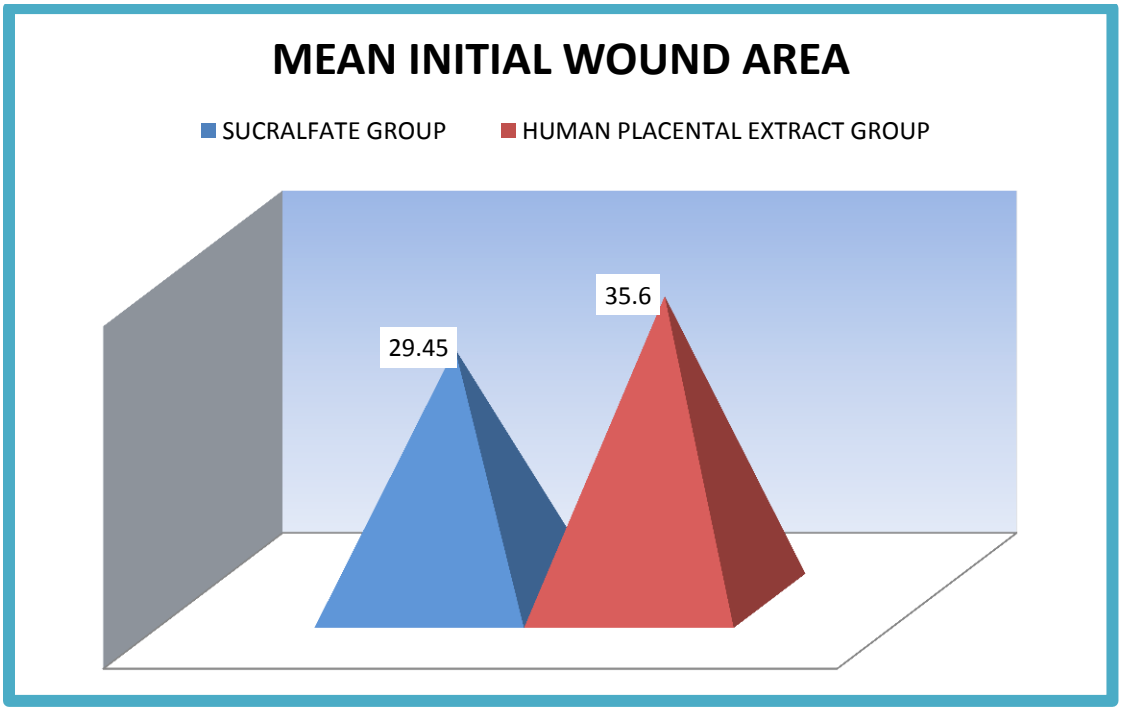
MEAN INITIAL WOUND AREA

The mean area at the beginning of the study was 29.45 sq cm in the sucralfate Group and 35.6 sq cm in the human placental extract group. The initial wound areas were statistically not significant (p= 0.06) between two groups.

TABLE 3: MEAN INITIAL WOUND AREA

INITIAL WOUND AREA	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MEAN ± SD	29.45±14.58	35.60±18.32	0.066

GRAPH 3 : MEAN INITIAL WOUND AREA



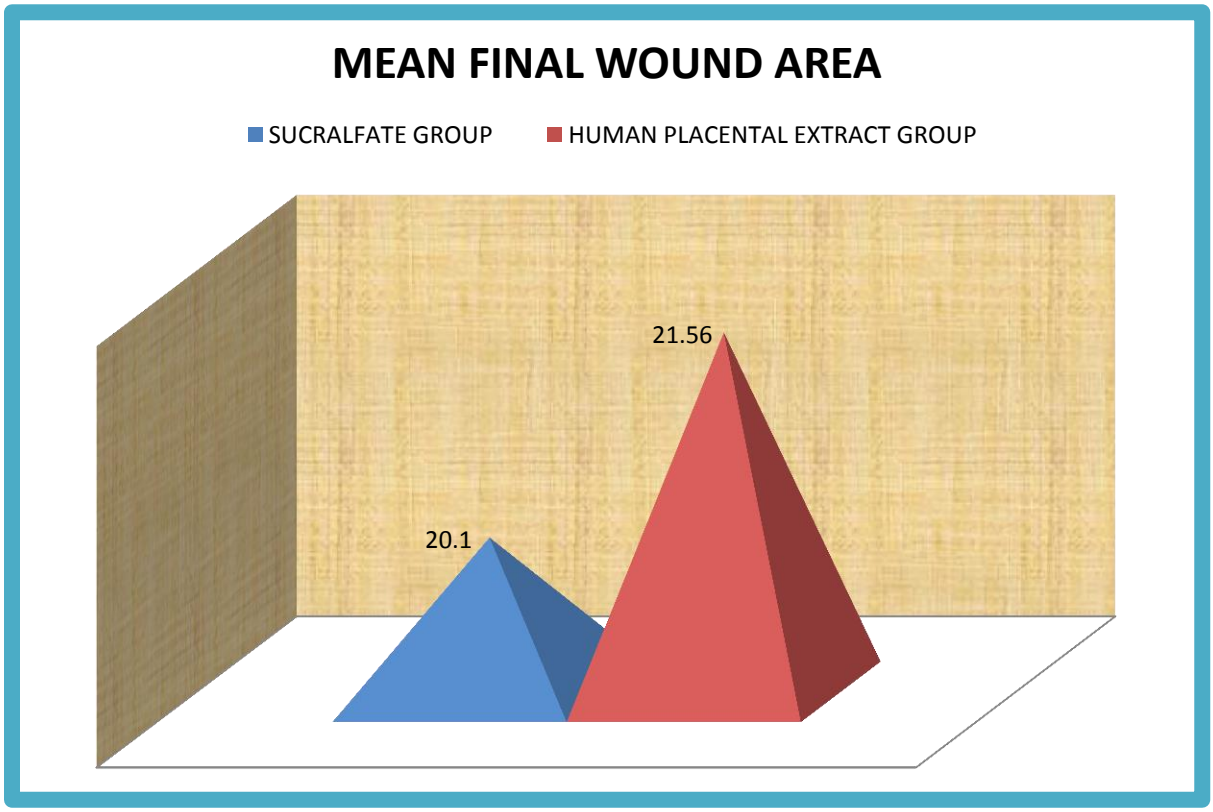
MEAN FINAL WOUND AREA :

At the end of the study the mean area was 20.1 sq cm in the group treated with sucralfate dressings and 21.12 sq cm in the group treated with human placental extract dressings which was found to be statistically not significant (p=.525)

TABLE 4: MEAN FINAL WOUND AREA

FINAL WOUND AREA	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MEAN ± SD	20.10±10.11	21.56±12.59	0.525

GRAPH 4: MEAN FINAL WOUND AREA



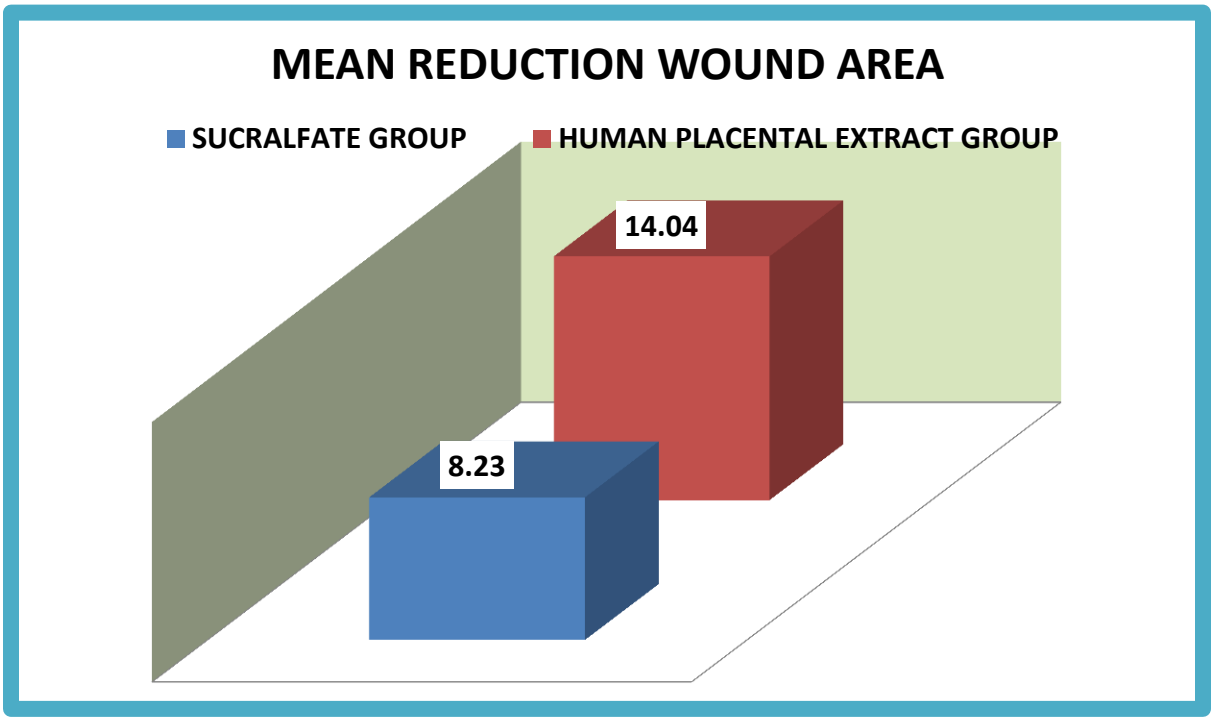
MEAN REDUCTION OF WOUND AREA.

The study showed that the mean reduction of wound area achieved between the two groups were 8.23 sq cm in patients treated with sucralfate dressing and 14.04 sq cm in patients treated with human placental extract dressing. Reduction of wound area was considerably high in human placental extract group than sucralfate group which was statistically significant with p value of <0.001.

TABLE 5 :MEAN REDUCTION OF WOUND AREA

MEAN REDUCTION WOUND AREA	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MEAN ± SD	8.23±3.08	14.04±6.2	<0.001

GRAPH 5 : MEAN REDUCTION OF WOUND AREA



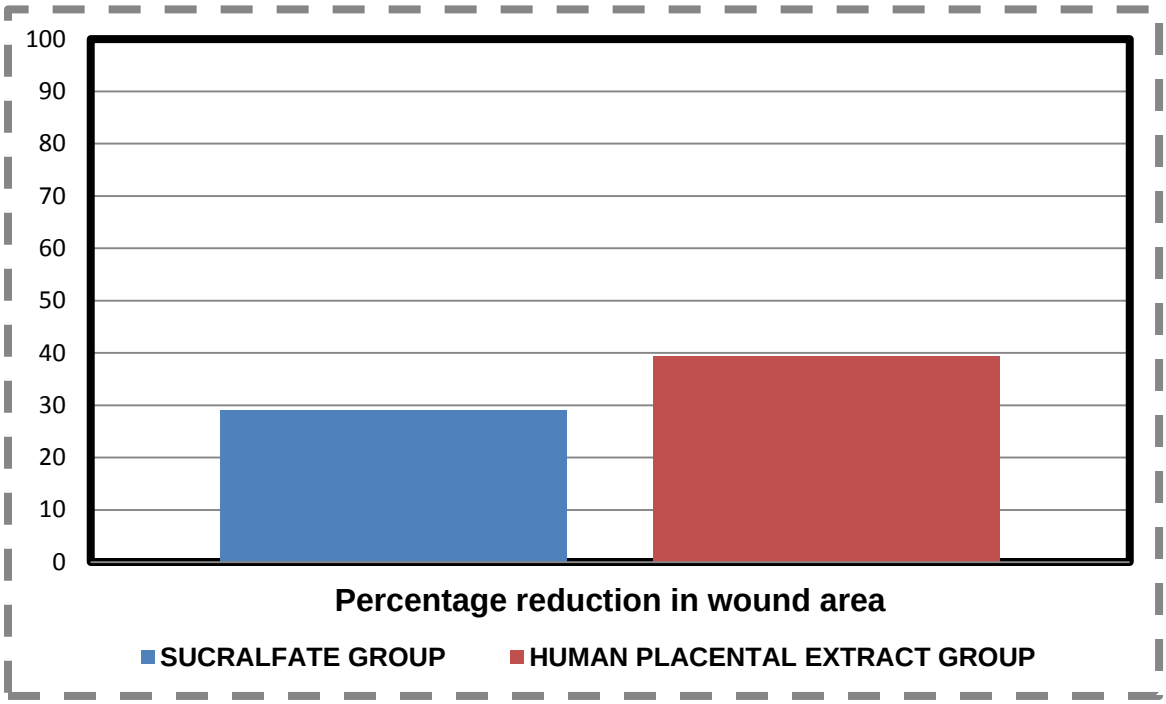
MEAN PERCENTAGE REDUCTION OF WOUND SURFACE

The study shows that the mean percentage of reduction of wound area achieved was 29.04% in patients treated with sucralfate dressing and 39.04% in patients treated with human placental extract dressing. Reduction percentage was considerably high in Human placental extract group than sucralfate group and showed statistical significance with p value < 0.001.

TABLE 6: MEAN PERCENTAGE REDUCTION OF WOUND SURFACE

MEAN PERCENTAGE REDUCTION WOUND AREA	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
MEAN ± SD	29.04%	39.04%	<0.001

GRAPH 6 : MEAN PERCENTAGE REDUCTION OF WOUND SURFACE



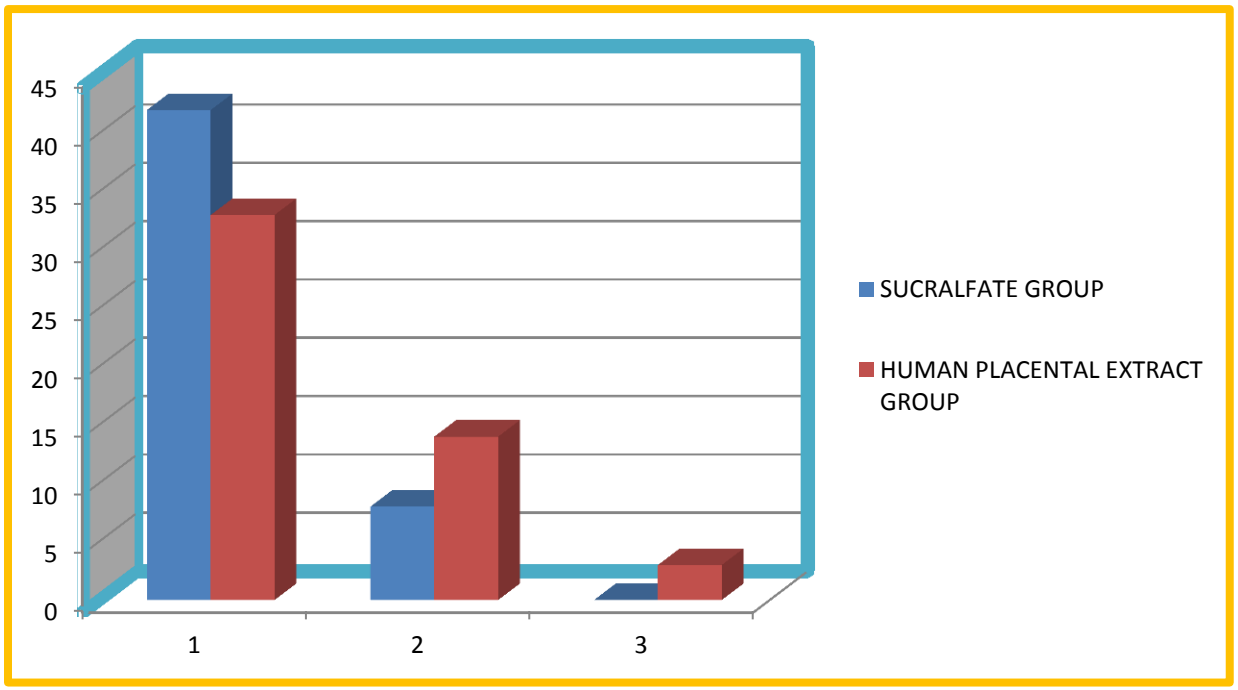
PRESENCE OF NECROTIC TISSUE OR SLOUGH

The study comprised of a total of 100 patients.50 patients received Human placental extract and the other 50 received sucralfate dressings for the healing of the ulcer. Both the groups had considerable amount of necrotic tissue at the time of admission which has been compared which was statistically not significant (p=.057).

TABLE 7: PRESENCE OF NECROTIC TISSUE

	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
1 (76-100%)	42	33	0.057
2(51-75%)	8	14	
3(26-50%)	0	3	

GRAPH 7 : PRESENCE OF NECROTIC TISSUE

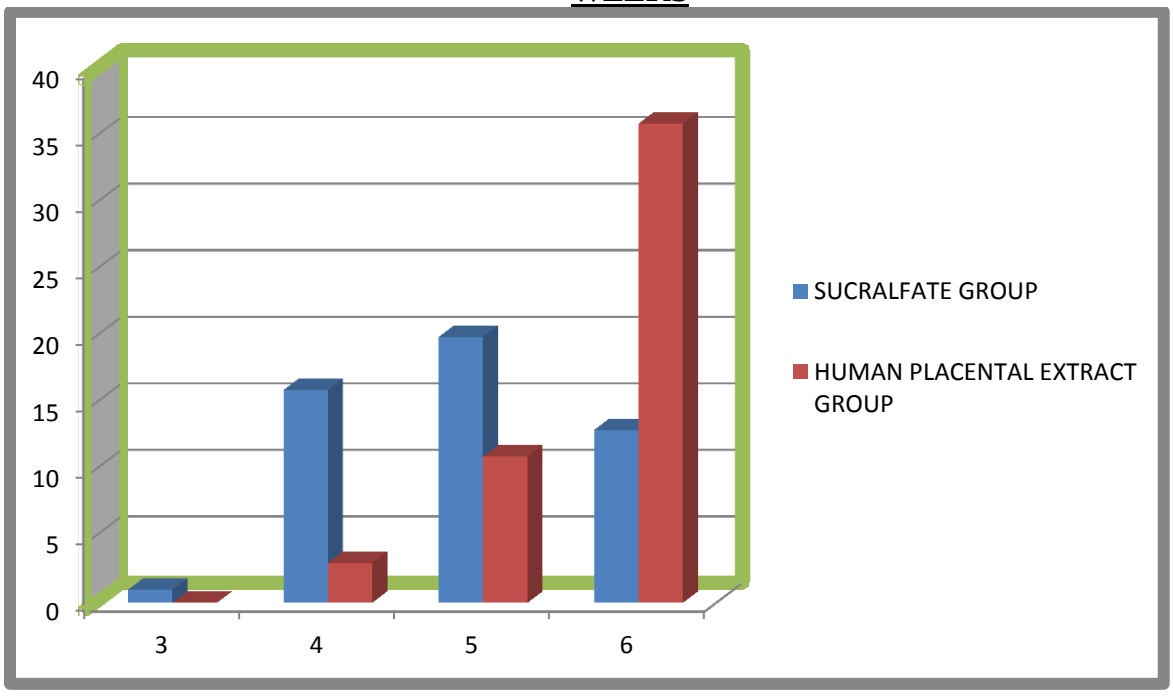


- 42 patients had 76-100% of area covered with necrotic tissue in sucralfate group and 33 patients in human placental extract group.
- 8 patients had 51-75% of area covered with the necrotic tissue in sucralfate group and 14 patients in human placental extract group.
- No patients had 26-50% of the area covered with the necrotic tissue in sucralfate group and 3 patients in human placental extract group.
- Both the groups had considerable amount of necrotic tissue at the time of admission which has been compared.(p=.057)
- Necrotic tissues compared after 4 weeks in both groups showed gradual decrease in the amount of necrotic tissue covering the wound surface area.
- Comparing the two groups

TABLE 8 : NECROTIC TISSUE COVERING WOUND SURFACE AFTER FOUR WEEKS

VISUAL SCORE	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
4	17	3	<0.001
5	20	11	
6	13	36	

GRAPH 8 : NECROTIC TISSUE COVERING WOUND SURFACE AFTER FOUR WEEKS



 In human placental extract group 3 Six patients had slough covering 11-25% wound area, 11 patients with 0-10% wound area covered with slough and 36 patients with no necrotic tissue.

- In sucralfate group 17 patients showed 11-25% wound with slough, 20 patients with 0-10% slough and only 13 patients with no necrotic tissue over the wound.
- Both groups were compared , which showed significant reduction of necrotic tissue in Placental extract group at the end of study.($p<0.001$).

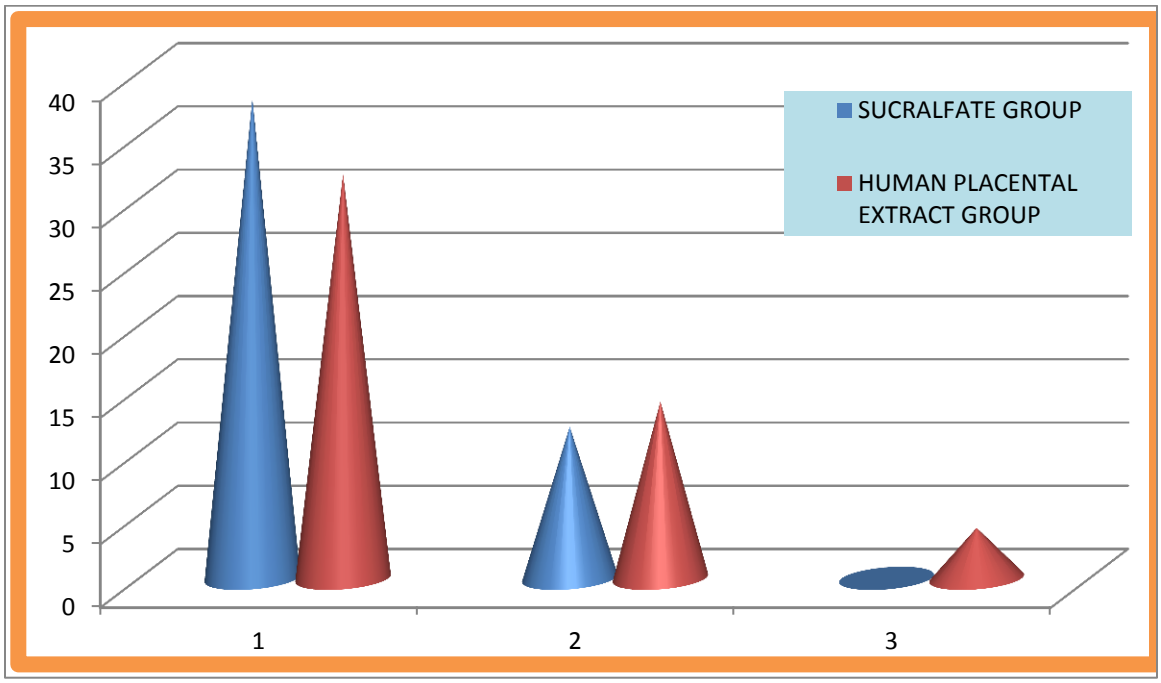
PRESENCE OF GRANULATION TISSUE:
COMPARING BOTH GROUPS :

- At the time of admission the number of patients in both the groups were compared regarding the presence of granulation tissue, in which baseline granulation tissue was statistically similar.($p=.096$)
- 38 patients had no granulation tissue and 12 patients had less than 25% wound filled with pink dull granulation tissue in sucralfate group .
- In the human placental extract group 32 patients had no granulation tissue and 14 patients had less than 25% wound filled with pink dull granulation tissue and 4 patients with bright beefy granulation tissue filling 25- 74% of wound.

TABLE 9: BASELINE DISTRIBUTION OF GRANULATION TISSUE

VISUAL SCORE	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
1(NO GRANULATION TISSUE)	38	32	0.096
2(<25%)	12	14	
3(24-75%)	0	4	

GRAPH 9: BASELINE DISTRIBUTION OF GRANULATION



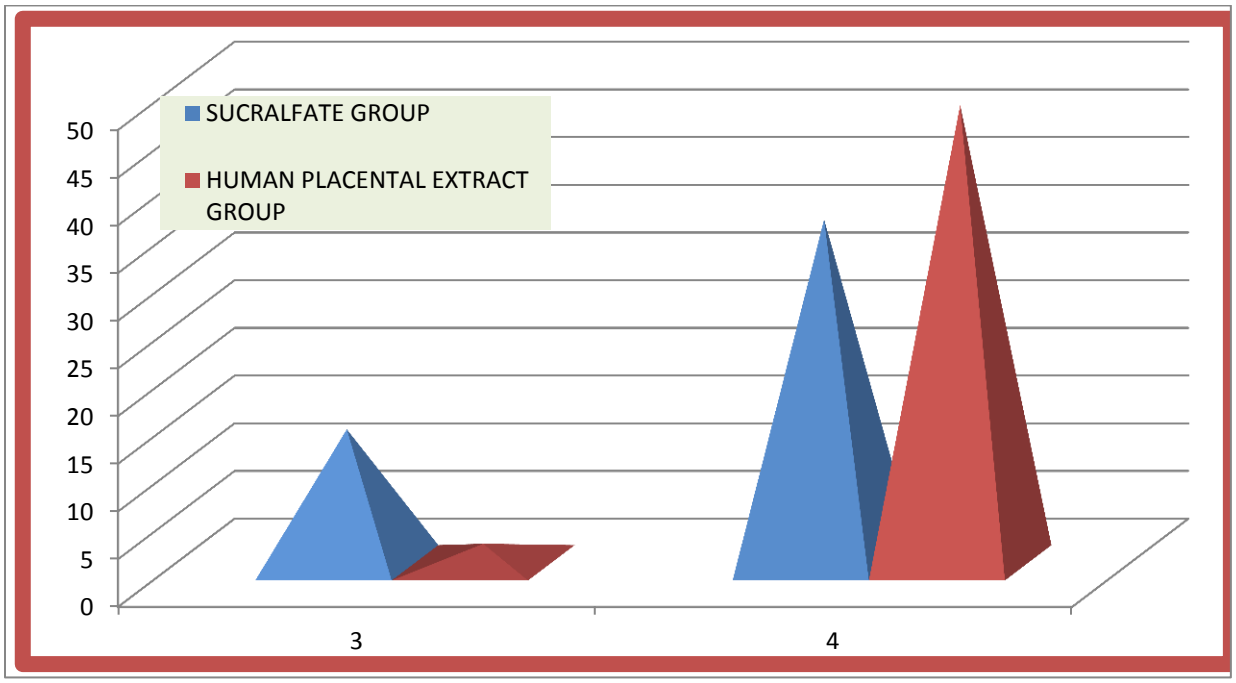
GRANULATION TISSUE FILLING THE WOUND AFTER FOUR WEEKS

- Both groups were compared for granulation tissue filling the wound after four weeks.
- 14 patients had bright beefy granulation tissue 25-74% filling the wound and 36 patients had bright beefy red granulation tissue filling the wound in the sucralfate group after four weeks.
- In the human placental extract group 2 patients had bright beefy granulation tissue 25-74% filling the wound and 48 patients with bright beefy red granulation tissue filling the wound after four weeks.
- Both groups were compared which showed significant granulation tissue covering the wound in human placental extract group than sucralfate group at the end of the study .(p=0.002)

TABLE 10: GRANULATION TISSUE FILLING THE WOUND AFTER FOUR WEEKS

VISUAL SCORE	SUCRALFATE GROUP	HUMAN PLACENTAL EXTRACT GROUP	P VALUE
3(25-74%)	14	2	0.002
4(75-100%)	36	48	

GRAPH 10: GRANULATION TISSUE FILLING THE WOUND AFTER FOUR WEEKS



6. DISCUSSION

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates and controlling local infections by local medications to the level of providing adequate environment promoting wound healing. This has been achieved by modern wound dressing agents which promote granulation tissue formation.

Derived from folklore, human placental preparations show immense therapeutic value. The aqueous extract of human placenta is a scientifically proven potent wound healer. A fibronectin type III-like peptide present in the aqueous extract appears to be one of the key components for wound healing. Placental extract aids in absorption of exudates by controlling its formation, removal of unhealthy tissue by debridement and management of bacterial load that are required for good wound bed preparation.

In this study on 100 subjects, 50 patients received sucralfate dressings and 50 patients received human placental extract dressings. Base line characteristics like age, sex, initial wound surface area, necrotic tissue or slough, granulation tissue and final wound area were matched.

Majority of patients in the study fell in the age group of 61-70 years showing that diabetic foot ulcers being common in the elderly age group. Male Sex distribution was more in comparison to female sex with male: female ratio of 3:1 in human placental extract group and 2:1 in sucralfate group.

Mean initial wound area at the beginning of the study was 29.45±14.58 in sucralfate group and 35.60±18.32 in human placental extract group. There was no statistical difference between the initial wound surface areas with p=0.066. After receiving the treatment for a period of four weeks in both the groups, the wound surface area considerably decreased in both the groups. The mean final wound area in the sucralfate group was 20.10±10.11 and in human

placental extract group was 21.56±12. Mean percentage reduction of wound area was calculated in both the groups.

Human placental extract group showed considerable result in having better reduction percentage with 39.04% % and 29.04% in sucralfate group which was statistically significant (p=<0.001). Base line necrotic tissue in both the groups were statistically similar. After receiving the dressings in both group there was considerable decrease in the necrotic tissue which was statistically significant (p=<0.001).

Amount of good granulation tissue is a major indicator of healthy healing. During the study there was very good progression of granulation tissue in the human placental extract group when compared to the sucralfate group. There was high statistical significance (p=0.002).Speeding up of granulation tissue thus provides faster healing and faster wound bed preparation which was shown in the study.

This comparative study shows a significant reduction in final wound area when treated with human placental extract which is achieved obviously by its efficacy in drastically promoting granulation tissue formation.

Limitations of our study:

- Smaller sample size- Though 100 patients is sufficient for statistical analysis, a randomized control comparative study with a much larger population may help to further substantiate findings.
- Cost burden on patient not analyzed.
- Not a blinded study.

7. CONCLUSION

With the use of Human Placental extract dressing in comparison with the sucralfate dressings for the treatment of diabetic ulcers of lower limb, the following conclusions were derived;

- Human placental extract dressing showed faster and better healing rates among the study group.
- Area reduction and percentage reduction was better in Human placental extract group.
- Considerable amount of necrotic tissue was reduced with human placental extract group.
- Granulation and epithelialisation appeared to occur early in ulcers treated with Human placental extract dressings than with sucralfate dressings, thus preparing the wound bed and facilitating early cover of raw area by split skin grafting.

8.SUMMARY

The present study was conducted in R.L.J.H, Kolar and attached hospitals to SDUMC.

Total of 100 diabetic patients with lower limb ulcers were included in the study. The objective of the present study was to assess the efficacy of human placental extract dressing in comparison with sucralfate dressings in terms of duration of healing andwound surface area.

The patients were randomized into two groups (Group I= sucralfate & Group II= human placental extract) comprising 50 in each group. There was no statistical difference in the baseline characteristics like age, sex, initial wound area of ulcer, baseline necrotic tissue covering ulcer and granulation tissue filling wound between the two groups. There was good progression of granulation tissue during treatment in the human placental extract group and was statistically significant. The final wound area reduced was considerably more in the human placental extract group and percentage reduction of wound area was high in human placental extract group and it showed statistical significance when compared with sucralfate group.

Thus, human placental extract dressing therapy in the treatment of diabetic foot ulcers was found to be more effective, safe, promoter of wound healing, and hence can be recommended for the treatment of diabetic foot ulcers.

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ANNEXURE I

PROFORMA

"A COMPARATIVE STUDY OF TOPICAL HUMAN PLACENTAL EXTRACT WITH TOPICAL SUCRALFATE IN THE MANAGEMENT OF DIABETIC FOOT ULCERS".

Name: DOA:

Age: DOD:

Sex: Hospital no:

Address: Religion:

Occupation: Socioeconomic class:

History

Onset of ulcer: Trauma ☐ Spontaneous ☐

Site of ulcer:

Duration of Ulcer:

Progress: Progress gradual ☐ Rapidly ☐

Pain: Yes ☐ No ☐

Discharge: Pus ☐ Serous ☐ Sero-sanguinous ☐

Treatment: Received ☐ Not Received ☐

Diabetic History:

History of diabetes Mellitus:

Type of diabetes Mellitus:

Duration of diabetes Mellitus:

Type of Treatment at Admission: Oral ☐ Parenteral ☐

Treatment for Diabetes: Regular ☐ Irregular ☐

History Of Any Other Illness:

History Of Alcohol & Tobacco:

Foot Examination:

Skin dry: Yes ☐ No ☐

Edema: (site)

Erythema: (site)

Heel fissures:

Scratch marks:

Signs of infection:

Any Deformities: Yes ☐ No

Examination Of Foot Ulcer:

Side:	**Right**	**Left**
Site		
Size		
Shape		

Margin

Edge

Floor

Depth

Duration

Granulation

Peri ulcer edema

Slough

Exposed tendon

Necrotising fasciitis

Pulse: Normal (N), Week (W), Absent (A)

	Right	Left
Femoral	☐	☐
Popliteal	☐	☐
Post. tibial	☐	☐
D. pedis	☐	☐

Investigations:

Hametological

Hb%-	PCV-	T.C-	D.C-	R.B.C-
Platlets-	E.S.R-	B.T-	C.T-	Blood grouping-

Bl. Urea- S.Creatinine-

FBS- PPBS-

Urine examination:

Albumin- Sugar- Ketones-

Doppler studies (if needed):

X-Ray of foot:

Pus for Culture Sensitivity

Follow-up:

Clinical features	baseline	Follow-up					
		1st week	2nd week	3rd week	4th week	5th week	6th week
1. Presence of necrotic tissue by clinical evaluation							
Visual scores: 1=76-100%, 2=51-75%, 3=26-50%, 4=11-25%, 5=0-10%, 6= No necrotic tissue covering the ulcer							
2. Presence of Granulation tissue by clinical evaluation							
Visual scores: 4= bright beefy red 75-100% wound filled 3=bright beefy 25-74% wound filled 2= pink/dull <25% wound filled 1= No granulation tissue covering the ulcer							
3. Wound surface area (cm2) By scale measurement							
4. Wound debridement done							

Any Other Findings:

Comments by the patient:

ANNEXURE II

INFORMED CONSENT

"A COMPARATIVE STUDY OF TOPICAL HUMAN PLACENTAL EXTRACT WITH TOPICAL SUCRALFATE IN THE MANAGEMENT OF DIABETIC FOOT ULCERS".

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institution ethical committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ Provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation.

Contact no :9449253243.

Subject name: DATE:

Signature/ thumb print:

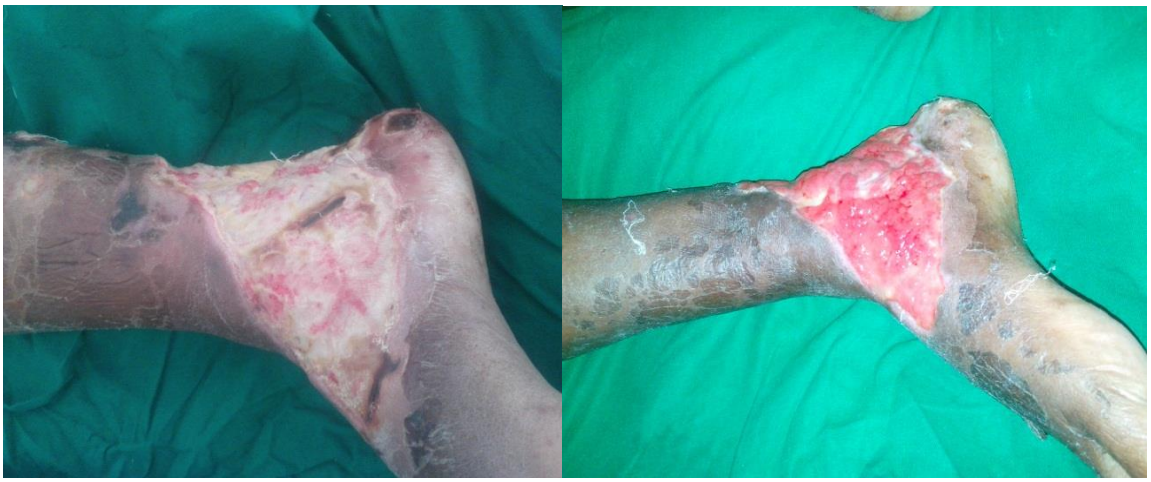
Parents/ guardians name: DATE:

Signature/ thumb print:

Signature of person taking consent: DATE

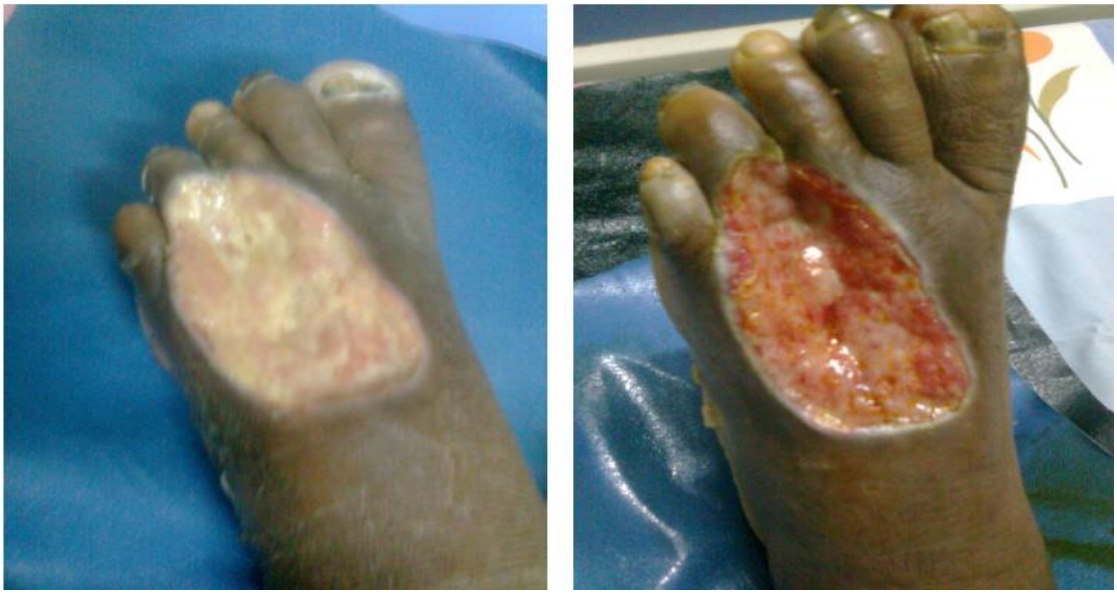
ANNEXURE III

PICTURE GALLERY



BEFORE AFTER

PHOTOGAPH 1:WOUND BEFORE AND AFTER IN HUMAN PLACENTAL EXTRACT GROUP



PHOTOGAPH 2:WOUND BEFORE AND AFTER IN HUMAN PLACENTAL EXTRACT GROUP

PHOTOGAPH 3:SUCRALFATE TABLETS USED FOR THE STUDY

PHOTOGAPH 4:HUMAN PLACENTAL EXTRACT GEL USED FOR THE STUDY

ANNEXURE IV

KEY TO MASTER CHART

M MALE

F FEMALE

R RIGHT

L LEFT

Sl.no	NAME	AGE	SEX	HOSPITAL NO	SITE	AL WOUND	PRESENCE OF NECROTIC TISSUE					PRESENCE OF GRANULATION TISSUE					L WOUND A
							BASE LINE	1 WEEK	2ND WEEK	3RD WEEK	4TH WEEK	BASE LINE	1ST	2ND	3RD	4TH	
1	HANUMANTHAPPA	70	M	907878	GREAT TOE (R)	36.4	2	2	3	4	4	2	2	3	3	3	21.85
2	VIJAYAKUMAR	48	M	981026	MEDIAL ASPECT ®	24.4	1	1	3	4	5	1	2	2	4	4	14.15
3	KARTHIK	45	M	102026	DORDUM ®	15	3	3	4	4	5	3	3	4	4	4	8.25
4	VENKATESH	53	M	21010	PLANTAR ASPECT (L)	18	1	2	2	4	5	1	2	2	3	4	10.26
5	NARASIMHAIAH	42	M	31951	DORSUM ®	64	2	2	3	4	5	2	2	3	3	4	39
6	KRISHNAPPA	48	M	20995	DORSUM (L)	46.8	1	2	4	6	6	1	3	4	4	4	25.2
7	NARAPPA	65	M	47387	DORSUM ®	44.08	1	3	4	6	6	1	2	4	4	4	24.5
8	LAKSMIPATHI	58	M	57945	MEDIAL ASPECT (L)	40	2	2	3	4	4	2	2	3	3	4	24
9	LAKSHMAN	65	M	1019196	LATERAL ASPECT (L)	51	1	2	4	6	6	1	3	4	4	4	26
10	DASTAHGIRI SAB	49	M	65914	DORSUM OVER 1ST TOE (L)	16	3	3	4	5	6	3	3	4	4	4	8.8
11	GANGAPPA	83	M	88906	DORSUM OF LEFT FOOT	36.8	2	3	5	6	6	3	3	4	4	4	21.7
12	VENTARAMAPPA	40	M	93984	DORSUM ®	24.6	2	2	4	6	6	2	2	3	3	4	14
13	GANGI REDDY	65	M	102340	DORSUM (L)	84.6	1	1	2	2	4	1	1	2	2	3	54
14	MUNISWAMY	85	M	118542	MEDIAL ASPECT ®	16	2	2	3	4	5	2	2	3	4	4	7.2
15	BASAVARAJ	50	M	125954	LATERAL ASPECT ®	14.6	3	4	5	6	6	3	3	4	4	4	8.67
16	KONDAPPA	50	M	157934	DORSUM ®	16.9	2	3	4	6	6	2	3	4	4	4	9
17	ABDUL KHADAR	64	M	136925	PLANTAR ASPECT OF RT FOOT	76.36	1	2	2	3	5	1	2	2	3	4	49.6
18	NAGARAJ	34	M	138498	DORSUM®	12.8	2	2	3	4	5	2	2	3	4	4	6.4
19	SHAWAR	64	M	164222	DORSUM(L)	15.6	1	2	3	5	6	1	2	3	4	4	8.75
20	MUNIYAPPA	60	M	164262	MEDIAL ASPECT (L)	26.46	1	2	4	5	6	1	2	4	4	4	17
21	RAMAKRISHNAPPA	53	M	153328	LATERAL ASPECT ®	10.5	2	3	4	6	6	2	3	4	4	4	5.77
22	SRINIVASAPPA	45	M	175143	DORSUM®	25.2	1	3	4	5	6	1	3	4	4	4	11.34
23	PILLAPPA	80	M	200423	DORSUM®	41.6	1	1	3	3	5	1	2	2	4	4	24.5
24	NARAYANA GOWDA	85	M	875164	DORSUM(L)	30.36	2	3	4	4	6	2	3	4	4	4	17
25	DODDA NARASIMHAPPA	55	M	996341	LATERAL AND DORSUM (R(	45.58	1	2	4	5	6	1	2	4	4	4	24
26	KRISHNAPPA	65	M	906038	LATERAL ASPECT ®	40	1	2	3	6	6	1	2	4	4	4	25.6
27	MURTHY	70	M	967150	DORSUM(L)	32.76	2	3	5	6	6	2	3	4	4	4	21.95
28	VENKATESH	40	M	3279	PLANTAR®	16.83	2	2	3	5	6	2	2	4	4	4	6.73
29	SEENAPPA	45	M	3099	DORSUM AND MEDIAL ASPECT (L)	64.8	1	2	3	5	6	1	2	3	4	4	42
30	RAJANNA	45	M	40206	DORSUM(L)	17.48	1	2	4	5	6	1	2	4	4	4	9
31	THYAGARAJACHARI	65	M	45173	LATERAL ASPECT ®	22.5	1	3	6	6	6	1	2	4	4	4	12.14
32	NARAYANAPPA	70	M	50899	DORSUM ®	44.1	1	2	2	4	5	1	2	3	4	4	27
33	MUNIRATHNAMMA	46	F	59082	DORSUM(L)	49.8	1	2	2	3	5	1	2	3	3	4	36
34	ANUSUYA	60	F	93518	MEDIAL ASPECT ®	34.77	1	2	4	5	6	1	2	4	4	4	23
35	RAZIYA SULTHANA	60	F	124365	DORSUM ®	32.5	1	3	6	6	6	1	3	4	4	4	22.75
36	FATHIMA	54	F	73475	PLANTAR (L)	20.88	1	3	4	6	6	1	3	4	4	4	11.45
37	SHANTHI	40	F	164664	DORSUM ®	27.5	1	3	3	5	6	1	3	4	4	4	17.6
38	ARUNA	55	F	179050	DORSUM (L)	19.8	2	2	4	5	6	2	2	4	4	4	10.5
39	SUDHA	45	F	200709	MEDIAL ASPECT ®	37.8	1	2	3	5	6	1	2	3	4	4	23
40	KENCHAMMA	72	F	100950	PLANTAR ®	17.6	2	3	5	6	6	2	3	4	4	4	8.1
41	TABASSUM	65	F	22645	DORSUM ®	59.2	1	2	4	6	6	1	2	4	4	4	34.34
42	LAKSHMI	56	F	2042	DORSUM (L)	36.3	1	2	4	6	6	2	3	4	4	4	23.23
43	VALLIYAMMA	62	F	62097	DORSUM ®	25.76	1	3	4	4	6	1	3	3	4	4	14.68
44	KASTHURI	35	F	202778	MEDIAL AND DORSUM (L)	46.2	1	2	2	4	6	1	2	2	4	4	32
45	SAB JAAN	55	M	53908	LATERAL ASPECT ®	50.4	1	2	3	5	6	1	2	3	4	4	34.78
46	LAKSHMAN	65	M	61270	DORSUM (L)	65.6	1	2	2	3	5	1	2	2	3	4	41.33
47	SANJEEVAPPA	65	M	74257	DORSUM ®	46.62	1	2	4	5	6	1	2	3	4	4	29.4
48	VENKATANARAYANAPPA	65	M	94384	PLANTAR (L)	24	1	2	4	6	6	1	2	4	4	4	12.75
49	VENKATAMUNIYAPPA	64	M	84604	LATERAL ASPECT ®	36.8	1	3	6	6	6	1	3	4	4	4	23.5
50	MUNIVENKATAPPA	65	M	96804	MEDIAL AND DORSUM (L)	76.4	1	2	3	5	6	1	2	3	4	4	54.24