"ROLE OF EFFECTIVENESS OF AUTOLOGOUS PLATELET RICH PLASMA IN HEALING OF CHRONIC ULCER"

A DISSERTATION SUBMITTED TO THE TAMILNADU

DR MGR MEDICAL UNIVERSITY

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BRANCH – I

Register No: 221711351

DEPARTMENT OF GENERAL SURGERY

TIRUNELVELI MEDICAL COLLEGE

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DECLARATION BY THE CANDIDATE

I solemnly declare that the dissertation titled **"ROLE OF EFFECTIVENESS OF AUTOLOGOUS PLATELET RICH PLASMA IN HEALING OF CHRONIC ULCER"** is done by me at Tirunelveli Medical College hospital, Tirunelveli. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, or diploma to any other University, Board, either in or abroad. The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.S. Degree (Branch I) in General Surgery.

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PRINCIPAL INVESTIGATOR: POST GRADUATE STUDENT
DESIGNATION OF PRINCIPAL INVESTIGATOR: DR.A.ARUN RAJA, MBBS.,
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Dear Dr.A.ARUN RAJA, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during The IEC meeting Held on 01.09.2017.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of The Principal Investigator ☐
8. Insurance /Compensation Policy ☐
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11. DCGI/DGFT approval ☐
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1. The approval is valid for a period of 2 year/s or duration of project whichever is later
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This is to certify that this dissertation work titled **"ROLE OF EFFECTIVENESS OF AUTOLOGOUS PLATELET RICH PLASMA IN HEALING OF CHRONIC ULCER"** of the candidate **Dr. A. ARUN RAJA** with registration Number **221711351** for the award of **M.S.** Degree in the branch of **GENERAL SURGERY.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1 Percentage** of plagiarism in the dissertation.

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CONTENTS

INTRODUCTION

Chronic ulcers typically occur in lower extremities that do not respond to initial therapy or continue despite adequate care and do not progress towards healing with an underlying aetiology that may be associated with systemic disease or regional disorders within a defined time span[1,2]. Some forms of chronic ulcers can include venous, arterial, inflammatory, stress, or traumatic ulcers. The normal process of wound healing is dynamic and complex with three phases: inflammation, tissue formation and remodelling of tissue. However, if the normal healing process is disrupted, due to the lack of growth factors and cytokines that hinder the healing process, an ulcer can become recurrent in nature[3]. The aim of ulcer care is to achieve the closure of wound as quickly as possible. Conventional treatment of chronic ulcers includes wound washing, necrotic tissue debridement, prevention, diagnosis, and, where possible, infection control, mechanical off-loading, blood glucose regulation, and regional dressing ulcer care[2,4,5]. These types of ulcers not only affect the quality of life and productivity of the patient but also become a substantial financial burden for the patient and the healthcare system[6]. Nonetheless, some risk factors generally influencing and leading to slow wound healing include: 1) local causes such as the involvement of debris or necrotic tissue, ulcer infection, tissue hypoxia, and repetitive trauma; 2) systemic diseases such as diabetes mellitus, immunodeficiency, or malnutrition; and 3) medications such as corticosteroids[3].

The standard treatment modalities available for non-healing ulcers address these issues and provide adequate local ulcer therapy with necrotic tissue debridement and moist wound healing setting, wound area pressure relief, antibiotic infection control, antiseptics and topical antibacterial agents, ischemic management, and co-morbidity medical management. A wide range of innovative non-healing ulcer treatments include hyperbaric oxygen therapy, skin grafting. Following treatment, most chronic ulcers fail to heal or linger for months / years and/or recur after healing, requiring additional advanced wound care therapies for sufficient healing. Over the past two decades, novel cell therapies such as platelet-rich plasma (PRP) therapy have gained significant interest for their potential use in regenerative medicine[7,8]. Autologous PRP is a plasma-derived platelet suspension that is commonly used in clinical practice to treat recurrent ulcers in whole blood. The PRP platelet density is 2–6 times greater than the whole blood concentration[9]. PRP's curative effects are based on the fact that platelets are a cellular reservoir of a variety of growth factors with healing roles that play an active role in the regeneration of tissues. Several studies have also been published on the role of platelet rich plasma for the treatment of non-healing ulcers with positive response[10]. PRP is most often mixed with thrombin before application in order to generate a fibrin gel, and a platelet-growth-factors-rich exudate[11]. Thrombin activated platelets release numerous growth factors from their α-granules[12] that can modulate cell proliferation and differentiation and accelerate soft tissue repair in vivo[13]

AIM AND OBJECTIVES OF THE STUDY

- To study the role of effectiveness of autologous platelet rich plasma in healing of chronic ulcers.

- To study the percentage of reduction of area of the ulcer every week for 4 weeks.

REVIEW OF LITERATURE

DEFINITION OF AN ULCER:

An ulcer is a break in the continuity of the epithelium covering — skin or mucous membrane. It can either result from molecular death or traumatic removal of the surface epithelium.

PARTS OF AN ULCER:

- Margin
- Edge
- Floor
- Base

MARGIN:

Junction between normal epithelium and the ulcer. It is the boundary of the ulcer.

EDGE:

It is the area between the margin and the floor of the ulcer. The 5 common types are:

- Undermined edge
- punched out edge
- Sloping edge

- Raised and pearly white beaded edge
- Rolled out or everted edge

1) **Undermined edge:**

E.g.: tuberculosis.

The disease causes the ulcer to spread in and destroys the subcutaneous tissue faster than it destroys the skin. The overhanging skin is thin, friable, reddish blue and unhealthy.

2) **Punched out edge:**

E.g.: gummatous ulcer or deep trophic ulcer

The edge drops down at right angle to the skin surface as if it has been cut by a punch. The diseases which cause the ulcers are limited to the ulcer itself and do not tend to spread to the surrounding tissue.

3) **Sloping edge:**

E.g.: healing traumatic or venous ulcers.

Every healing ulcer has a sloping edge, which is reddish purple in colour and consists of new healthy epithelium

4)**Raised and pearly white beaded edge:**

E.g.: rodent ulcer

This type of edge develops in invasive cellular disease and becomes necrotic at the centre

5) **Rolled out or everted edge:**

E.g.: squamous cell carcinoma or ulcerated adeno-carcinoma

This ulcer is caused by fast growing cellular disease, the growing portion at the edge of the ulcer heaps up and spills over the normal skin to produce an everted edge.

FLOOR:

It is the exposed surface of the ulcer

BASE:

On which the ulcer rests. It is better felt than seen. Base will be felt by picking up the ulcer between the thumb and the index finger.

CLASSIFICATION OF ULCERS:

Two types of classification of ulcers are possible:

1) Clinical

2) Pathological

Clinical classification: Ulcer may be of either 3 types

- Spreading ulcer
- Healing ulcer
- Callous or chronic ulcer

Pathological classification: ulcer can be classified into

- Non- specific ulcer
- Specific ulcer
- Malignant ulcer

CLINICAL CLASSIFICATION:

Spreading ulcer:

Skin of the ulcer is inflamed and the floor is covered with profuse and offensive slough without any evidence of granulation tissue. The edge is inflamed, oedematous and ragged. It is a painful ulcer. The draining lymph nodes are enlarged, inflamed and tender and may be suppurated with abscess.

Healing ulcer: It means the ulcer is healing. The floor is covered with pinkish or red healthy granulation tissue. The edge is reddish with granulation. The margin is bluish with growing epithelium. The discharge is slight and serous.

Callous or Chronic ulcer:

It means the ulcer shows no tendency towards healing. The floor is covered with pale granulation tissue. It may show typical wash-leather slough in gummatous ulcer which is an example of this type. Discharge is scanty or absent. The base is indurated and so is the edge and the surrounding skin.

PATHOLOGICAL CLASSIFICATION:

i) **NON- SPECIFIC ULCERS:** These ulcers can be further classified into the following categories

Traumatic : mechanical, physical, chemical

Arterial : Atherosclerosis, Buerger's disease, Raynaud's disease

Venous : Varicose ulcer

Neurogenic (Trophic): Bed sore, perforating ulcer

Associated with malnutrition: Tropical ulcer

Ulcers associated with diseases: gout, diabetes, anaemia, avitaminosis, erythrocyanosis frigida, rheumatoid arthritis

Other types: Bazin's ulcer, Martorell's ulcer.

ii) **SPECIFIC ULCERS:**

- Tuberculous
- Syphilitic
- soft sores
- actinomycosis
- Meleney's ulcers.

iii) **MALIGNANT ULCERS:**

- Epithelioma
- Marjolin's ulcer
- Rodent ulcer
- Malignant melanoma

WOUND HEALING

Wound healing process involves structurally and clinically stabilizing the wound. The primary goals for wound healing are:

1. Restore all barriers from outside to prevent fluid loss and infection entry.
2. It is necessary to maintain mechanical integrity.
3. Normal blood flow and lymphatic flow to the injured tissues must be re-established for the tissue to survive.

Regeneration is the ideal cycle of wound healing in its true sense, but it is technically only available during embryo development. Nevertheless, it is present in some lower-level species such as salamanders. It is also present in bone and liver tissues. Such tissues can be regenerated. The accuracy of wound healing was found to be impaired in adult human species for the rate of tissue repair.

Both tissues go through the same series of events, and they are separated into different stages for ease of understanding. Nevertheless, in both time and operation, these stages overlap. Each wound goes through similar basic tissue repair steps.

There are variations in healing, however, between acute and chronic wounds. In a more proper, orderly way and within a short time, acute wounds heal. Chronic wounds are harder to treat because they will be trapped in an inflammatory process and will not give way to spontaneous healing immediately. Closures of wounds are graded as primary, secondary and tertiary healing types.

HEALING BY FIRST INTENTION: clean wounds heal by intention. These primarily include clean, uninfected surgical wounds, Graft wounds, Flap cover, clean wounds that are simply sutured.

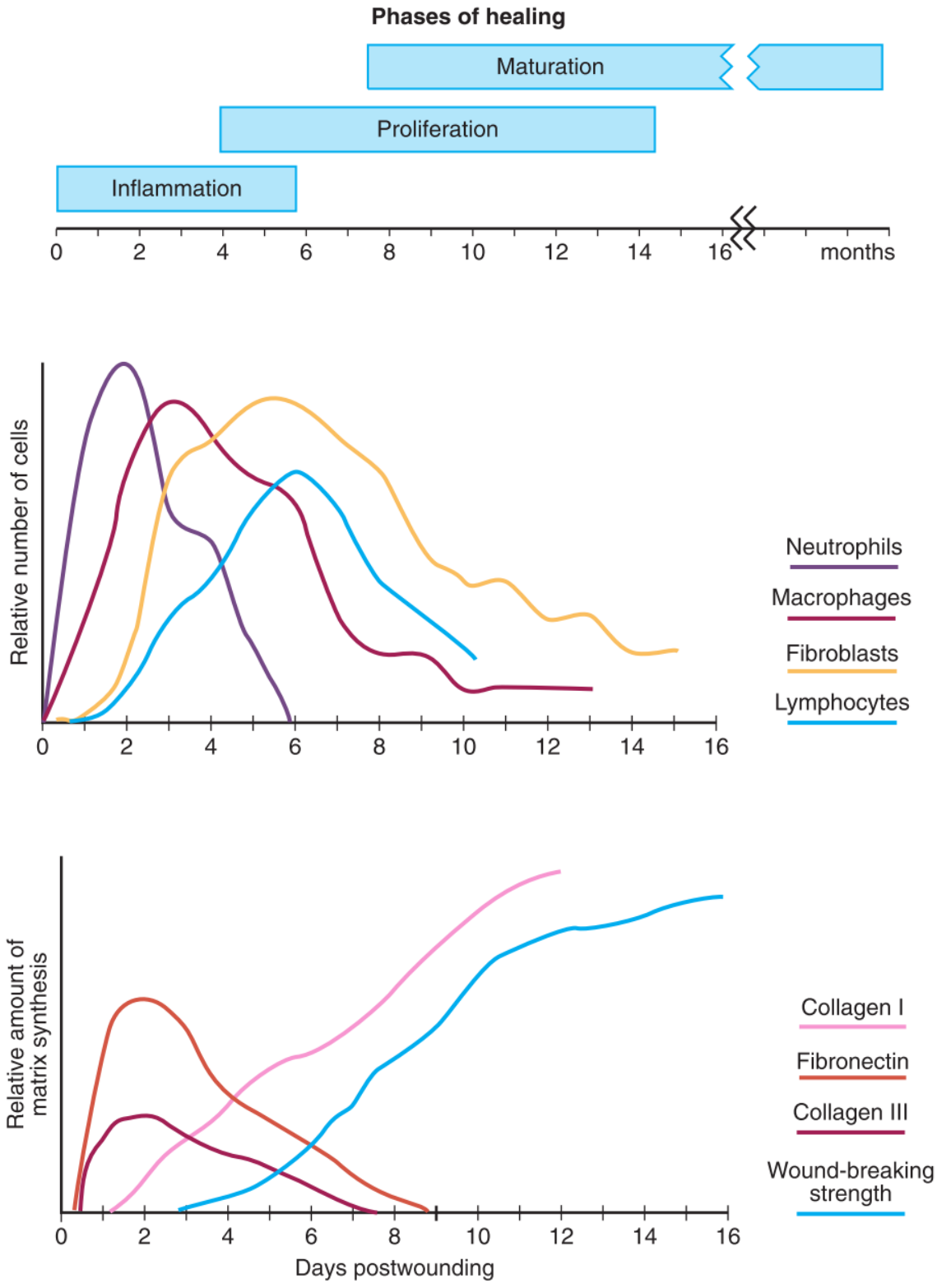
SECONDARY (SPONTANEUS): Contaminated wounds are included. This recovers by re-epithelialization and contraction of cut. There is no process as effective as primary healing.

HEALING BY TERTIARY INTENTION: The wound is initially infected in tertiary intention healing. Normal dressings and slow excision protect it. Once the wound is ready for closure and slough-free, it is sutured and skin grafting or flap covering is performed.

PHASES OF WOUND HEALING:

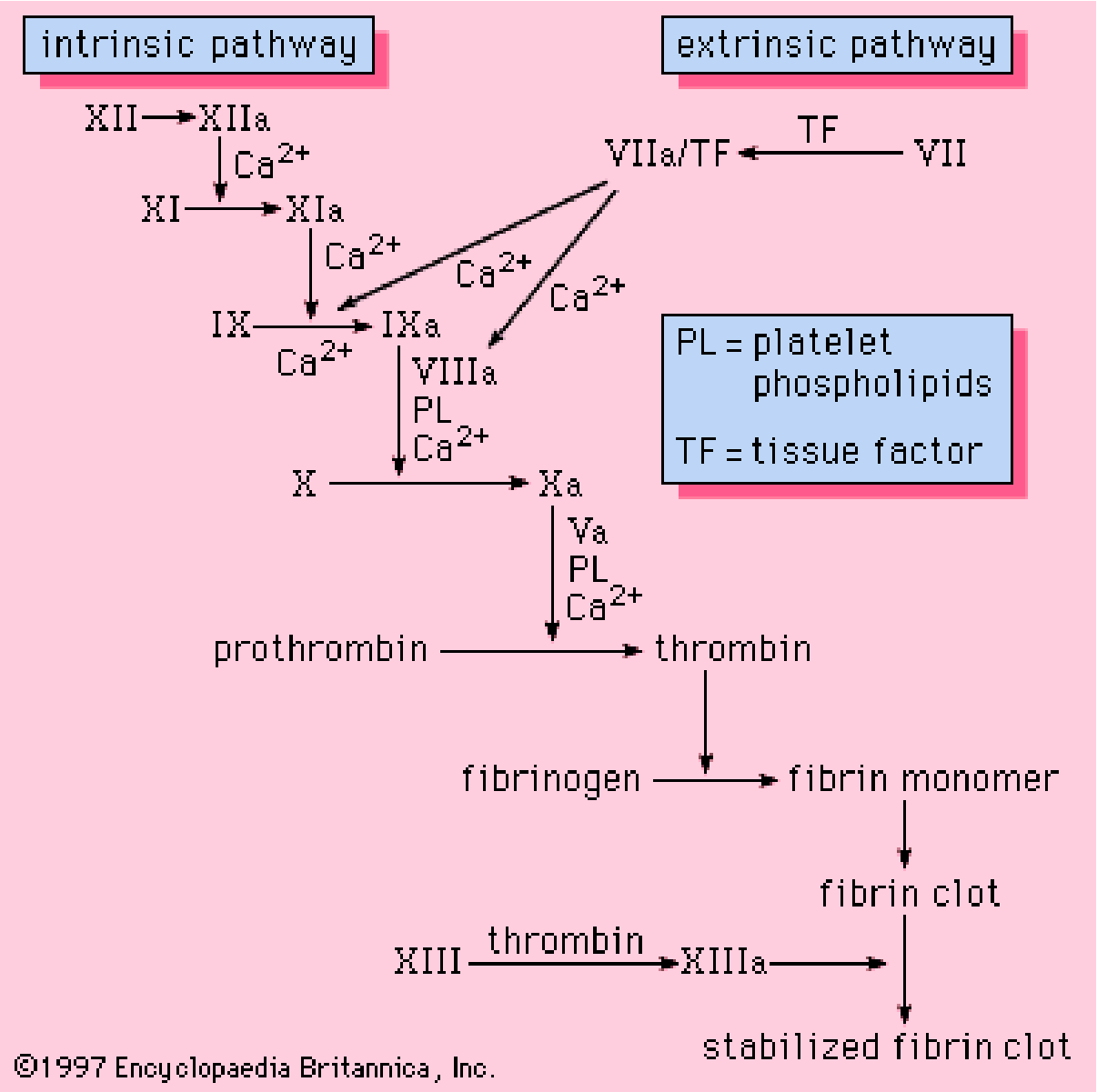
John Hunter (1728–1793), a keen observer of biological phenomena, said: "In all situations, the trauma itself tends to produce the nature and the means of cure." Typical wound healing has three phases of haemostasis and inflammation (days 1 to 4) proliferation (days 5 to 20) maturation and remodelling (days 20) This sequence of events is dynamic and overlapping, and this sequence of events is overlapping.

Inflammatory (also known as reactive) step is the immediate response to injury. The protections of the body are intended to limit the amount of damage and avoid further harm. The reparative cycle is the proliferative (also called regenerative or reparative) stage, consisting of re-epithelialization, matrix synthesis, and neovascularization. The final phase of maturation (or remodelling) is the time of scar contraction with cross-linking of collagen, shrinking, and oedema loss.

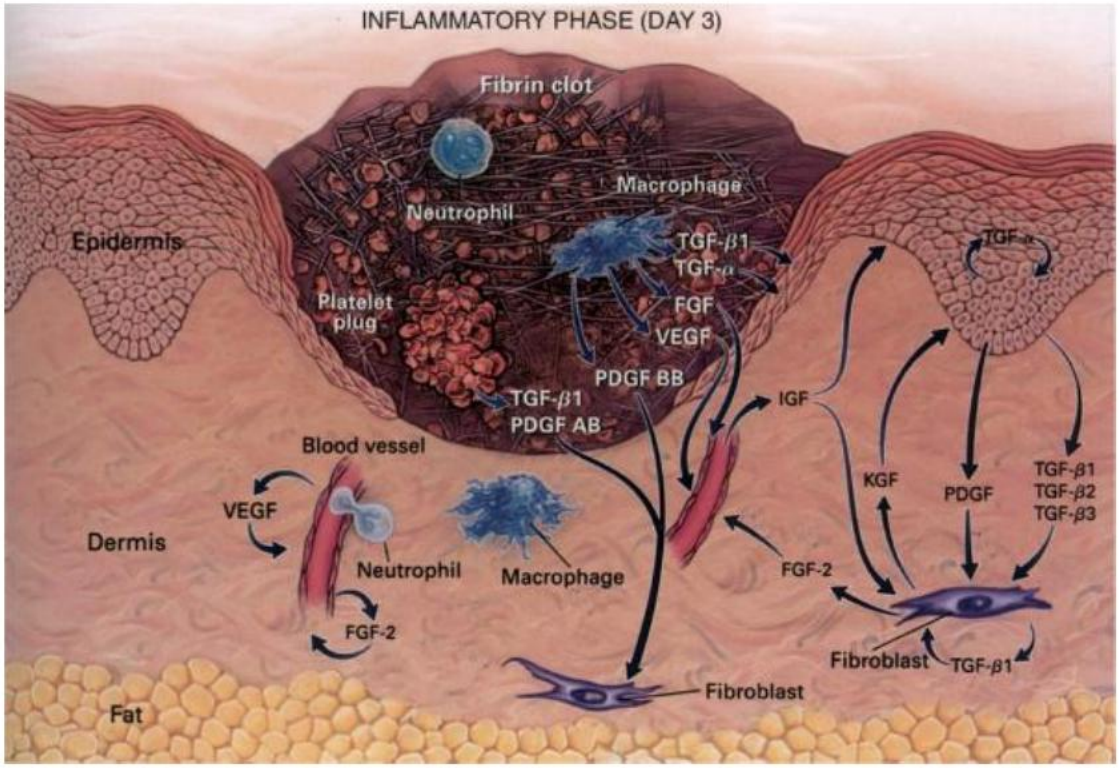


The cellular, biochemical, and mechanical phases of wound healing.

HEMOSTASIS AND INFLAMMATION:



THE INFLAMMATORY PHASE:



Three days after trauma, a superficial injury. It demonstrates the cells and growth factors required to facilitate the movement of cells into the wound. FGF, growth factor for fibroblasts; IGF, growth factor related to insulin; KGF, growth factor for keratinocytes; PDGF, growth factor derived from platelets; TGF, transforming growth factor; VEGF, growth factor for vascular endothelia.

Haemostasis and inflammation occur during the tissue's immediate response to injury. This process is an attempt to limit damage by preventing bleeding, covering the wound's surface, and removing any existing necrotic tissue, foreign particles, or bacteria. The inflammatory process is characterized by increased vascular permeability, chemotaxis migration of

cells into the injury, cytokine secretion and growth factors into the wound, as well as activation of migratory cells.

PROLIFERATIVE PHASE:

As the acute responses of hemostasis and inflammation start to resolve, the scaffolding is set up by angiogenesis, fibroplasia, and epithelialization to heal the injury. This stage is characterized by the formation of granulation tissue, consisting of a capillary bed, fibroblasts, macrophages, and collagen, fibronectin, and hyaluronic acid loose arrangement.

A) Angiogenesis-it is the process of the formation of new blood vessels and it is necessary to support the wound healing community. Activated endothelial cells destroy the basement membrane of postcapillary venules after trauma, thereby allowing cells to migrate through this gap. Division of these endothelial migratory cells results in development of tubules or lumens. Finally, the basement membrane deposition occurs, resulting in capillary maturation.

B) Fibroplasia-Fibroblasts are specialized cells that differ in connective tissue from resting mesenchymal cells; diapedesis of circulating cells does not occur in the wound cleft. The primary function of fibroblasts is to synthesize collagen that they start producing during the inflammation cell cycle. Upon injury, the normally quiescent and sparse fibroblasts are chemoattracted to the inflammatory site where

the ECM components are separated and formed. The fibroblast, which is normally halted in the G0 stage, undergoes replication and proliferation after stimulation by macrophage-and platelet-derived cytokines and growth factors. Platelet-derived TGF-β by releasing PDGF indirectly induces the proliferation of fibroblasts. The fibroblast can also induce replication by releasing FGF-2 in an autocrine manner. Fibroblasts need more stimulation by factors such as EGF or IGF-I in order to continue to proliferate. Although fibroblasts need proliferation growth factors, growth factors do not need to survive.

C) Epithelialization-The epidermis functions as a physical barrier to prevent loss of fluid and invasion of bacteria. In the epithelium, close cell junctions contribute to its impermeability, and the basement membrane area provides structural support and connection between the epidermis and the dermis.

D) Extracellular Matrix (ECM)-The ECM exists as a scaffold to stabilize the tissue's physical structure, but it also plays an active and complex role in regulating the behaviour of the contact cells. Cells within it contain macromolecular components, including the following-Glycosaminoglycans (GAGs) or polysaccharide chains, usually found covalently bound to protein in the form of proteoglycans Fibrous proteins such as collagen, elastin, fibronectin and laminin

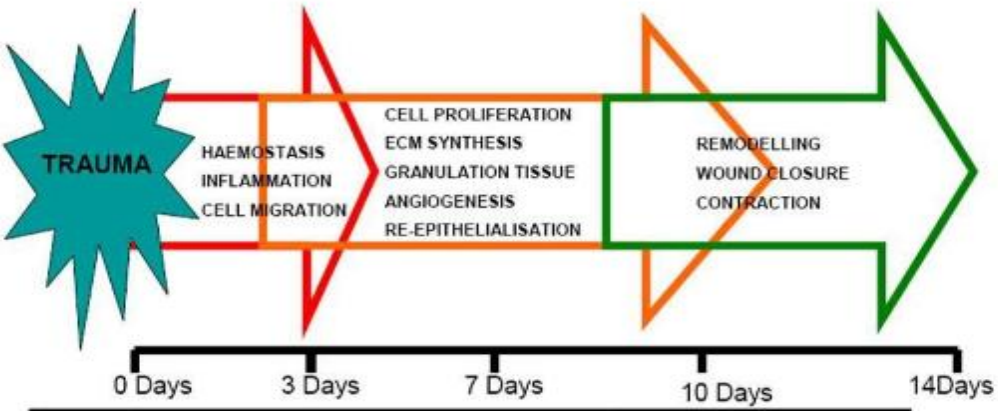
E) Collagen structure and synthesis-Collagens are found in all multicellular animals and are secreted by a variety of cells. They are a major skin and bone element and constitute 25% of the total mammalian protein mass. There are at least 20 types of collagen, with types I, II, III, V, and XI being the primary constituents of connective tissue. Type I is and is the most common collagen of skin and bone. The skin is about 80% Type I and 20% Type III in adults. Type III collagen content in new-borns is lower than that observed in adults. There is also increased expression of type III collagen in early wound healing there. Type I collagens are collagens that form fibrillar or fibril. They are secreted into the extracellular space, where they assemble into collagen fibrils (10-300 nm in diameter), which then aggregate into larger, cable-like bundles called collagen fibres (several diameter micrometres)

F) Elastic Fibres-Tissues such as skin, blood vessels, and lungs require strength and elasticity to function. Elastic fibres in these tissues ' ECM provide the resilience after transient stretching to allow recoil.

G) Extracellular matrix degradation–Regulated ECM turnover is crucial for many biological processes. Localized ECM degradation occurs in injury or infection in order to allow cells to migrate across the basal lamina to enter the injury or infection site.

THE REMODELLING PHASE: It is characterized by collagen maturation (type I replacing type III until it reaches a ratio of 4:1). Due to fibroblast and myofibroblast activity, collagen fibres are realigned along the tension lines, reduced wound vascularity and wound contraction.

STAGES OF NORMAL WOUND HEALING:



AETIOLOGY OF LEG ULCERS:

- Venous disease leading to local venous Hypertension (e.g. Varicose Veins)
- Arterial disease, either large vessel (Atherosclerosis) or Small Vessel (Diabetes)
- Arteritis associated with autoimmune disease (Rheumatoid Arthritis, Lupus, etc.,)
- Trauma: could be self-inflicted
- Chronic Infection – Tuberculosis / Syphilis
- Neoplastic – Squamous or basal cell Carcinoma, Sarcoma

DETERRENTS OF WOUND HEALING

Local Factors	Systemic Factors
Continued Pressure	Old Age
Desiccation and dehydration	Obesity
Trauma and Oedema	Chronic Diseases (e.g., Diabetes, Anaemia)
Infection or Heavy Colonization	Mal-Nutrition
Necrosis	Vascular Insufficiency
Incontinence leading to maceration.	Immuno Deficiency
Lack of Oxygen delivery to the tissues	Smoking
	Stress
	Poor Health

CHRONIC WOUNDS – PATHOPHYSIOLOGY:

Chronic wounds are characterized as wounds that fail to heal and produce an unsatisfactory anatomical functional integrity in the orderly process of healing[43]. Repeated injury, hypoxia, inadequate perfusion, and prolonged inflammation exacerbate the chronicity of wounds. Failure to respond to normal regulatory stimulus of wound healing, resulting in failure of proper synthesis of growth factor. In chronic wounds, growth factors with over-expression of proteolytic activity and failure of normal anti-protease inhibitor pathways have been shown to have increased breakdown. Senescent fibroblasts with low proliferative capacity and decreased receptor expression of growth factor in chronic wounds are present[44]

WOUND HEALING IN DIABETICS:

The different factors of impediments to wound healing in diabetics are[45]

- Vascular
    - Atherosclerosis
    - Increased viscosity
- Neurologic
    - Insensate foot
    - Decreased flare reaction
- Infection
    - Inadequate debridement
    - Poor blood supply
    - Microthrombi
    - Hypoglycaemia
    - Decreased poly morphonuclear neutrophil function
    - Polymicrobial infection
    - Changing bacterial flora
    - Osteomyelitis
- Mechanical
    - Edema
    - Weight bearing

- Poor nutrition
    - Low serum albumin level
- Poor patient compliance
- Decreased growth factors

Multiplication of bacteria within the wound can reach a stage of "critical colonization" in which the host defences are unable to maintain a balance, thus resulting in delayed healing[46]. Many authors have reported healing to be delayed in a variety of wounds by an excessive bacterial burden, and the likely-hood of infection rises as the bacterial burden of more than 10 cfu of bacteria per gram of tissue is required to cause wound infection[47]. Wound healing is a multistep process and in diabetic foot ulcers requires angiogenesis deposition of extra cellular matrix, contraction and epithelisation[48].

The observed in wound healing rates is thought to be secondary to the depressed inflammatory response. Connective tissue derangements are due to hyperglycaemia. Both collagen and keratin undergo glycosylation producing abnormally rigid tissues that may increase the likely-hood of tissue breakdown. This tissue is also resistant to collagenase activity, which further diminishes wound-healing capacity[49].

PATHOPHYSIOLOGY:

No single hypothesis is available to explain, the diverse pathological changes of diabetes mellitus. Recent advance in molecular biology have added substantial in right into the pathophysiology of this disease and opened advances for treatment. Neuropathy, ischemia and hyperglycaemia are the three complication of diabetes mellitus, which are primary underlying risk factor for the development of foot ulcers and their complication.

ETIOLOGY / PREDISPOSING FACTORS[50]

- Metabolic factor
- Neuropathy
- Peripheral Vascular disease Infection
- Immunology
- Edema
- Foot deformity

METABOLIC:

Hyperglycaemia is the common characteristic present in the two major etiological types of diabetes[50].

Evidence suggests that the effects of hyperglycaemia on two metabolic pathways influence the development of complication of diabetes

a. In the polyol pathway glucose is reduced to sorbitol; through various and complex mechanisms this leads to sorbitol accumulation in certain tissues, such as nerve, retina and kidney.

b. The other potential metabolic disturbance is glycation of proteins, including hemoglobin, albumin, collagen, fibrin, lipoproteins.

Glycated proteins, and the cross-linked advanced glycation end products they form, appear to contribute to both the microvascular and macrovascular derangements of diabetes.

Fasting hyperglycemic represents a catabolic state, with a negative nitrogen balance as a consequence of gluconeogenesis from protein break down. This is problematic because an integral part of wound healing is the synthesis of protein such as fibroblast and collagen[51].

NEUROPATHY:

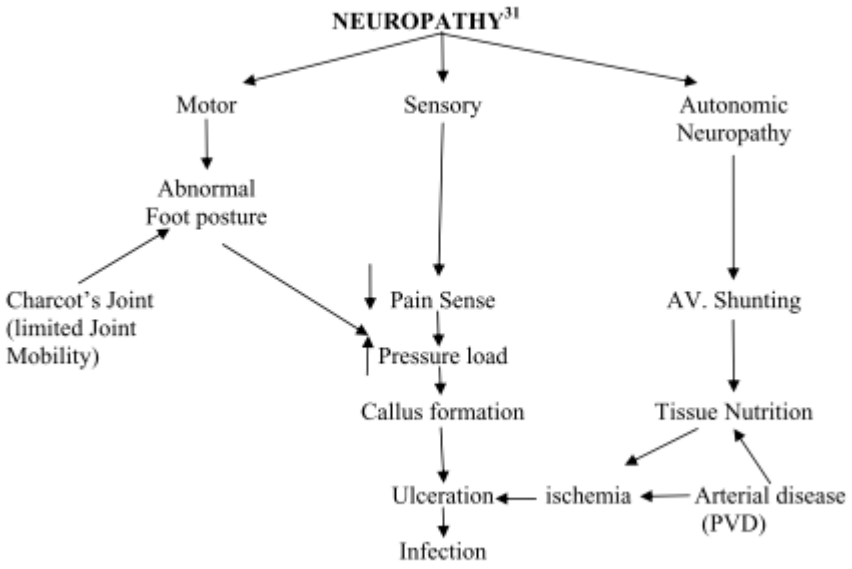
Diabetic polyneuropathy[52]

The major components of diabetic poly neuropathy are

A. Sensory Neuropathy

B. Motor Neuropathy

C. Autonomic Neuropathy



A] Sensory Neuropathy It may be painful or painless, depends on which fibres are predominantly involved. If it is painless neuropathy that leads to ulceration. Painless neuropathy as there is loss of ability to feel a painful. Stimulus allows the patient to injure the foot, either suddenly or gradually, without being aware of the damage that is occurring. When patients with neuropathy develop ulcers, it may only be a smell, blood stain on the socks, or somebody else's observation that makes them aware of the problem[53]

B] Motor Neuropathy It leads to weakness of the intrinsic muscle of the foot, which in turn causes an imbalance between the long flexor and extensor tendons. This imbalance leads to the typical caves or high arched foot seen in people with diabetes, along with clawing of the toes[53].

This clawing of the toes draws the fat pad, normally under the toes bear 30%and under certain circumstances may bear up to 50% of the load transmitted through the foot. With severe clawing the toes become non-

weight bearing and this increases the load under the metatarsal heads in addition to loss of fat pads under metatarsal head and heel become atrophied. Which further reduces their cushioning ability. All of this increased pressure leads to callus formation under the areas of high pressure, generally the heel and metatarsal heads, and these callosities in themselves contribute to the increase pressure

C] Autonomic Neuropathy

It causes verities of central complication such as postural hypotension, diarrhoea and impotence[53]

Foot complication:

Loss of sweating leads to dry foot that may fissure and crack and changes in normal microcirculation autoregulation.

Loss of sympathetic tone

⇩

Increased peripheral flow

⇩

Loss of Postural vasoconstriction

⇩

Increased Pressure in the capillaries

⇩

Basement membrane thickening

⇩

Arteriovenous Shunting

Arteriovenous shunting might be expected to reduce nutritive skin blood flow, hence contribute to the development of foot ulcers[53].

PATHOLOGY OF HUMAN DIABETIC NEUROPATHY:[54]

Pathological examination of affected nerves shows segmental demyelination and axon loss, more severe distally. The demyelination could be secondary to axonopathy. The neuropathy is now thought to be due to a metabolic disturbance and not ischaemia. Biochemical mechanisms that have been implicated include, an accumulation of intra neural sorbitol, a deficiency of nerve myoinositol, glycosylation of nerve protein and a reduction of axonal transport

ANGIOPATHY:

Various abnormalities in the pathogenesis of diabetic angiopathy are[55]

- Basement membrane thickening
- Impaired transmission of macromolecules across the micro vasculature
- Accumulation of glycation end products.
- Endothelial cells and smooth muscle cells dysfunction
- Epineural vessel atherosclerosis
- Nerve hypoxia

A] Macrovascular complication

Macrovascular disease in the form of increased atherosclerosis affects the large peripheral arteries of the lower limbs in patients with diabetes. Within the large vessels endothelial cells and smooth muscle cells dysfunction are also present.

a. Endothelial cell: Reduced ability to proliferate and migrate this effect may result from hyperglycemia and exposure to oxidized lipids.
b. Smooth muscle cells: Increased migration, adhesion and proliferation it may contribute to the development of atherosclerosis.

These changes are believed to be due to hyperglycemia, which alters[55]

1. Non-enzymatic glycation
2. Diacylglycerol – Protein Kinase C activate
3. Sorbitol – polyol pathway utilization
4. Redox alteration

B] Microcirculatory complication

i. Impaired transit of macromolecules across the micro-circulature Inhibition of leukocyte migration and a blunted hyperaemic response Basement membrane thickening
ii. Accumulation of advanced glycation end products on the basement membrane reduces its charges transmigration of albumin and other end products

iii. Due to autonomic neuropathy it may leads to A.V. shunts. All above three contributes to the decreased Neural blood flow decreased O2 and altered vascular permeability[55].

INFECTION:

Infection has been defined as the product of the entrance, growth, metabolic activities and ensuring pathophysiological effects of microorganisms in the tissues of a patients[56].

Clinical diagnosis of infection considers 3 elements.

i. The presence of purulent discharge
ii. The classical sign of inflammation around the ulcer (i.e. heat, redness, edema and pain)
iii. Systemic sign of fever and leucocytosis[57]

Aerobic gram-positive cocci (Especially staphylococcus aureus and streptococci) are the predominant pathogens Gram-negative as well as Anaerobes are often isolated as well, especially in more severe infection[50].

IMMUNOLOGY:

Patients with diabetes have been shown to be at a higher risk of acquiring or of having a more severe presentation of various infections disease. Several defects in host immunity are more common in patients with diabetes[50].

These include impairment of some polymorphonuclear leukocyte functions such as migration, phagocytosis, intracellular killing and chemotaxis. Some evidence suggest that cellular immune response is also reduced as well. Poor Granulation formation, prolonged persistence of abscesses and impaired wound healing are additional factors. Because of these immunological disorders, diabetes has been classified by the WHO as a secondary immunodeficiency disease.

EDEMA:

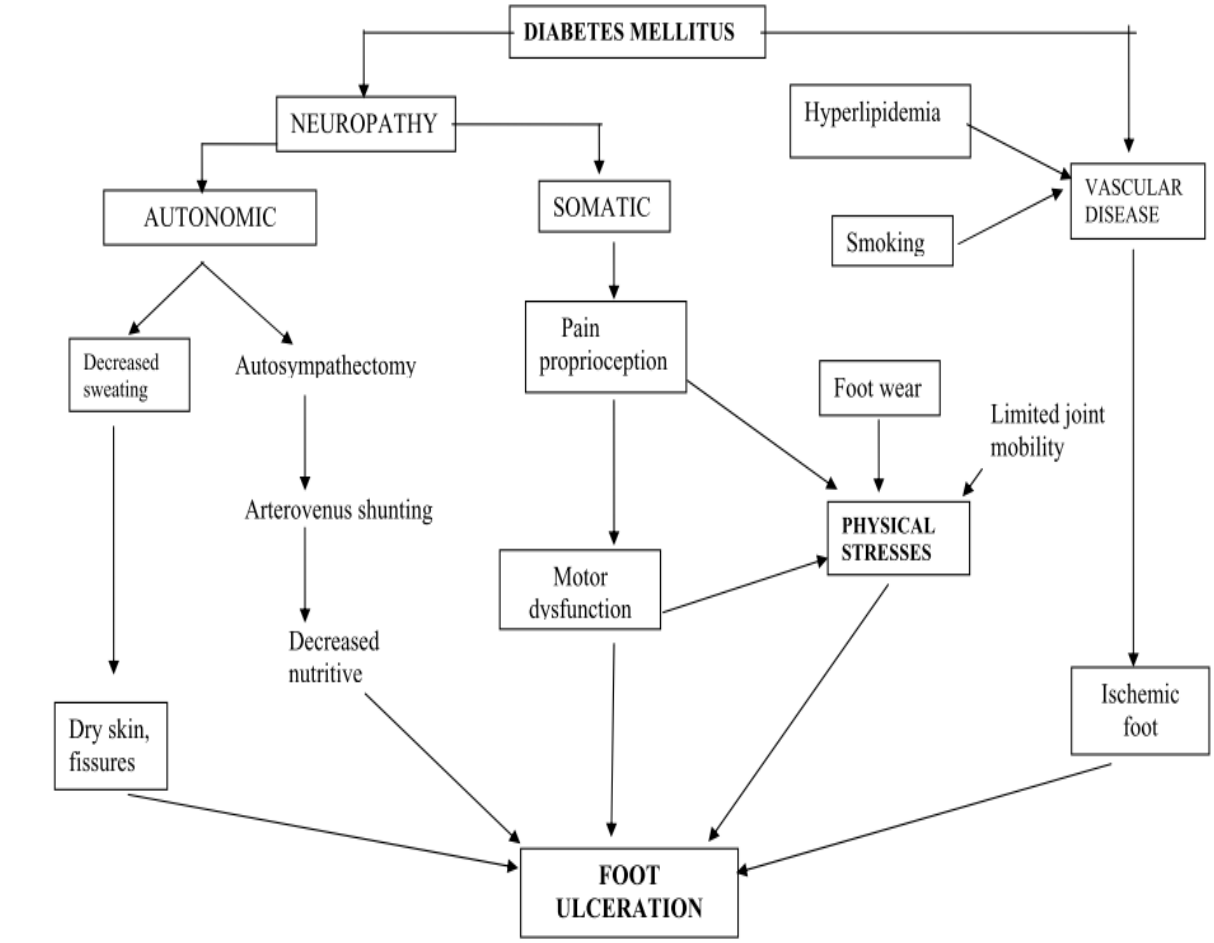
Lower extremity edema, which is common in older patients with diabetes and is usually related to cardiac, renal and venous disorders, can be painful even in neuropathic patients with sensory loss.

It may impair the cutaneous circulation and delay wound healing. Lower extremity edema predisposes the tissue to minor trauma and ulceration in patients with sensory loss, especially if foot wear does not accommodate the edematous foot. Treatment of lower extremity edema is directed to its etiology. i.e. Optimizing cardiac and Renal function, good glycaemic control, nutritional repletion and central of infection are helpful.

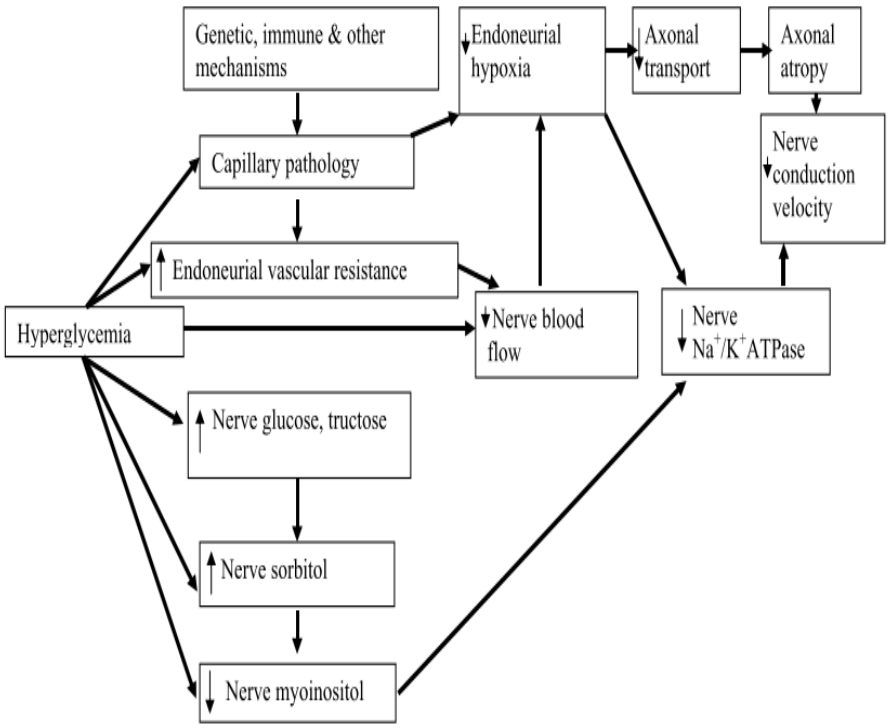
DEFORMITY:

It will lead to neuropathic ulcer in deformed pressure points.

Pathway to diabetic foot ulceration[37]



Suggested pathogenesis of diabetic neuropathy[38]



CLASSIFICATION:

A] Wagner classification system[53]

GRADE	DESCRIPTION
0	No open ulcer
1	Full thickness ulcer, but depth does not go beyond loss of skin
2	Deeper, tendon or joint capsule may be present
3	Open to bone, Osteomyelitis
4	Wet or dry gangrene plus or minus cellulites
5	Extensive gangrene indicating higher amputation

B] Liverpool classification system for DFU (diabetic foot ulcers)

Primary

Neuropathic

Ischemic

Combination of both

Secondary

Uncomplicated

Complicated i.e. presence of cellulites, Abscess or Osteomyelitis

C] The depth/Ischemia classification of Diabetic foot lesion[60]

Depth classification

GRADE	DESCRIPTION
0	The "at risk" foot previous ulcer or neuropathy with deformity that may cause new Ulceration
1	Superficial ulcer not infected
2	Deep ulcer exposing a tendon or joint
3	Extensive ulceration with exposed bone and deep infection

Ischemic classification:

A	Ischemia without gangrene
B	Partial gangrene of the foot
C	Complete foot gangrene

D] University of Texas classification:[61]

GRADE	DEPTH OF LESION
0	No open ulcer or deformity
1	Superficial ulcer
2	Penetration to tendon or Joint capsule
3	Penetration to bone and joint space

After grading then stage

A	No infection
B	with infection
C	with ischemia
D	ischemia + infection

University of Taxes classification is better than Meggitt Wagner system

CLINICAL PRESENTATION:

Patient may or may not have a history of trauma or previous infection He/she may presents with local cellulites. Deep skin soft tissue infection, Acute osteomyelitis, abscess necrotizing fasciitis, callous formation, chronic osteomyelitis, septicaemia. Patient might present with peripheral neuropathy the symptom of this includes.

- Hyper aesthesia
- Paraesthesia
- Dysesthesia
- Radicular Pain
- Anhydrosis

Patient might present with peripheral vascular disease. The sign and symptoms includes.

-Intermittent claudication
- Cold feet
- Nocturnal pain
- Rest pain
- Pain relived with dependency
- Absent or feeble pulsation
- Blanching on elevation
-Delayed venous filling after elevation
- Dependent rubor

- Atrophy of subcutaneous fatty tissue
- Shiny appearance of skin
- Loss of hair on foot and toes
- Thickened nails, often with fungal infection
- Gangrene.

Along with local symptoms & signs patients also presents with systemic sign of toxicity such as leucocytosis, fever, chills these appear late in the course of a diabetic foot infection. Although patients with deep or serious foot infection often complain of flu like symptoms. (Diabetic foot flu) Sometimes a patient presents with a hot, red, swollen foot that is difficult to diagnose clinically which may represent cellulites, an abscess or an acutely inflamed Charcot's joint[62]. Patient might present with ulcers. Plantar ulcers most commonly at the head of the 5th metatarsal or at heel.

Dorsal ulcer –over the tip of toes.

Neuropathic ulcers classically seen under metatarsal head but is more frequently found on the tip of the toes and occasionally on the dorsum of the toes and on the heel. Ulcers on the plantar surface of the feet are usually circular with a punched out appearance often penetrating to involve deep tissue including bone along with loss of sensation. Structural deformities such as claw toes are seen due to paralysis of the small muscles as a result of motor neuropathy claw foot leads to prominence of metatarsal heads in the ulcerated foot.

Complication of Diabetic foot:

Necrotizing fasciitis

Charcot's foot

Necrotizing fasciitis:

Rare complication of diabetic foot. It is an acute infection of subcutaneous fascia resulting in its necrosis along with non-crepitus gangrene of the overlying skin. Usually due to streptococcus pyogenes but may occasionally be caused by staphylococcus aureus.

Charcot's Foot:

In IDDM patients, it can be defined as a chronic painless degenerative process affecting the weight bearing joints of the foot. It occurs in <1% of people with diabetes, most commonly during the 5th and 6th decade.

INVESTIGATION:

Blood Investigation

a) Hb% (Hemoglobin): It indicates the general status as well as nutrition states of the individual. Normal for men: 12-15gr% for female : 11-14gr% if decreased in Hb% is a risk factor for non-healing of ulcer. It is also helpful to decide the fitness of the patient for distinctive operative procedure.

b) Total WBC count: normal: 4000-11000/cumm. Indicate Immune mechanism of the body. It increases in cases of infection and inflammation.

c) Differential WBC count: in case of acute infection neutrophil count is raised and in case of chronic infection lymphocyte count is increased. So, it given idea about the acute or chronic infection.

d) ESR: It is raised in infection.

e) RBS: It is done initially to rule out diabetes in patients with foot infection or cellulites or gangrene.

f) Blood urea, serum creatinine These two are sensitive indication of the renal function, which may be hampered in diabetic nephropathy and associated diseases.

g) BT/CT: Gives idea about bleeding disorder. It is mandatory in all patient who are supposed to undergo surgery.

h) FBS/PPBS: These are the correct guide lines for starting and dose adjustment of anti-diabetic treatment and also to assess degree of control of diabetes.

i) Glycosylated haemoglobin: It is one of the investigations to know whether the patient who is having diabetes is under control or not for the past two months. It is a form of hemoglobin used primarily to identify the average plasma glucose concentration over prolonged period of time. It is possible to get fairly good idea of the average blood glucose levels over the past two months. Based on currently carried out HbA1c reading.

HbA1c	Average blood glucose level (mg/dl)
4	60
5	90
6	120
7	150
8	180
9	210
10	240
11	270
12	300

Conversely, the patient who has been in good control but due to some reason like suffering from ‘flu’ attack, shows a higher than acceptable blood glucose levels would manifest a basically an acceptable HbA1c level as the deterioration in the blood glucose values in the past couple of days would not significantly alter the levels. This would enable us to understand that the patient is basically under good control possibly for some reason presently has a high blood glucose level. This would make us search for the cause of the deterioration rather than making blind increasing in the medication which may expose the patient to a risk of hypoglycemia.

URINE EXAMINATION:

- Urine sugar: To know whether the patient is diabetic or not
- Urine albumin: To know whether patient is having diabetic nephropathy.

- Urine for Ketone bodies: To know whether the patient is having diabetic Ketoacidosis or not.

Bacteriology:[63] Pus for culture and sensitivity The usual organism isolated in diabetic foot infection include.

AEROBES:

Gram -Negative Bacilli

Proteus mirabilis

E-coli and proteus

Pseudomonas species.

Klebsiella Spp.

Gram – Positive Cocci

Enterococcus species

Staphylococcus aureus

Group B – Streptococcus

Group D – Streptococcus

ANAEROBES:

Bacteroides

Peptostreptococcus Spp. Staphylococcus Spp. And Streptococcus Spp. Which formed nearly 3/4th of the clinical isolates.

Ankle – brachial pressure index:

The ankle pressure is compared with the higher of the 2 brachial artery Pressure[64].

This test has limitation however only those lesions that cause a decrease in pressure can be detected generally lesion that reduces the diameter of vessels by ≥ 50% with collateralized occlusion cannot be differentiated from poorly collateralized occlusion, calcified vessels, a hallmark of diabetic occlusive disease reduce the sensitivity of the test.

"Ankle brachial pressure index is very often misleading."

X-RAY FOOT:

Although radiographs are still the mainstay of diagnosis of osseous disorders of the diabetic foot, they are limited in sensitivity (75%), accuracy and the range of disorders that they can detect.

The characteristic findings on plain films are worth summarizing and knowing. The common findings include a combination of bone alterations, including gross destruction, fragmentation, periosteal new bone formation, pointed bone deformity, osteosclerosis, calcification of the arteries (also known as medial arterial calcification or Monckeberg's arteriosclerosis) are common findings in patients with diabetes mellitus.

Osteolysis in the bones of a diabetic patient, especially in the distal segments such as the phalanges, is often mistaken for osteomyelitis, even in the absence of clinical signs and symptoms of infection. The characteristic "penciling" of the distal metatarsal or "vanishing phalanx" is usually not associated with infection. When osteolysis is neuropathic in origin in the absence of infection, it occurs most often in the distal part of the forefoot,

usually distal to the metatarsal level and involving the distal metatarsals and the phalanges.

BONE SCANS AND MRI[62]

Technetium-99 bone scans and MRI are both very much more sensitive in detecting early bone changes of osteomyelitis and Charcot joints than plain radiographs. However, MRI is significantly more sensitive than bone scans and detects osteomyelitis earlier than the bone scan. The bone scan is still considerably less costly than an MRI study in most institutions and so still serves a purpose for screening.

Neither the bone scan, radiographs, nor any other single study represents the sine qua non in diagnosing infection or arthropathy in the diabetic foot and must be combined with clinical examination, history and other diagnostic modalities.

COMPUTED TOMOGRAPHY[62]

Computed tomography is a valuable test for anatomic localization of infection and pathology such as an abscess in the deep structures of the foot. Prior to the advent of MRI, it was the best technique for obtaining information on the non-osseous pathology of the foot and especially of the deep structures. The weakness of the CT scan is the poor differentiation or wide transition zone between normal and infected tissues. MRI has since

surpassed it, which is superior in its ability to differentiate a wider range of different tissues in their normal and abnormal states.

GALLIUM SCANS

Gallium scans are too non-specific to be helpful in making the distinction between a Charcot joint and osteomyelitis and are usually not helpful in the diagnosis of a diabetic foot. By contrast, the use of Indium labelled white blood cells may be quite useful based on the greater specificity of this study for infection.

DOPPLER ULTRASOUND:

It will assess both anatomical and functional abnormality in the various arterial segments. Significant stenosis is indicated by a peak systolic velocity ratio greater than two across the arterial lesion. Waveform analysis can give additional information about the degree of stenosis[65].

This instrument works on the principles that moving blood shifts the ultrasound frequency emitted by piezoelectric crystal. The instrument is able to convert the frequency changes to an audible sound.

The Doppler sounds of a normal, complaint artery are triphasic. When arterial obstruction is present the Doppler sounds becomes monophonic.

TRANSCUTANEOUS OXYGEN PRESSURE MAPPING (TCPO2)

It can be used to determine the severity of foot ischemia. Thus aiding selection of appropriate treatment and decreasing the total cost of care. If TcPo2 level is 30 mmHg or greater treatment should be conservative

comprising local wound care, debridement or a minor ablative procedure. If TcPo2 level is below 30mmHg it will anticipate the need for vascular reconstruction.

DUPLEX SONOGRAPHY

It can provide accurate information with little risk to the patient and therefore should be readily obtained.

This is investigative technique of major importance in vascular disease. A duplex scanner uses a 'B' mode ultrasound to provide an image of vessels. A second type of ultrasound, namely Doppler ultrasound is then used to insonate the imaged vessels and the Doppler shift is analysed by a computer in the duplex scanner itself. Such shift can give detailed knowledge of vessel blood flow, turbulence etc. Some scanners have the added sophistication of colour coding which allows visualization of blood flow on the image. The various colour indicate change in direction and velocity of flow; points of high flow generally indicate a stenosis. It allows cross sectional area of arterial lumen to be measured. By use of colour, the flow towards or away from the transducer can be easily distinguished so that peripherally running arterial flow (red) can be immediately distinguished from centrally directed venous flow (blue); the intensity of colour increases with the velocity of flow.

Duplex sonography combines the ability to view the anatomy of the vessel by ultrasound as well as the ability to make haemodynamic assessment by spectral doppler interrogation.

ANGIOGRAPHY

It remains the 'Gold Standard' for assessment of the lower arterial system prior to any intervention. It can be performed via femoral or brachial catheterization, with iodine-based contrast used to visualize the blood vessels. Angiography is not without complication; in particulars bleeding, dissection, embolization and nephrotoxicity. Intravascular contrast injection is associated with an increased risk of lactic acidosis; a condition that can have a high mortality, especially in diabetics on metformin.

Indication

1) Ischemic rest pain

2) Disabling claudication

3) Gangrene

4) In who arterial revascularization is planned

MAGNETIC RESONANCE ANGIOGRAPHY (MRA):[65]

It is likely to be the future investigation of choice. Diabetic patients with poor renal function may benefit from MRA. MRA is significantly better than digital subtraction angiography in revealing peripheral run-off vessels and patent pedal vessels suitable for distal bypass grafting.

If osteomyelitis is suspected, plain radiographs remain of use. Three phase bone scintigraphy or infection specific radiopharmaceuticals may aid diagnosis MR imaging is extremely valuable to show even very early infection, with changes in bone marrow, edema of soft tissue, cavitation and sinus formation.

TREATMENT

1) Primary treatment

2) Evaluation of diabetic foot ulcer assessment

3) Indication for hospitalization

4) Measurement of wound

5) Medical care

    a. Optimal glucose control

    b. Systemic antibiotics

6) Surgical care

    a. Debridement

` b. Revisional surgery

    c. Vascular surgery

    `d. Option for soft tissue coverage of the clean but non-healing wound

7) Offloading

8) Wound management

    a. Moist wound environment

b. Growth factor

c. Biological therapies

d. Hyper baric oxygen therapy

9) Amputation

10) Education.

1. PRIMARY TREATMENT OF DIABETIC FOOT ULCERS

A) Evaluation

a) Clinical appearance

b) Depth of penetration

c) X-rays to detect

* Foreign body

* Osteomyelitis

* Subcutaneous gas

d) Location

e) Biopsy

f) Blood supply (non-invasive vascular studies)

B) Debridement

C) Bacterial cultures (aerobic and anaerobic)

D) Metabolic control

E) Antibiotics

* Oral

* Parenteral

F) Foot care

G) Decrease edema

H) Non-weight bearing

* Bed rest

* Crutches

* Wheel chair

* Special Sandals

* Contract casting

I) Improve of circulation (Vascular surgery)

Treatment of diabetic foot ulcers requires the establishment of depth and degree of ulceration. What may appear to be a superficial ulceration may in fact penetrate deep into the tissues.

X-ray films are necessary to rule out osteomyelitis, gas formation and the presence of foreign objects.

Biopsy should be considered when the ulcer appears at the atypical location (e.g. not over the metatarsal heads or the plantar surface of the hallux), when it cannot be explained by trauma and when it is unresponsive to aggressive therapy.

2. **EVALUATION – DIABETIC FOOT ULCER ASSESSMENT**[66]

A) General Wound Parameters

* Peri wound erythema – congestive or exudative redness surrounding wound caused by engorgement of the capillaries in the lower layers of the skin.

a) None: Blanches on digital pressure

b) Mild: Redness that does not blanch with digital pressure, may or may not be warm to touch

c) Marked prominent redness or bluish discoloration; usually warm to touch.

* Peri wound edema: an excessive accumulation of tissue fluid in the tissue surrounding the wound. Graded none, mild or marked.

* wound fibrin: A yellowish white meshwork not removable with a sterile swab or gauze. It adheres to the wound but can be removed with a scalpel blade by gentle scraping. Graded: none, mild or marked

* Limb pitting edema: Localized excessive accumulation of interstitial fluid.

a) None-Absent

b) Mild-digital pressure leaves a small but rebounding depression at the site.

c) Marked Digital pressure for 30 seconds leaves a persistent depression at the site.

* Limb brawny edema: A solid wood like appearance to the lower limbs

a) None – Absent

b) Mild – appears in a limited area

c) Marked – whole leg involvement

* Wound granulation: Formation of small granular masses in the base of the wound that have a beefy red appearance.

a) None-absent

b) Mild-beginning to fill in and may not be epithelialized.

c) Marked-epithelialized and filling in.

B) **ANATOMIC CONSIDERATIONS:**

Dorsalis pedis pulsation: Artery is usually palpable in the groove between the first tendons on the medial side of the dorsum.

a) 0 – 1 +: Not palpable of the foot

b) 2 +: Present but diminished

c) 3—4 +: Normal

3. Indications for Hospitalisation

- H/O Trauma to the foot with K|C|O DM.
- Acute infected ulcer
- Penetration of digital infection into the forefoot
- Infected gangrene
- Uncontrolled diabetes
- Patient with a minor infection on the plantar surface of foot but with evidence of infection on the dorsum of foot suggested by erythema.
- Patients with severe PVD
- Cellulitis, of foot e uncontrolled diabetes.

4. MEASUREMENT OF WOUND BY PLANIMETER:[67]

Treatment of diabetic foot ulcers requires the establishment of depth and degree of ulceration.

a) Size (cm2) a standard metric circle template is used to approximate the area of the ulcer.

b) Depth (mm): Measure the wound at its deepest part at a 90-degree angle to the skin. Use a sterile swab as an aid. Graded :<5, 5-10, 10-20 mm

c) Undermining (mm) Measure the deepest part of any tunnelling or shearing. Use a sterile swab as an aid.

d) Duration: calculate the approximate duration from the wound's onset (break in the skin) to the date of assessment.

At least once a week the length and width of the wound must be measured all patients.

5. MEDICAL CARE

* Optimal glucose control and nutrition

* Systemic antibiotics

Optimal Glucose Control and Nutrition

Treatment of diabetic foot ulcers includes the treatment of diabetes itself. Blood glucose control is well known to be complicated or made more difficult, if not wildly unstable, in the presence of an acute infection. Once the foot abscess has been drained, the patient often returns to his or her

normal insulin requirements. Recent studies have suggested that enhanced glucose control may improve healing or decrease the incidence of infection.

Control of hyperglycemia is an essential part of management; in patients already on insulin, an increased dose is usually necessary. In those on diet or tablet, regular monitoring of capillary blood glucose is important during the acute admission. It is usually best to used insulin if the blood glucose is consistently > 11 mmol /lit and a basal bolus regimen offers most flexibility.[68]

Insulin Regimen for Inpatients with Diabetic Foot[68]

Example: Regimen for 70 kg man normally on gliclazide 80mg b.d admitted with infected neuropathic foot ulcer with fasting capillary blood sugars 13-15 mmol/lit and PPBS 18-25 mmol/lit.

Initial daily insulin dose: 0.5 x 70 = 35 units Suggested basal bolus regimen: 60% soluble insulin (3 equal doses) 40%isophane insulin.

	Pre –breakfast (Units)	pre-lunch (Units)	pre-evening meal (Units)	pre-bed (Units)
Soluble insulin	8	8	8	
.Isophane				12

Dose should be adjusted daily depending on pre meal capillary blood glucose measurements.

NUTRITION

Some studies have indicated that one source of poor wound healing is due to poor nutrition. Simple indices of adequate surgical nutrition can be helpful or even predictive of successful wound or amputation healing.[62]

Basic indices of surgical nutrition

- Total lymphocyte count :> 1500/ml
- Albumin :> 3.5 g/dL
- Total protein :> 6.2 g/dL
- Hemoglobin :> 11 g/dL
- Hematocrit :> 32%

SYSTEMIC ANTIBIOTICS

Antibiotics therapy should be targeted against identified organisms whenever possible. Pending identification, broad spectrum antibiotics can be given[69].

An empirical antibiotic sensitivity information is available. In the patient who has been pre-treated with oral antibiotics and negative culture have resulted or in the patient in whom deep cultures cannot be obtained for whatever reason then an empiric regimen is the only choice. In general, the empiric regimen must be aimed at a broad spectrum of coverage. Newer third generation cephalosporins have found a special place in their drug regimens, while most of these have an enhanced spectrum of coverage of gram-negative organisms, they are less effective than first generation cephalosporins against

+ Gram 55 selection is necessary until specific culture and positive cocci. Another 3rd generation cephalosporine, ceftazidime, is unique in its applicability against pseudomonas aeruginosa. Imipenem a new carbapenem drug is a penicillin related drug that has activity against staphylococcus enterococcus, Anaerobes and pseudomonas although resistance to the drug can develop in pseudomonas infection.

'Other newer drug that can be used in combination in the treatment of diabetic foot infection includes.

- Linezolid: it is an bacteriostatic oxazolidinone, inhibiting ribosomal protein synthesis. It is active against gram positive bacteria including vancomycin resistant E-coli Limited activity against gram negative bacteria. Dosage -600mg IV OD dose.

- Azithromycin: Macrolide antibiotic having broad spectrum it blocks transpeptidation by binding to 50s ribosomal sub unit of susceptible organisms & disrupting RNA dependent protein synthesis. Dosage - 500mg oral OD dose.

- Piperacillin tazobactam combination: it is broad spectrum antibiotic active against K.pneumonea, P. aeruginosa, B- lactamase producing bacteria. Dose – 4.5gm IV BD dose.

6] **SURGICAL TREATMENT**

Debridement Types

- Surgical
- Autolytic
- Enzymatic
- Biological
- Mechanical

A] Surgical debridement

Debridement is the first and most important step in healing a diabetic foot ulcer. The foundation of comprehensive care for diabetic foot ulcer is removal of all non-viable infected tissue from open wounds as well as surrounding calluses, until a new border of healthy bleeding soft tissue and uninfected bone is created. More extensive ulcer should be debrided in the operating room.

Surgical debridement with a sharp knife (even if down to the bone) can remove all devitalized portions of a wound so that scar and infection are no longer present and thus has proved safe and therapeutic the wound margins should be extended approximately 2-3mm into healthy bleeding soft non-hyper Keratotic skin. Sharp excisional debridement accomplishes four goals.

1) It removes local contaminated bacteria

2) Stimulates healing

3) Document the absence of hyperkeratotic tissue and

4) Decreases local infection

B] Autolytic[51]

Use of occlusive dressings (hydrogels, calcium alginates)

C] Enzymatic[51]

Topical collagenase, papain

D] Biological[51]

Use of maggots larva of Green blow fly (Licilia sericata), removes necrotic tissue and their antimicrobial secretion has anti-bacterial action against staphylococcus A, streptococcus A, methicillin resistant staphylococcus Aureus.

E] Mechanical:[51]

Non selective, painful wet to dry gauze dressing it is potentially damaging to healthy granulation tissue and new epithelium.

REVISIONAL SURGERY:

Revisional bone surgery may be required to remove pressure points, including metatarsal head resection or ostectomy.

VASCULAR SURGERY:

Indication

- Intractable foot ulcers

-Intractable pain at rest or at night

- Impending or Existing gangrene

Procedures

1] Balloon angiography: Femoro-popliteal lesion

2]Stents these are metallic and permanent and may be self-expanding or require balloon expansion.

Balloon angioplasty of distal popliteal and crural runoff vessels is achievable using a small balloon for a short stenosis.

The outcome depends on the site, length, morphology of the lesson and the state of the distal run-off vessels.

3] Bypass surgery

In flow reconstructions can be achieved surgically with an Aorto-bifemoral, Axillo-bifemoral by pass in case of bilateral disease. Femoro-femoral cross over, ilio-femoral bypass can be used in unilateral disease. Femoral endartectomy with or without profundoplasty, remains a very useful and simple procedure.

OFF LOADING OR PRESSURE RELIEF:

It is an essential part of diabetic wound care. Bed rest or total contact plaster cast (TCC) can be used to accelerate healing.

It has been established that minor trauma, such as repetitive stress and shoe pressure are significant components of the etiology in the pathway to ulcerations[67].

Peak plantar pressure is highest in the forefoot compared with the rear foot and medial arch[70]. Reducing pressure applied to the wound especially to

the forefoot is essential for optimal treatment. Even light pressure applied to a healing wound can be detrimental to healing. Unrelieved pressure impairs healing and increases the risk of complications[45]. A TCC is minimal padded a moulded carefully to the shape of the foot. These special casts redistribute weight of the ulcer site and allow patients to walk while the ulcer heals. The goals of tissue load management are to create an environment that enhances soft tissue viability and promoter wound healing. TCC should not be used in patients with active deep foot infection, causing marked swelling or with fluctuating edema because of the ischemic damage inside the cast. New offloading modalities include removable cast walkers and half shoes.

WOUND MANAGEMENT:

The goal of wound bed preparation is to have well vascularised granulation tissue without signs of local infection (drainage cellulites and odour). Removing scar tissue is also essential. Proper debridement simultaneously prepares the wound bed and stimulate wound healing process. In preparing the wound bed one must ensure that there is

(1) creation of a moist wound healing environment and facilitation of the formation of granulation tissue and

2) Treatment of the underlying pathophysiology.

After debridement, tissue should be kept moist to prevent formation of devitalized tissue and subsequent deepening of the wound. Keeping a wound

moist facilitates more rapid migration of epidermal cells across the wound bed which enhances epidermal migration and promotes angiogenesis and connective tissue synthesis.

Different wound condition needs different wound coverage.

Exudative wounds: absorptive dressing, such as calcium alginate is highly absorptive and can be used in exudative wound dressing.

Infected wounds: If the patient is not allergic to sulfa medication, silver sulfadiazine. Bacitracin zinc or Neosporin ointment is fine if they are allergic to sulfa. Where there is significant bacterial contamination of deep wound, oxem is used for dressing (it is a super-oxidized solution for debriding, irrigating and moisturizing acute and chronic wounds).

Dry wounds: Hydrocolloid dressing such as duoderm or hydrocolloid intrasiteis impermeable to oxygen, humidity and bacteria maintain a humid environment and support autolytic debridement.

Hydro fibre dressing: It provides 1. Excellent absorption and retention capabilities for moderate to highly exuding wounds. 2. Conforms to the wound surface to form an intimate contact. 3. Helps reduce wound pain while the dressing is in situ and upon removed. 4.Supports wound healing by providing a moist wound healing environment. 5. Able to modulate serious infections reaction. 6. Strong bacteriostatic action.

Honey dressing:

Antiseptic properties are derived from multiple factors. High sugar content, low water content and acidity present microbial growth in all undiluted honey samples.

Topical application of honey to wounds causes increased exudation by osmotic effects.

Eusol dressing:

Eusol (Edinburgh university solution of lime) is a calcium hypochlorite solution, containing <0.25% w/v available chlorine usually administered as a half strength wet to dry solution 3 to 4 times per day.

Nitric oxide in a diabetic wound:

The role of nitric oxides as a mediator in wound healing has been recently elucidated. Administration of supplemental L- arginine, the sole substrate for inducible nitric oxide synthetase improves wound healing in experimental models. Nitric oxide in vitro by an unknown mechanism and accelerates the wound closure when applied topically.

Super oxidized solution (Oxem) :

It contains super oxidized water 99.9% with salts like hypochlorite. It is used in the debridement, irrigation and moistening of acute and chronic wounds. It reduces the microbial load through its bactericidal action and assist in creating a moist environment there by enabling the body to perform its wound healing process.

Iodine based dressing: (Povidone - Iodine)

It is known to be powerful broad-spectrum germicidal agent effective against a wide range of bacteria, viruses, fungi, protozoa and spores.

Mechanism of action :

Oxidized cell constituents especially proteins at – SH group; iodinates, proteins and inactivates them frequently to tyrosine residues. Some pseudomonas can survive in iodophores.

Collagen / Oxidized regenerated cellulose dressing:

1. It helps in better tissue regeneration.
2. It increases the concentration of endogenous growth factors, which are highly altered in neuropathic diabetic foot ulcer patients and presents them from being degraded.

Platelet – derived growth factor (PDGF):

A new tool in treatment of diabetic foot ulcers. These are small proteins naturally produced during wound healing. These factors stimulate wound granulation and healing. Made using by Recombinant DNA. Application: 1. Smear the gel over the ulcer evenly. 2. Apply a saline soaked gauze pad and wrap with a gauze bandage

HISTORY OF PRP:

It is documented that the first use of Autologous PRP injections was in open heart surgery in 1987[14]. Particularly after 2009, interest in PRP therapy has increased intensively in the last one decade. In 2009, it was revealed that

before their win at the Super Bowl, two of the Pittsburgh Steelers earned PRP for their ankle injuries[15]. PRP became an approved but unproven procedure of sport-related injuries due to media coverage[16].

PLATELET RICH PLASMA:

Platelet-rich plasma (PRP) is defined as a portion of the autologous blood plasma fraction with a platelet above baseline concentration. A standard blood sample consists of 93% red blood cells, 6% white blood cells and 1% white blood cells. Platelets are anucleate megakaryocyte fragments that originate in the bone marrow and circulate for 7–10 days in the bloodstream. In their secretory granules, these cellular elements contain a large protein content (dense granules, lysosomes, and mostly α-granules)[17]. Platelets are stimulated in the injury site during the physiological wound-healing process and growth factors and cytokines are released during fibrin retraction over time. Such proteins may attach to the fibrin matrix and proteoglycans in the extracellular matrix, thereby providing a storage pool that can be released by proteinases secondarily[17]. Each growth factor stimulates one or more reaction pathways depending on the cell setting. Once a cell-surface receptor has been connected to the growth factor, a second messenger cascade is activated and the signal transmission remains active, even when growth factors vanish. A specific group of proteins is phosphorylated, and a change in cell activity occurs, depending on the growth

factor. The key families of growth factors released from platelets and involved in wound healing are as follows[18]:

- EGF–induces fibroblasts to secrete collagenases to dissolve the extracellular matrix during the remodelling phase; promotes the proliferation of keratinocytes and fibroblasts
- TGFα–mitogenic and chemotactic for keratinocytes and fibroblasts.
- VEGF induces angiogenesis in tissue hypoxia
- FGF promotes angiogenesis, granulation and epithelialization through endothelial cell, fibroblast, and keratinocyte migration, respectively
- Platelet derived growth factor (PDGF) improves migration of the tissue's cells, stimulates their migratory cells, promotes collagen upregulation and stimulates inflammation by the chemical attraction of inflammatory cells.

More than 800 different proteins are secreted into the surrounding media different origins, having a paracrine effect on different cell types:[19,21,22] tendon cells[3,19-27], myocytes[19,22,23], mesenchymal stem cells from different origin[28-31] osteoblasts[35,36], fibroblasts, chondrocytes[32-34] and endothelial cells[40]. There are various ways of preparing PRP in the market. Initially, simple centrifugation was used, and later many advances happened in many commercial systems. In newer systems, by adding collagen, calcium, thrombin, by glass contact or by freezing cycles, helps to activate platelets. Some systems use PRP as suspension, and some use it as gel. The technology is going through rapid growth in recent times.

SAFETY OF PRP APPLICATION IN WOUNDS:

PRP can be considered as a safe medication. No adverse effects were detected in clinical trials, such as increased risk of infection or hypersensitivity reactions[41]. With regard to oncogenic potential, no evidence supports a possible tumor triggering when possible coincidences between carcinogenesis and the mitogenic pathways used by growth factors have been evaluated. Once a growth factor has joined its membrane receptor, intracellular signal cascades are activated, normal genetic expression is encouraged and this process is regulated by various control mechanisms. Growth factor overexpression could lead to mutation of the receptor[42]. It can be concluded that therapeutic concentrate growth factor in PRP can act more as promoters than as carcinogenesis initiators, promoting the division and proliferation of previously mutated cells. The presence of an excessively large number of normal growth-factor-receptor copies in tumor cells induces increased sensitivity to the corresponding ligands, which can stimulate the cells and induce proliferation even at very low concentrations. In addition, tumor cells are unable to adequately suppress the mitogenic signals that are continually produced[42]. Consequently, as the use of growth factors in malignant wounds is contraindicated, if malignancy cannot be completely excluded, a skin biopsy should be taken before beginning PRP.

Growth factors in wound management:[72]

Growth factor applied topically to wounds can accelerate healing by stimulating granulation tissue formation and enhancing epithelialization[73].

Growth factors stimulate cellular proliferation, chemotaxis, angiogenesis, protein expression and enzyme production and may act on adjacent cells in a paracrine function, on cells that produce growth factors in an autocrine function, or within the cells in an intercine function

Growth factors or cytokines are biologically active polypeptides that act to alter the growth, differentiation and metabolism of target cells. All known growth factors are polypeptides that are they influence several aspects of cell behaviour and the majority affect several target cells[74].

Hyperbaric oxygen therapy (HBO):

As we know oxygen plays an important role in wound healing. The mechanism of oxygen effect in collagen biosynthesis is the hydroxylation of protein and lysine residues in procollagen.

HBO therapy has been proposed as a useful adjunct in the treatment of problematic wounds. HBO is defined as the administration of oxygen at pressure greater than 1 atm absolute and has been shown in vivo to cause hyper oxygenation of normal tissue with poor blood perfusion.[75]

Rheological agents in diabetic foot lesions:

Pentoxifylline improves intermittent claudication in approximately 60% of patients after 3 months, dose : 400mg BD. Cilastazol is an alternative for patient who cannot tolerate pentoxifylline, dose : 100mg BD. However, no conclusive evidence of any direct beneficial effect of either pentoxifylline or cilastazol exists. Antiplatelet therapy with aspirin or clopidogrel may be warranted in some cases for the prevention of the complication of atherosclerosis, although neither has a direct benefit in healing diabetic foot ulcers.

9. AMPUTATION:

Major amputation surgery in the diabetic is to be avoided if at all possible. Significant advances in blood flow determination, nutritional evaluation, antibiotic regimens and techniques for salvage of the diabetic foot have occurred in recent years making limb salvage rather than amputation the goal[76].

The indication for amputation is as follows

1. Life threatening infection is now rare because of use of antibiotics.
2. Removal of dead tissue (including osteomyelitic bone): Only exception are ill and old patients who cannot withstand the physical or psychological shock of amputation.
3. Intractable pain: in case of dry gangrene or severe ischemia

4. Lifestyle needs: These range from the inability of a wage earner to have the long period of rest sometimes necessary for conservative management, to undue boredom and deterioration of personality in an old person excessively confined whether in hospital or home through the immobility necessary to attempt healing.

MATERIALS AND METHODS:

- This is an observational study conducted in Tirunelveli Medical College Hospital from December 2017 to June 2019.
- Patients admitted in surgical ward of Tirunelveli medical college for chronic ulcer for more than 6 weeks between age group 18-80 years were studied.
- The study group consisted of 51 patients with chronic non healing ulcers.

METHOD OF DATA COLLECTION:

- Detailed history and thorough clinical examination of the patients was done.
- Ulcer and devitalized tissue accurately assessed
- Ulcer is measured using sterile gauze.
- Area of the ulcer is calculated in sq cm

INCLUSION CRITERIA:

Patients with chronic ulcers of duration more than 6 weeks

Age group from 18 to 80 years

EXCLUSION CRITERIA:

- Individuals with history of anticoagulant intake.
- history of immunosuppressive drugs intake.
- patients with severe cardiovascular disorder
- bleeding disorder

- peripheral vascular diseases
- severe anaemia

INVESTIGATIONS:

Complete blood count

FBS and PPBS

Renal function test

Wound culture and sensitivity

X-Ray of involved part

Doppler scan, if vascular compromise is suspected

SEQUENCE OF PROCEDURE:

- Wound preparation: The wound is debrided and slough are meticulously removed, treated with sensitive antibiotics and prepared for PRP application.
- Diabetic cases were started on insulin and optimal RBS achieved.
- In venous ulcers the varicose vein is treated.
- Application of PRP and nonabsorbent dressing.

PREPARATION OF PRP:

- Patients were thoroughly examined and ulcer size (length and breadth) was measured.
- Under aseptic precautions 20 ml of venous blood was drawn and added to a test tube containing EDTA centrifuged at 3000 rpm for 15 min to separate the red blood cells from the platelets and plasma.

- The supernatant and the buffy coat composed of platelets and plasma was collected and centrifuged again at 2000 rpm for 5-10 min.
- The bottom layer of about 5-8 ml was taken. This contains plasma that is rich in platelets, the supernatant fluid is discarded that is poor in platelet concentrate.

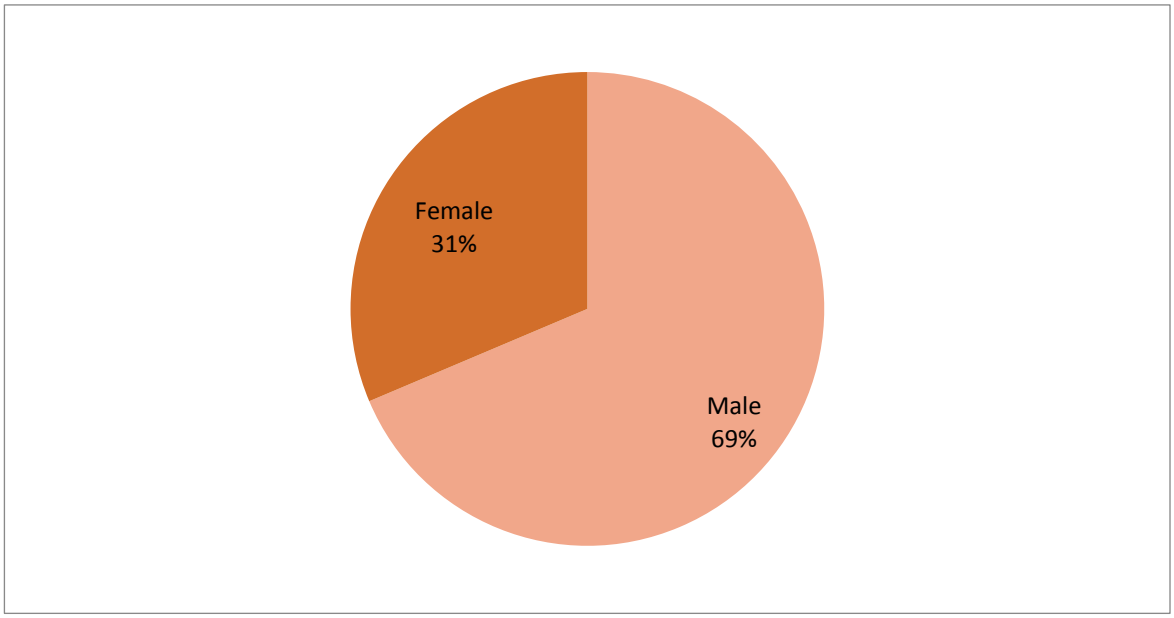
METHOD OF APPLICATION:

- The prepared PRP is applied onto the wound after proper surgical debridement and was dressed with a non-absorbent dressing (paraffin gauze).
- This process was repeated once weekly for 4 weeks. At every week the ulcer area was calculated. Wound area was calculated using the formula for an ellipse (Length × width × 0.7854)
- The treatment outcome was defined as a percentage change of the area

which was calculated as initial measurement minus assessment day measurement divided by initial measurement. An ellipse is closer to a wound shape than a square or rectangle that would be described by simple length × width. The use of an ellipse for calculating wound measurement has been used in RCTs in wound healing literature.

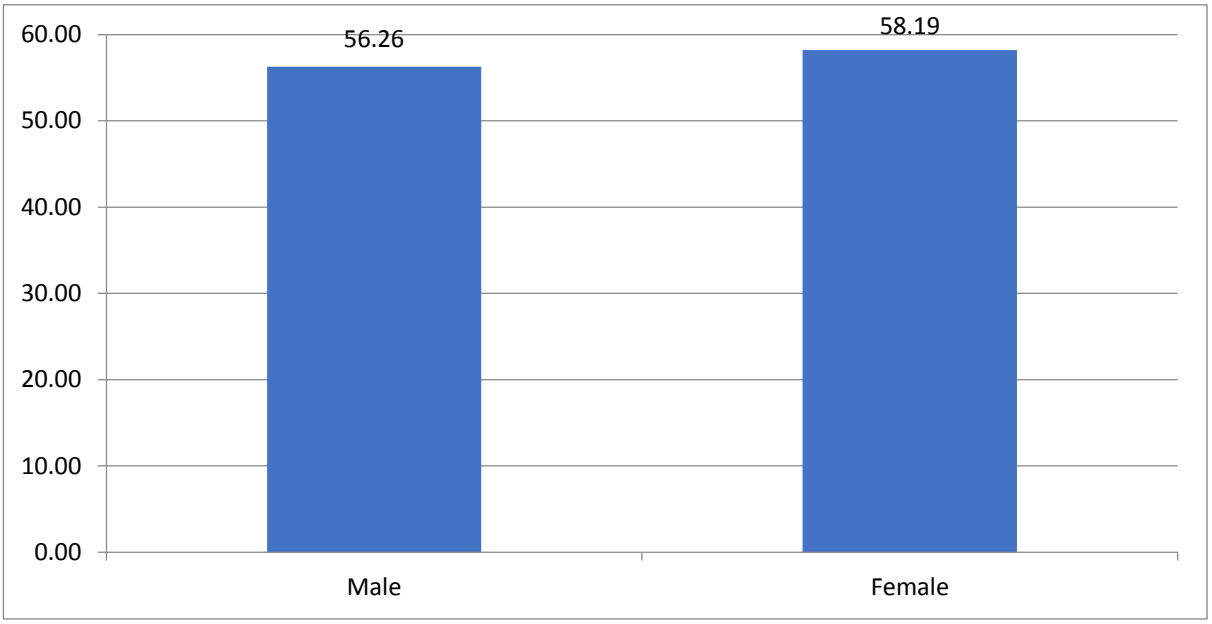
- At every week the area of the ulcer is calculated and the improvement in healing is assessed.

OBSERVATIONS AND RESULTS



Gender	N
Male	35
Female	16

The sex distribution of non-healing ulcers among the patients studied was, out of 51 patients, 35 patients were male (68.62%) and 16 patients were female (31.37%).

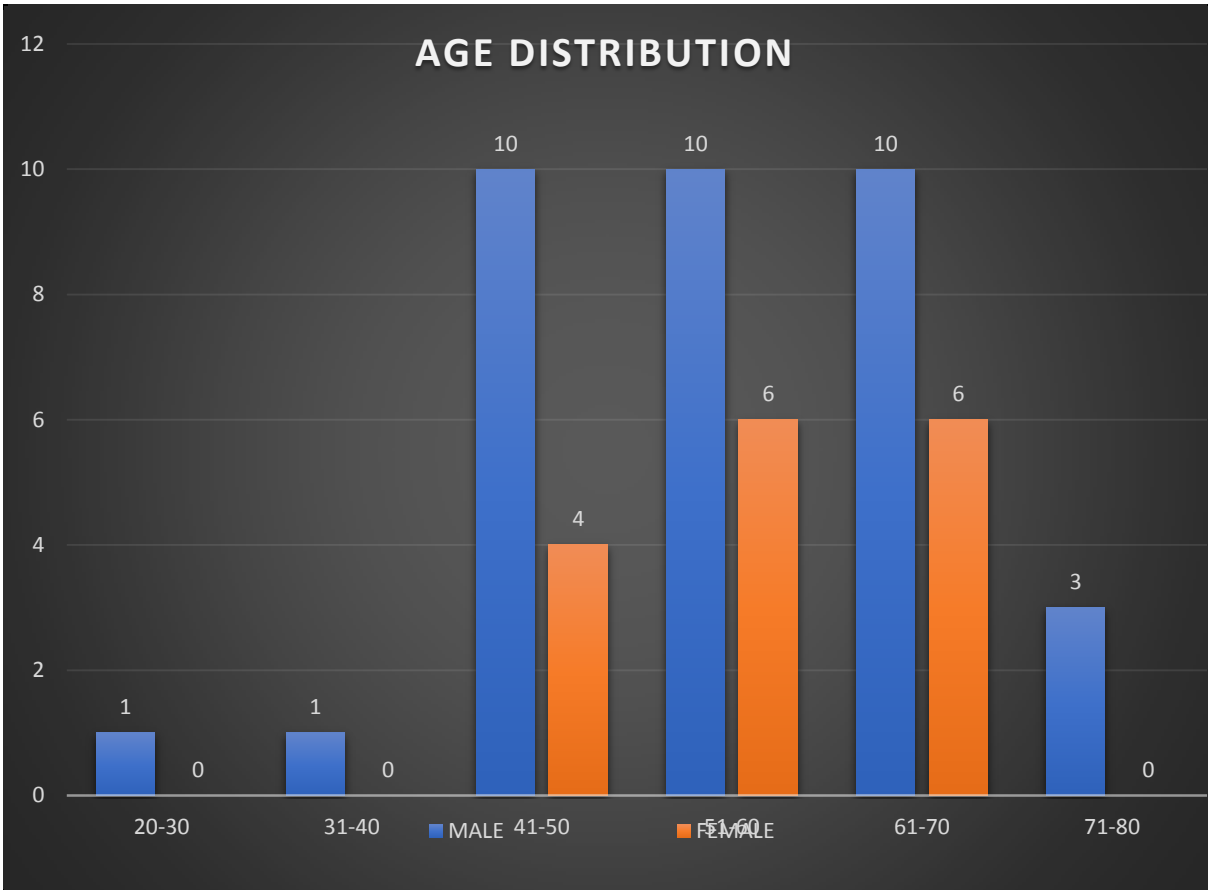


Group Statistics

gender		N	Mean	Std. Deviation	P value
age	Male	35	56.26	11.19	0.543
	Female	16	58.19	8.55	

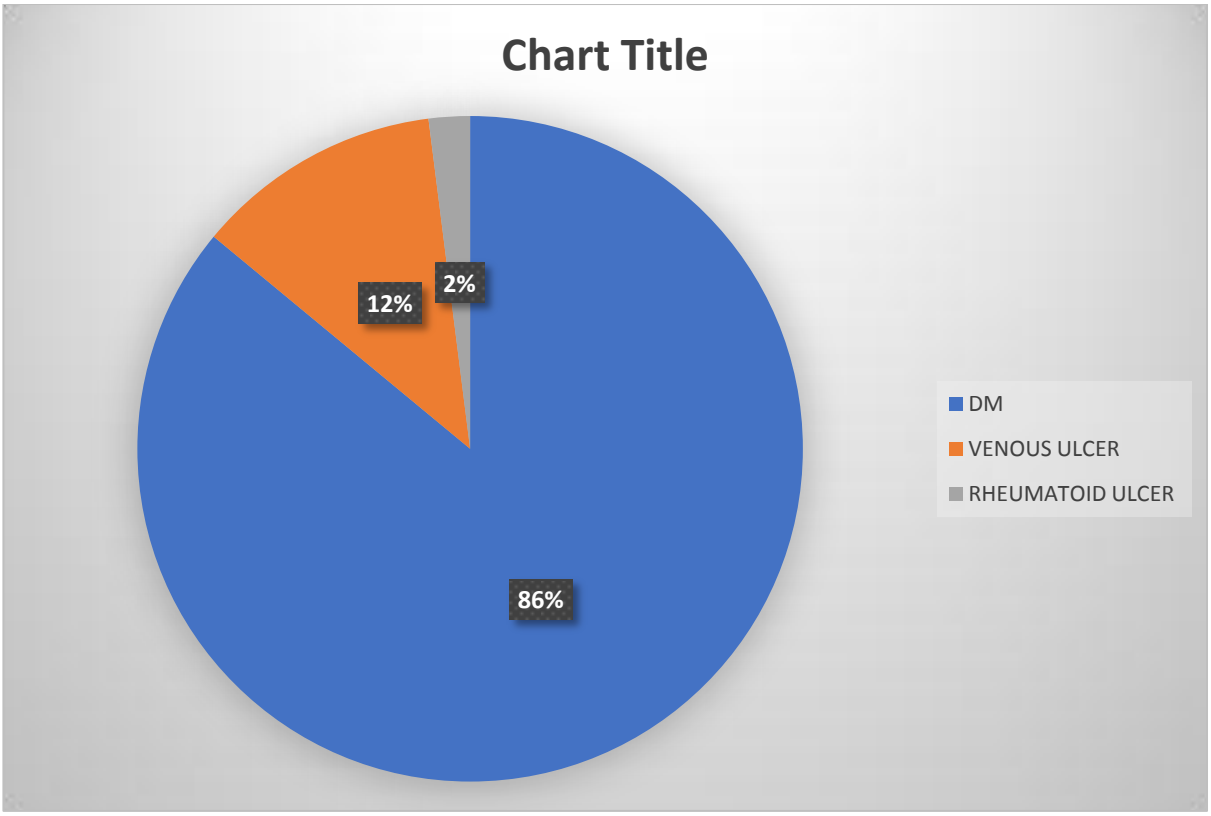
The mean age of the male patients affected was 56.26 years with the standard deviation of 11.19 years

The mean age of female patients affected was 58.19 years with the standard deviation of 8.55 years.

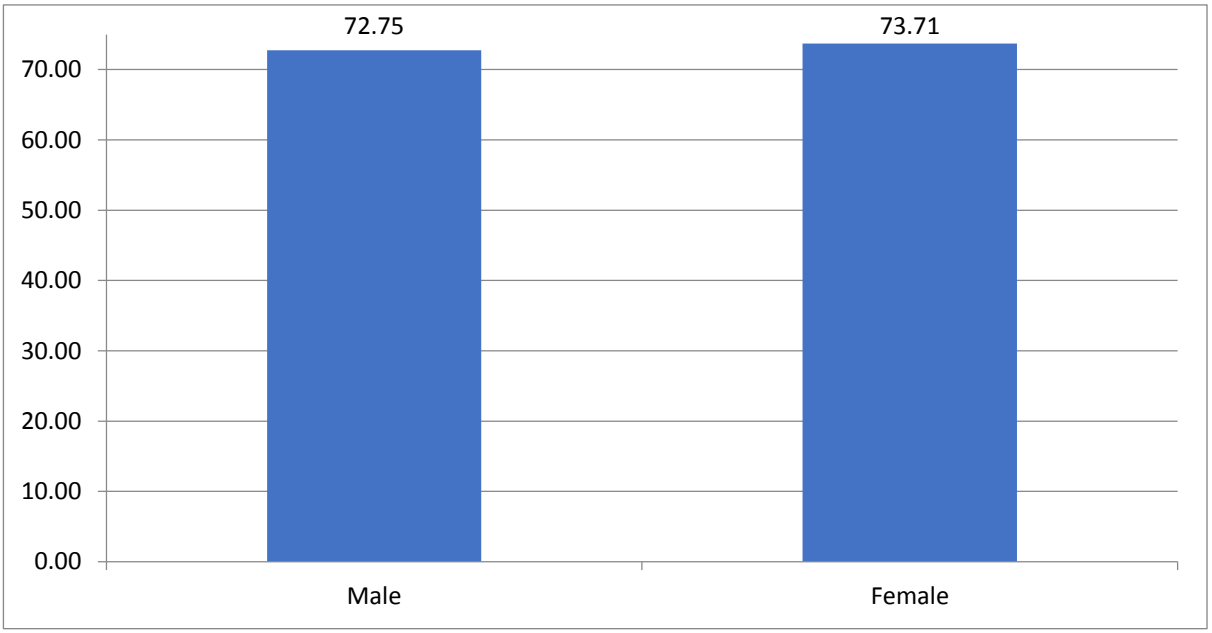


The maximum number of male patients affected with ulcers are between 40 to 70 years.

The maximum number of female patients affected with ulcers are between 50 to 70 years.



The etiology for chronic ulcers was diabetes in 86 %, venous causes in 12 % of the patients.

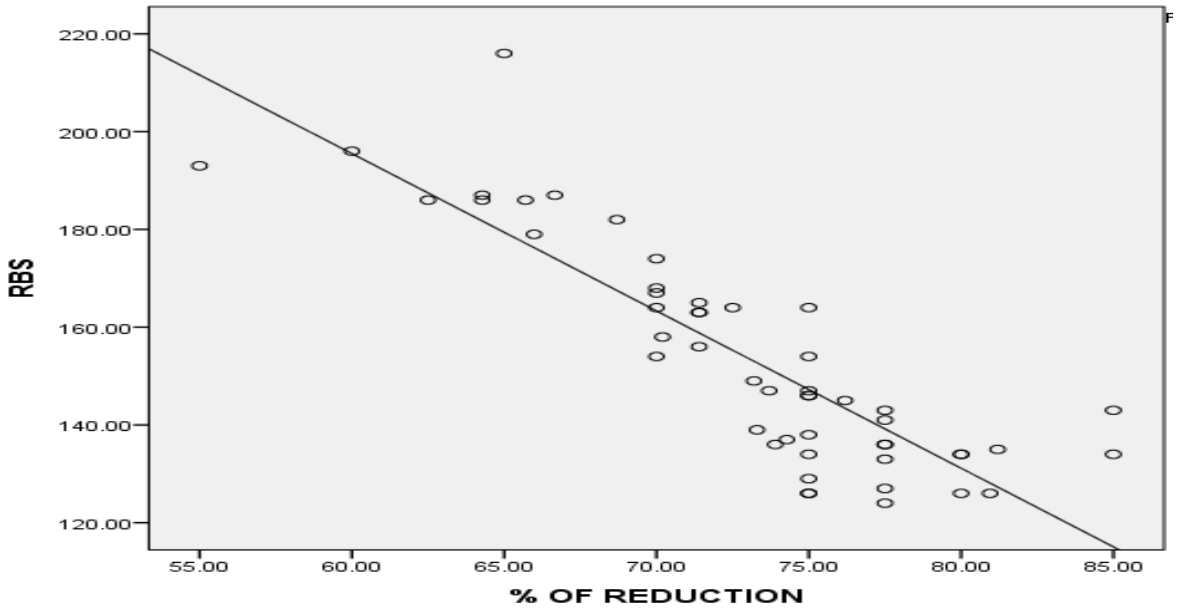


Group Statistics

GENDER		N	Mean	Std. Deviation	P value
% OF REDUCTION	Male	35	72.75	6.91	0.512
	Female	16	73.71	3.40	

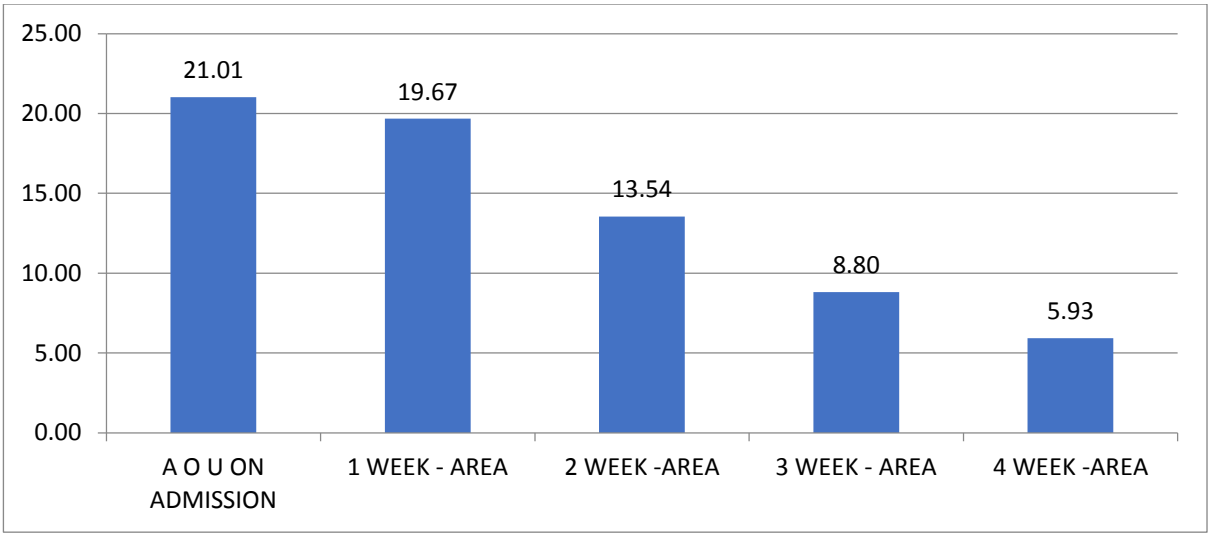
The mean area of reduction of ulcer in male patients was 72.75% with a standard deviation of 6.91%

The mean area of reduction of ulcer in female patients was 73.71% with a standard deviation of 3.40%



Correlations		
		% OF REDUCTION
RBS	Pearson Correlation	-.857**
	P value	.000
	N	51

The level of random blood sugar of the patient has an inverse relationship with the percentage of reduction of area of the ulcer.



Paired Samples Statistics

		Mean	Std. Deviation	P value
Pair 1	A O U ON ADMISSION	21.01	10.89	<0.0001
	1 WEEK - AREA	19.67	10.20	
Pair 2	A O U ON ADMISSION	21.01	10.89	<0.0001
	2 WEEK -AREA	13.54	7.86	
Pair 3	A O U ON ADMISSION	21.01	10.89	<0.0001
	3 WEEK - AREA	8.80	6.16	
Pair 4	A O U ON ADMISSION	21.01	10.89	<0.0001
	4 WEEK -AREA	5.93	3.98	

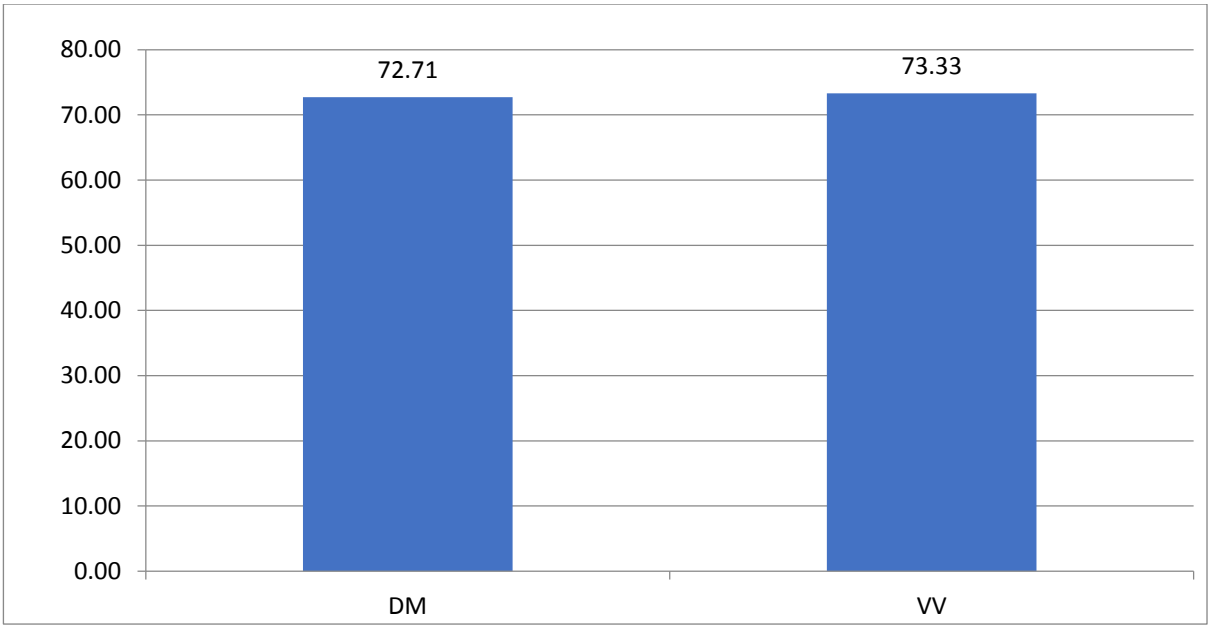
The mean area of ulcer of patients at admission was 21.01 cm^2

The mean area of ulcer of patients at 1^{st} week was 19.67 cm^2

The mean area of ulcer of patients at 2^{nd} week was 13.54 cm^2

The mean area of ulcer of patients at 3^{rd} week was 8.80 cm^2

The mean area of ulcer of patients at 4^{th} week was 5.93 cm^2



Group Statistics

H/O DM OR VARICOSE VEIN		N	Mean	Std. Deviation	P value
% OF REDUCTION	DM	43	72.71	5.42	.80900
	VV	6	73.33	9.17	

The percentage of reduction of area of ulcer in diabetic patients was 72.71% with standard deviation of 5.42.

The percentage of reduction of area of ulcer in venous ulcer was 73.33% with a standard deviation of 9.17.

DISCUSSION

An interventional study was carried out in Tirunelveli medical college hospital from December 2017 to June 2019.

It comprised of 51 patients with non-healing ulcers due to various origin.

Patients were selected based upon the inclusion and exclusion criteria for the study.

Patients were obtained consent and were treated with platelet rich plasma once in 4 weeks.

The results of the study were analyzed in terms of

Sex distribution of the chronic ulcers

Age distribution of the chronic ulcers

Various etiologies of the chronic ulcers

The percentage of reduction of the area of chronic ulcers

The relationship between the glycemic control and the percentage of reduction of the area of chronic ulcers.

The percentage of reduction of the area of chronic ulcers in various etiologies.

The sex distribution of non-healing ulcers among the patients studied was, out of 51 patients, 35 patients were male (68.62%) and 16 patients were female (31.37%).

The mean age of the male patients affected was 56.26 years with the standard deviation of 11.19 years

The mean age of female patients affected was 58.19 years with the standard deviation of 8.55 years.

The maximum number of male patients affected with ulcers are between 40 to 70 years.

The maximum number of female patients affected with ulcers are between 50 to 70 years.

The etiology for chronic ulcers was diabetes in 86 %, venous causes in 12 % of the patients.

The mean area of reduction of ulcer in male patients was 72.75% with a standard deviation of 6.91%

The mean area of reduction of ulcer in female patients was 73.71% with a standard deviation of 3.40%.

The level of random blood sugar of the patient has an inverse relationship with the percentage of reduction of area of the ulcer. i.e. when the random blood glucose increases the percentage of reduction of area of the ulcer decreases.

The mean area of ulcer of patients at admission was 21.01 cm^2

The mean area of ulcer of patients at 1^{st} week was 19.67 cm^2

The mean area of ulcer of patients at 2^{nd} week was 13.54 cm^2

The mean area of ulcer of patients at 3^{rd} week was 8.80 cm^2

The mean area of ulcer of patients at 4^{th} week was 5.93 cm^2

The percentage of reduction of area of ulcer in diabetic patients was 72.71% with standard deviation of 5.42.

The percentage of reduction of area of ulcer in venous ulcer was 73.33% in 4 weeks with a standard deviation of 9.17. which is comparable to the **Yilmaz et al** study where the area of reduction of ulcer was 94.7% in 6 weeks.

The mean percentage area of reduction of ulcer in the study is 73.0124% which is comparable to **Sakata et al** study where the percentage of area of reduction was 83% in 5 weeks.

12 patients were smokers and the percentage of reduction of the area of ulcer in them was below 70%

The management of non-healing ulcers is a challenging issue.
Delayed healing of wounds is the major problem in the community besides causing morbidity and disability in the patient, burden on our health resources.

The platelet rich plasma containing the important growth factors has a positive impact on wound healing by enhancing granulation tissue formation, also acts an anti-inflammatory agent and helps in reducing the wound size.

Nowadays PRP is being used in various fields like Orthopaedics, Sports medicine, Dentistry, Otolaryngology, Neurosurgery, Ophthalmology, Urology, Wound healing, Cosmetic, Cardiothoracic and Maxillofacial surgery

CONCLUSION:

Chronic ulcers come with cost and morbidity for patients and society also. PRP is a safe, simple, inexpensive and biocompatible procedure. In our study, PRP is found to be useful in enhancing the wound healing in chronic ulcers without any adverse events. The mean percentage area of reduction of ulcer in the study is 73.0124% which is a very significant reduction in the area of the ulcer. Hence PRP proves to be an effective method in healing of chronic ulcers.

The results of the study justify further research into the use of platelet rich plasma preparations in treatment of various wounds and ulcers.

CLINICAL PHOTOGRAPH

COLLECTION OF BLOOD

LOADING IN CENTRIFUGE MACHINE

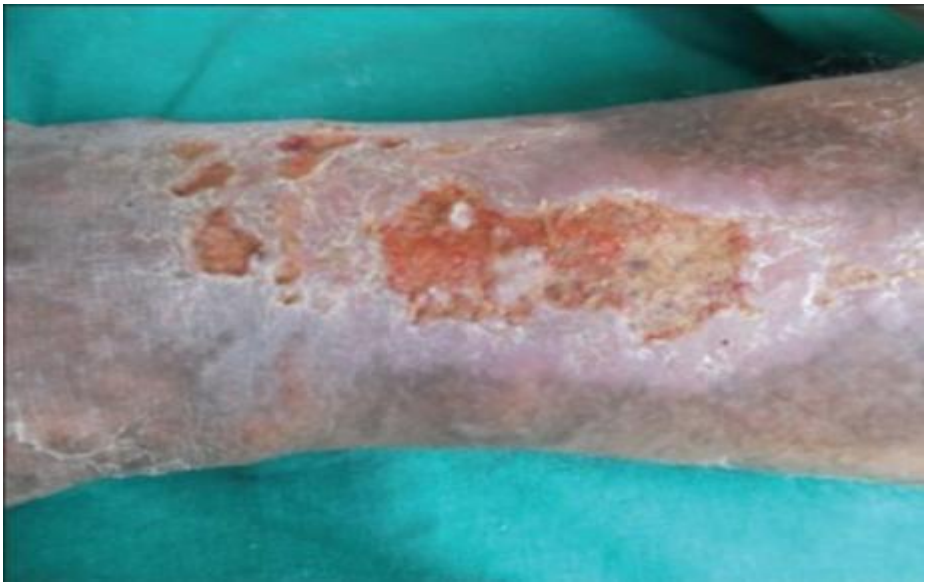
CENTRIFUGE

SEPERATION OF PLASMA AND RBC

BEFORE

AFTER

BEFORE



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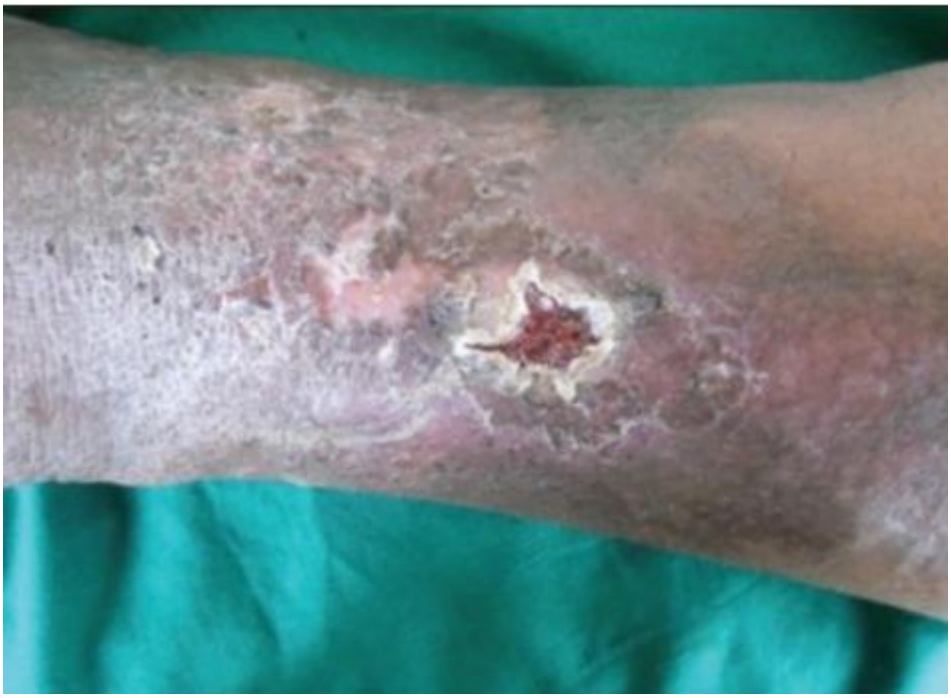

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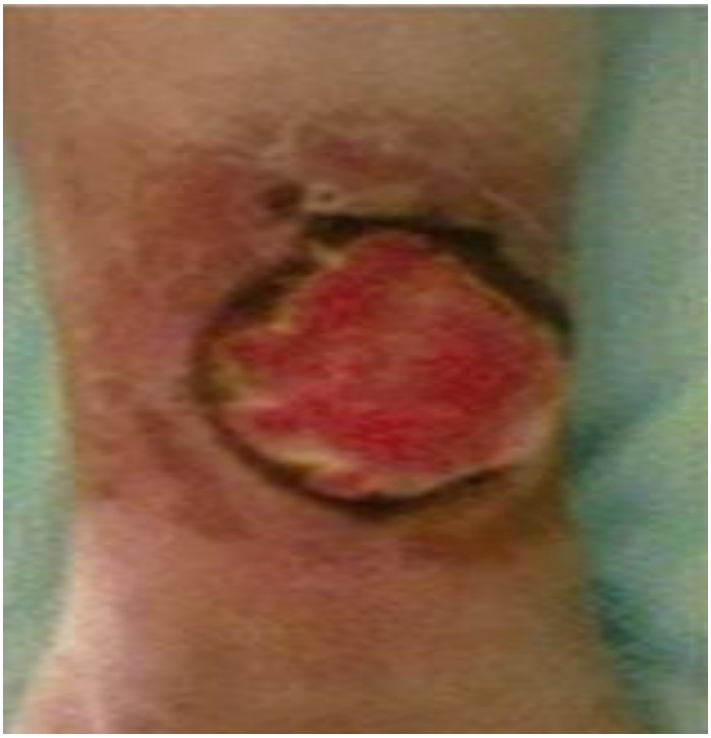

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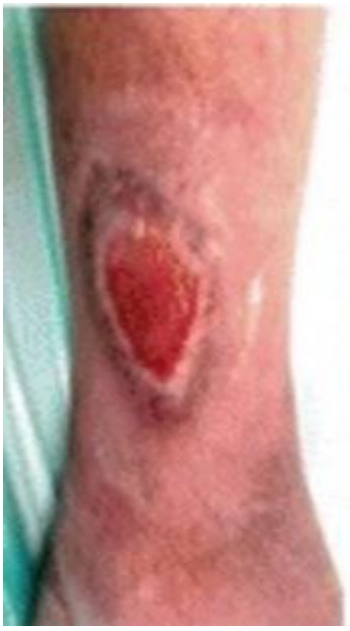

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PROFORMA

1. Case No :
2. Name :
3. Age Sex :
4. Address :
5. I.P. No :
6. Unit / Ward
7. Date of admission
8. Date of discharge

9 .History :

H/o bleeding disorder

h/o diabetes

h/o severe cardio vascular disease or other systemic diseases

h/o steroid intake

h/o smoking

10.General physical examination

Pallor / Icterus

BP

PR

Local examination of ulcer :

DAY	AT ADMISSION	1 WEEK	2 WEEK	3 WEEK	4WEEK
DESCRIPTION OF ULCER					
AREA OF THE ULCER					

11.Biochemical investigation

CBC

RFT

RBS

12. Arterial and venous Doppler (if necessary):

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பத்திற்கு)

ஆய்வு செய்யப்படும் தலைப்பு:
பங்கு பெறுவரின் பெயர்:
பங்கு பெறுவரின் வயது:

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
1.	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்களை படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்.	☐
2.	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3.	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்காள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4.	இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5.	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன் எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின் படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்றேன்.	☐

பங்கேற்பவரின் கையொப்பம் / ..... இடம் .....
கட்டைவிரல் ரேகை
பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....
ஆய்வாளரின் கையொப்பம் /..... இடம் .....
ஆய்வாளரின் பெயர் .....
மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் /..... இடம் .....
பெயர் மற்றும் விலாசம் ....

KEY TO USE MASTER CHART

D	-	H/O Diabetes Mellitus (+)
V	-	H/O Varicose Veins (+)
NO	-	No Co-Morbidities
Y	-	H/O Smoking (+)
N	-	No H/O Smoking
CR	-	Crossings
RBS	-	Random Blood Sugar
AOU	-	Area of Ulcer

1	AGE/SEX	DATE OF ADMISSION	H/O DM OR VARICOSE VEIN	SMOKING	HB IN GMS %	UREA/CR	RBS	A O U ON ADMISSION	A O U BEFORE TREATMENT	AOU AT 1 WEEK -	AOU AT 2 WEEK -	AOU AT 3 WEEK -	AOU AT 4 WEEK -	PERCENTAGE OF REDUCTION AREA OF ULCER
GANESAN	66/M	06-01-2018	D	Y	10.4	36/1.4	158	29.4	29.4	24.5	14	10.5	8.75	70.2
ULAGANATHAN	53/M	17-02-2018	V	N	10.4	26l1.2	126	8.4	8.4	8.4	4.2	2.8	2.1	75
MUTHIAH PANDIAN	77/M	24-03-2018	D	N	10.2	34/1.3	154	22.4	22.4	16.8	14.7	7	5.6	75
MARIAPPAN	42/M	10-04-2018	D	N	11.2	32/1.2	134	21	21	17.5	8.4	5.6	4.2	80
GUNASEKARAN	60/M	05-11-2018	D	Y	12.1	26/0.9	216	49	49	42	33.6	24.5	16.8	65
RAJAMMAL	43/F	13-11-2018	D	N	11.3	38/1.2	164	10.5/6.3	10.5/6.3	10.5/4.2	5.6/3.15	4.2/2.1	3.15/1.57	72.5
MOHANRAJ	49/M	18-11-2018	D	N	10.5	60/1.2	146	12.6	12.6	12.6	10.5	5.6	3.15	75
THIRUMALAI	72/M	18-11-2018	V	Y	12.6	17/0.9	193	28	28	28	22.4	14.7	12.6	55
MOHAMMED MEERAN	53/M	18-11-2018	D	Y	9.6	26/1.4	186	24.5	24.5	24.5	21	14	8.4	65.7
SHANTHI	46/M	19-12-2018	NO	N	11.8	26/1.0	143	14	14	14	8.4	4.2	2.1	85
VELAMMAL	58/F	25-12-2018	D	N	10.2	32/1.3	182	33.6	33.6	33.6	24.5	18.9	10.5	68.7
MANI	65/M	31-12-2018	D	N	10.4	24/1.2	126	29.4	29.4	24.5	16.8	10.5	5.6	80.95
PASUNKILI	65/M	31-12-2018	D	N	9.8	26/1.2	147	12.6	12.6	12.6	7	5.6	3.15	75
VENKATESH	47/M	07-01-2019	D	Y	10.3	24/1.1	196	21	21	21	14	10.5	8.4	60
ARUMUGAM	63/M	07-01-2019	D	Y	10.4	24/1.2	187	29.4	29.4	29.4	21	14	10.5	64.28
SEETHALAKSHMI	61/F	08-01-2019	D	N	9.8	34/1.2	165	29.4	29.4	29.4	21	12.25	8.4	71.4
LAKSHMI	70/F	22-01-2019	D	N	9.4	28/1.2	135	16.8	16.8	16.8	10.5	7	3.15	81.2
SATHYABAMA	60/F	26-02-2019	D	N	9.8	24/1.3	168	10.5	10.5	10.5	5.6	4.2	3.15	70
BALAMMAL	68/F	12-02-2019	D	N	9.8	24/1.2	163	29.4	29.4	29.4	21	14	8.4	71.4
THOMAS	67/M	11-02-2019	V	N	9.4	24/1.2	124	14	14	14	8.4	4.2	3.15	77.5
ABBAS ALI	68/M	11-02-2019	D	N	10.2	24/1.2	134	21	21	16.8	10.5	5.6	4.2	80

CHRISTOPHER	58/M	18-02-2019	D	N	10.6	26/1.3	145	29.4	29.4	24.5	16.8	10.5	7	76.19
THANGARAJ	80/M	25-02-2019	V	N	9.8	24/1.2	126	10.5	10.5	10.5	5.6	4.2	2.1	80
SYED SULAIMAN	29/M	11-03-2019	V	N	10.4	36/1.2	136	14	14	14	8.4	4.2	3.15	77.5
SIVALINGAM	55/M	18-03-2019	D	N	9.8	24/1.0	138	16.8	16.8	16.8	10.5	5.6	4.2	75
GANESAN	40/M	31-03-2019	V	N	11	18/1.0	134	16.8	16.8	16.8	10.5	5.6	4.2	75
KRISHNAN	46/M	01-04-2019	D	N	11.4	36/1.2	127	14	14	14	8.4	4.2	3.15	77.5
SUBBULAKSHMI	48/F	01-04-2019	D	N	9.4	31/1.2	149	39.2	39.2	39.2	29.4	21	10.5	73.2
PANCHAVARNAM	60/F	08-04-2019	D	N	9.6	36/1.3	143	14	14	14	9.8	4.2	3.15	77.5
GURUVAMMAL	65/F	15-04-2019	D	N	9.6	24/1.2	147	14	14	14	8.4	4.9	3.67	73.7
DURAIRAJ	60/M	16-04-2019	D	N	10.6	22/0.9	174	14	14	14	8.4	5.6	4.2	70
AYYAPPAN	60/M	23-04-2019	D	Y	10.8	28/0.9	186	19.6	19.6	19.6	12.6	10.5	7	64.28
MOHAMMED ISHA	50/M	29-04-2019	D	N	11.4	32/1.1	134	14	14	14	8.4	5.25	2.1	85
SEENIVASAN	45/M	29-04-2019	D	Y	10.9	24/1.2	186	56	56	56	39.2	33.6	21	62.5
SUNDARAJAN	49/M	02-05-2019	D	Y	10.4	22/1.1	154	14	14	14	8.4	5.6	4.2	70
KANNAN	42/M	13-05-2019	D	Y	10.4	24/0.9	179	29.4	29.4	29.4	21	14	10.5	65.98
MARIAPPAN	63/M	01-05-2019	D	Y	9.6	26/7.2	167	14	14	10.5	8.4	4.2	4.2	70
RAJENDRAN	61/M	08-05-2019	D	N	9.8	28/1.2	136	33.6	33.6	28	19.6	12.6	8.75	73.9
MARIAMMAL	59/F	08-06-2019	D	N	9.6	24/1.2	139	21	21	16.8	14	8.4	5.6	73.3
RAJESHWARI	56/F	22-06-2019	D	N	9.8	24/12	156	29.4	29.4	29.4	21	8.4	8.4	71.4
SUBBULAKSHMI	56/F	08-06-2019	D	N	9.7	24/1.2	133	14	14	14	8.4	4.2	3.15	77.5
MADASAMY	55/M	04-06-2019	D	Y	10.2	24/0.9	187	16.8	16.8	16.8	14	8.4	5.6	66.66
MAHALIGAM	55/M	17-06-2019	D	N	12.6	31/1.1	141	14	14	14	8.4	4.2	3.15	77.5
SAVARIMUTHU	45/M	11-06-2019	D	N	10.2	24/1.1	163	19.6	19.6	19.6	12.6	7	5.6	71.4

MURUGESAN	67/M	10-06-2019	D	N	10.4	26/0.9	126	5.6	5.6	5.6	4.2	3.15	1.4	75
SHENBAGAM	65/M	18-06-2019	NO	N	10.1	24/1.1	137	49	49	42	28	19.6	12.6	74.28
ESWARAN	51/M	08-07-2019	D	N	10.1	24/1.1	129	16.8	16.8	16.8	10.5	8.4	4.2	75
MEENAKSHIAMMAL	66/F	05-07-2019	D	N	10.2	24/1.2	136	14	14	10.5	7	5.6	3.15	77.5
RANJITHA	50/F	12-07-2019	D	N	9.7	26/1.2	146	21	21	16.8	14	8.4	5.25	75
SEETHALAKSHMI	68/F	19-07-2019	D	N	10.5	28/1.2	164	14	14	10.5	8.4	5.6	4.2	70