# “A RANDOMISED CONTROL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH COLLAGEN GRANULES VERSUS CONVENTIONAL DRESSING IN MANAGEMENT OF DIABETIC FOOT ULCERS”

REG.NO. BH0112006

## Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. S.
in
GENERAL SURGERY

**DEPARTMENT OF SURGERY,**
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# ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"A RANDOMISED CONTROL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH COLLAGEN GRANULES VERSUS CONVENTIONAL DRESSING IN MANAGEMENT OF DIABETIC FOOT ULCERS"** is a bonafide research work done by **CANDIDATE REG. NO. BH0112006**.


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# LIST OF ABBREVIATIONS USED

| | | |
|---|---|---|
| AP | - | Anteroposterior |
| BC | - | Before Christ |
| CBC | - | Complete blood count |
| CDC | - | Centers for Disease Control |
| cms | - | Centimeters |
| $CO_2$ | - | Carbon dioxide |
| CVD | - | Cerebrovascular disease |
| D.O.A | - | Date of admission |
| D.O.D | - | Date of discharge |
| DC | - | Direct count |
| DM | - | Diabetes mellitus |
| E | - | Eosinophil |
| e.g. | - | For example |
| ECM | - | Extracellular matrix |
| EDTA | - | Ethylene diamine tetraacetic acid |
| EGF | - | Endothelial growth factor |
| FBS | - | Fasting blood sugar |
| FGF | - | Fibroblast growth factor |
| g | - | Gram |
| GAGs | - | Glycosaminoglycans |
| Hb | - | Haemoglobin |
| i.e. | - | That is |
| I.P/ O.P.D NO.- | | In patient / Out patient Department Number |
| IDDM | - | Insulin Dependent Diabetes Mellitus or type 1 DM |

| | | |
|---|---|---|
| IGF-1 | - | Insulin-like growth factor |
| IL-1 | - | Interleukin 1 |
| Lat. | - | Lateral |
| mg/dl | - | Milligram per deciliter |
| mg/dL | - | Milligram per deciliter |
| mmHg | - | Millimeters of mercury |
| MMP | - | Matrix metalloproteinases |
| MOA | - | Mechanism of action |
| MRI | - | Magnetic resonance imaging |
| MRSA | - | Methicillin resistant staphylococcus aureus |
| n | - | Total number |
| NIDDM | - | Non Insulin Dependent Diabetes Mellitus or Type 2 DM |
| ORC | - | Oxidized regenerated cellulose |
| p | - | Probaility |
| PDGF | - | Platelet derived growth factor |
| PEDIS | - | Perfusion, extent/size, depth/tissue loss, infection and |
| PMN | - | Polymorphonuclear |
| PVD | - | Peripheral vascular disease |
| RCTs | - | Randomized controlled trials |
| SD | - | Standard deviation |
| | | sensation |
| sq mm | - | Square millimeter |
| Sr. | - | Serum |
| TGF-b | - | Transforming growth factor-beta |
| TIMPs | - | Tissue inhibitors of matrix metalloproteinases |

| | | |
|---|---|---|
| TLC | - | Total leukocyte count |
| TNF-α | - | Tumor necrosis factor alpha |
| VEGF | - | Vascular endothelial growth factor |
| VRE | - | Vancomycin-resistant enterococci |
| vs | - | Versus |
| WBP | - | Wound bed preparation |

# ABSTRACT

## Background and Objectives

Diabetic foot problems are the commonest reason for hospitalization of diabetic patients. The present study was aimed to compare the efficacy of collagen granule dressing over the conventional dressing in the healing of diabetic foot ulcers.

## Methodology

The present one year randomized controlled trial was carried out under the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 60 patients having diabetic foot ulcers were studied. Patients were divided into two groups of 30 each as group A (Topical collagen granules dressing) and group B (Conventional dressing).

## Results

In this study most of the patients were males with male to female ratio of 2.75:1 in group A and 1.5:1 in group B ($p=0.273$). Mean age in group A was 49.00±8.15 years and in group B it was 49.60±10.39 years ($p=0.804$). The ulcer characteristics including site of ulcer, size, shape, discharge and slough/necrotic tissue were comparable between group A and B ($p>0.050$). After 10 days of dressing, positive culture was noted in 3.33% of the patients in group A compared to 6.67% in group B ($p>0.050$). Wound observation at end of second week revealed significantly lower number of patients with pale floor (3.33%) and slough/necrotic tissue (6.67%) in group A ($p<0.001$). Discharge was comparable

in group A and B (96.67% vs 86.67%; p=0.112). At the end of fourth week none of the patient had pale floor and discharge in group A compared to 36.67% and 23.33% in group B (p<0.001 and p=0.005 respectively). The reduction in wound area at the end of second week was significantly high group A (16.53±6.60 sq mm p<0.001).

**Conclusion and interpretation**

Treatment of diabetic foot ulcers with collagen granule helps in reduction in wound area, slough / necrotic tissue and discharge leading to early wound healing compared to conventional dressing.

**Keywords**

Conventional dressing; Diabetic foot ulcer; Topical collagen granules dressing;

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# INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia, resulting from defects in insulin secretion and insulin action or both.[1] The vast majority of cases of the diabetes fall into two broad categories: those having little or no endogenous insulin secretory capacity known as Insulin Dependent Diabetes Mellitus (IDDM or type 1 DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response known as Non Insulin Dependent Diabetes Mellitus (NIDDM, or Type 2 DM).[1,2]

Diabetes is considered as a disease of developed countries and is one of the most common endocrine disorders that reached epidemic proportions worldwide. A report by Centers for Disease Control and Prevention (CDC) estimated that nearly 26 million Americans have diabetes in 2011. Type 2 DM accounts for more than 90% of the diabetic population world wide.[3]

The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. It is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world which is a major and growing threat to global public health.[1]

The metabolic deregulation associated with diabetes mellitus (DM) causes secondary pathophysiological changes in multiple organ systems which impose tremendous burden on the individual with diabetes and on the health care system.

Lots of complications are associated with DM. Those complications arise chiefly from the disruption of the vascular system which can result in inadequate circulation to the peripheral body. This places the foot at higher risk of ulceration and infection. Every chronic disease brings with it fears, concerns, and people with Diabetes face an especially daunting possibility, infections that never heal, potentially ending in the loss of the limb.[4]

One-third of all diabetic patients have significant peripheral neuropathy and/or peripheral vascular disease (PVD). Diabetic foot problems are the commonest reason for hospitalization of diabetic patients (about 30% of admissions) and absorb some 20% of the total health-care costs of the disease more than all other diabetic complication.[5,6] In India prevalence of foot ulcers in diabetic patients in clinic population is 3%. The prevalence of PVD increases with advancing age and is 3.2% below 50 years of age and rises to 55% in those above 80 years of age[7] Similarly it also increases with increased duration of diabetes, 15% at 10 years and 45% after 20 years.[8]

The management of diabetic foot disease may seem poorly defined by comparison with complications such as nephropathy, hyperlipidemia and retinopathy, for which clear guidelines exist. A multidisciplinary team, approach, particularly in specific diabetic foot clinics, is very successful in avoiding and treating foot complications. This strategy has been shown to reduce both the incidence of major leg amputation (by 40% or more), and the duration of in-patient admissions for the treatment of diabetic foot ulceration.[9]

Patient suffering from diabetic ulcer often require hospitalization. One of the major causes of non-healing of ulcer in diabetes is infection. It is caused by a variety of micro-organism. Most common are *Staphylococcus aureus* and *Pseudomonas aeroginosa* which invade the wound and multiply, producing harmful toxic substances, causing destruction of tissue and disturbance in wound healing.[10]

The management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear,[11] daily saline or similar dressings to provide a moist wound environment,[12] debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present,[12] optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. Numerous topical medication and gels are promoted for ulcer care and healing. An ideal wound care product in addition to controlling the infection should also protect the normal tissues and not interfere with normal wound healing. Presently diabetic foot ulcers are being managed by local dressing with agents like Povidine Iodine, EUSOL and Hydrogen Peroxide but have their own limitations. COLLAGEN granules may present an effective alternative to the currently used conventional method of dressings of diabetic wounds.

Proteins are natural polymers and make up almost 15% of the human body. The building blocks of all proteins are amino acids. Collagen is the major protein of the extracellular matrix (ECM) and is the most abundant protein found in mammals, comprising 25% of the total protein and 70% to 80% of skin (dry weight). Collagen acts as a structural scaffold in tissues. The central feature of all collagen molecules is their stiff, triple-stranded helical structure.[14] Types I, II, and III are the main types of collagen found in connective tissue and constitute 90% of all collagen in the body. It

is now evident that collagen and collagen-derived fragments control many cellular functions, including cell shape and differentiation, migration, and synthesis of a number of proteins;[15] so collagen plays a key role in each phase of wound healing.

Considering advantages of collagen granule dressing for better control of wound healing the present study was planned to compare the efficacy of collagen granule dressing over the conventional dressing in healing of diabetic foot ulcers.

# OBJECTIVES

The objective of the present study was to compare the efficacy of collagen granule dressing over the conventional dressing in healing of diabetic foot ulcers.

# REVIEW OF LITERATURE

## DIABETES MELLITUS

### Definition

"Diabetes mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrates, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both".[16-22]

### Classification[16-22]

***Type I***

***Type I Pathology***

IA : Autoimmune beta cell destruction leading to insulin deficiency.

IB : Lack of immunologic markers indicating, an autoimmune destructive process of the beta cells..

***Type II***

It is a heterogeneous group of disorders characterized by:-

- Impaired insulin secretion.
- Variable degree of insulin resistance.
- Increased glucose production

**Chronic Complications of Diabetes Mellitus**[16-22]

The chronic complications of DM affect many organ systems and those may be responsible for the majority of morbidity and/or mortality associated with the disease.

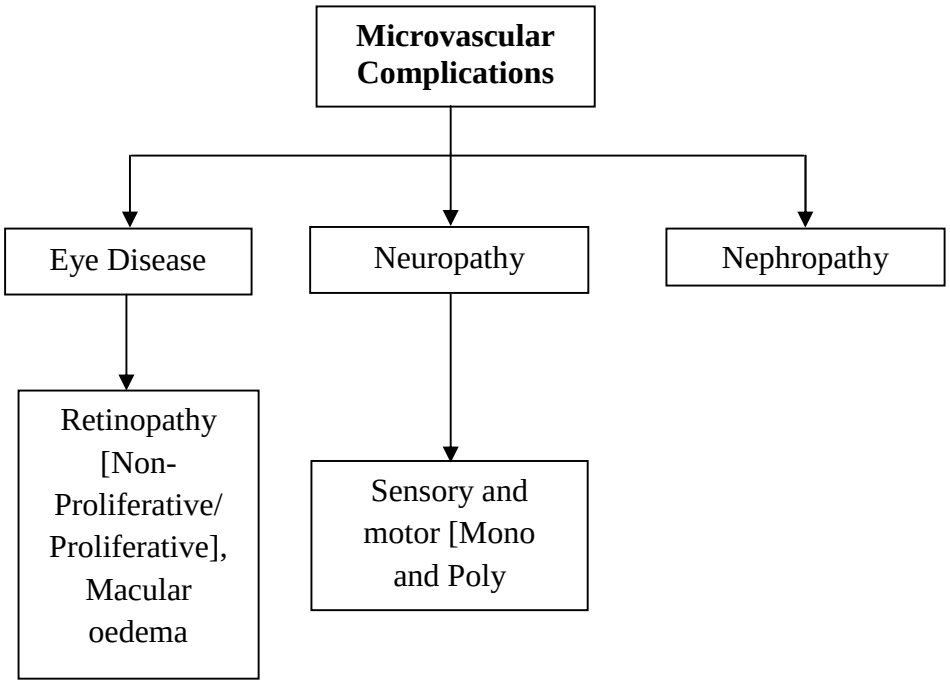



**Figure 1. Microvascular complications seen in diabetes mellitus**

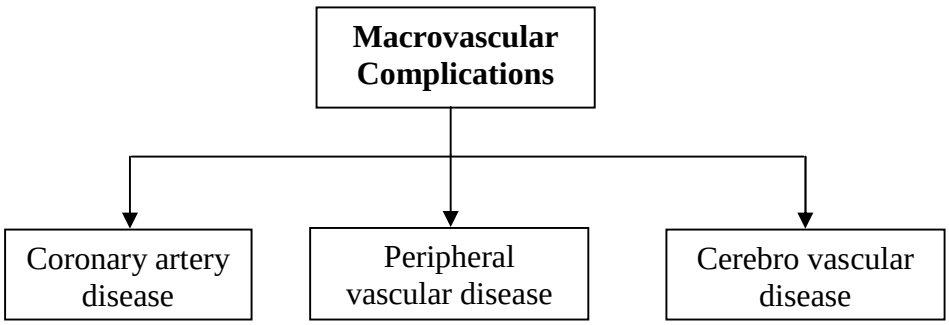



**Figure 2. Macrovascular complications seen in diabetes mellitus**

**Other complications seen in diabetes mellitus:**[16-22]

- Gastro-intestinal problems [Gastroparesis, diarrhea]
- Genitor-urinary problems [ Uropathy / Sexual dysfunction]
- Dermatologic problems.
- Infections.
- Cataracts and Glaucomas.

Microvascular complications in both type 1 and type 2 diabetes mellitus, results from chronic hyperglycemia.

**Complications in lower extremities and diabetes mellitus:**[16-22]

- Foot ulcers and infections are major and important source of morbidity in persons with DM.
- The reasons for the increased incidence of these disorders in DM is because of the interaction of several pathogenic factors:
    - Neuropathies.
    - Peripheral arterial diseases.
    - Abnormal foot biomechanics.

***Neuropathy:***

Neuropathy is present in over 80 percent of the patients with foot ulcers.

*Peripheral sensory neuropathy:*

It interferes with normal protective mechanisms and allows the patient to sustain major or minor trauma to the foot repeatedly, often without knowledge of the injury to the patient.

*Motor and sensory neuropathy:*

It generally lead to abnormal foot muscle mechanics and structural changes in the foot [e.g., hammer toe, claw toe deformity, prominent metatarsal heads, Charcot arthropathy].

Charcot arthropathy (Diabetic neuropathic arthropathy):

It is characterized by collapse of the arch of the mid foot and bony prominences in peculiar places, which is caused by triad of;

a. Small muscle wasting.
b. Decreased sensation.
c. Abnormal distribution of weight while standing.

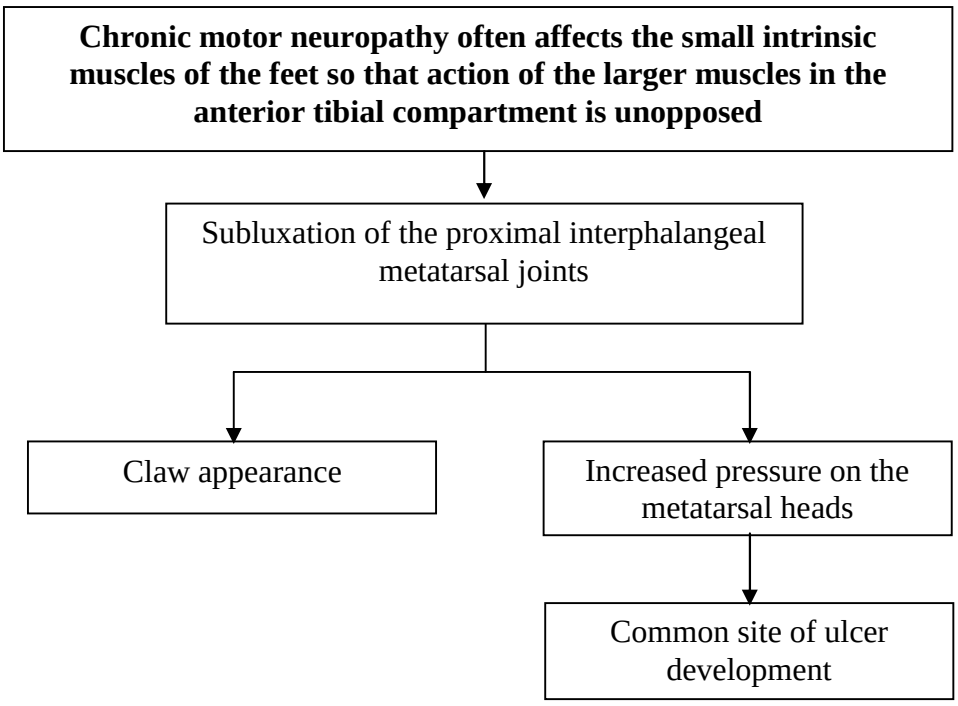



**Figure 3. Pathophysiology of Charcot arthropathy**

*Autonomic neuropathy:*

Results in anhidrosis and altered superficial blood flow in the foot. It promotes drying of the skin and fissure formation.

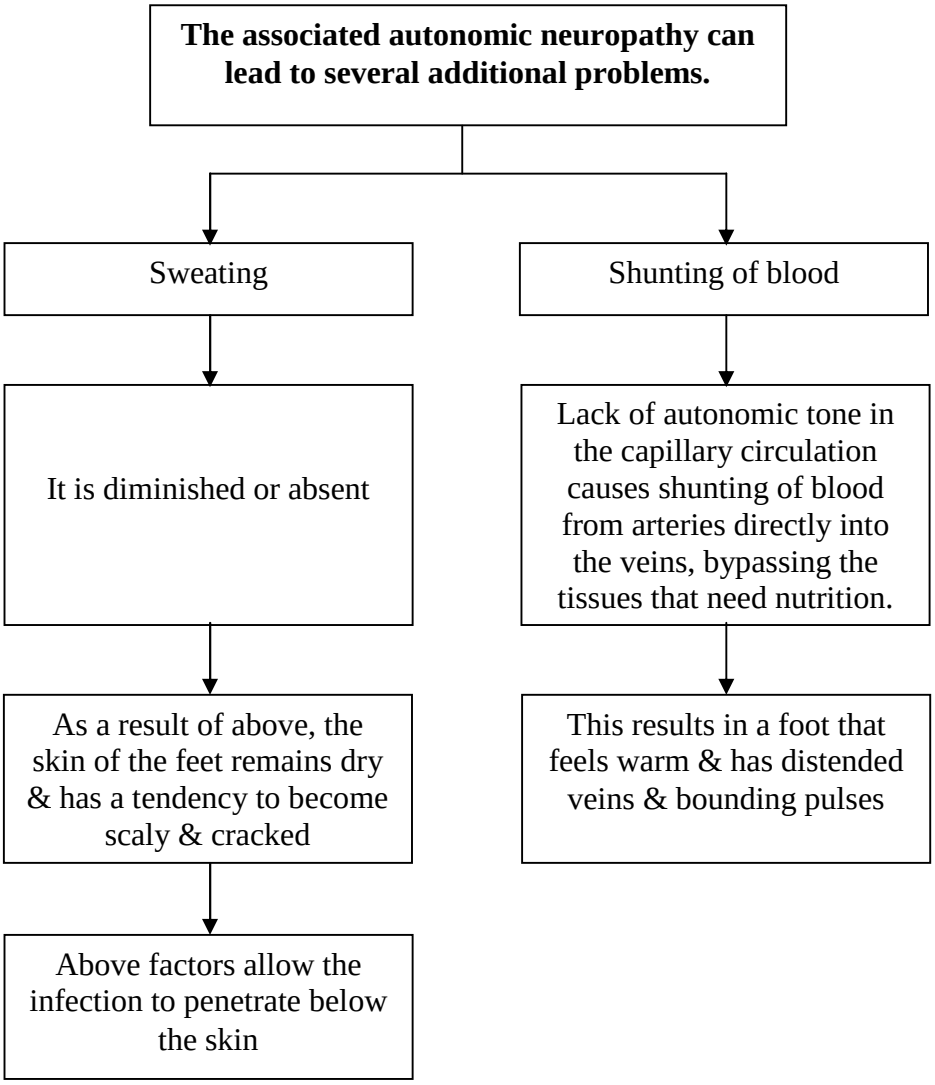



**Figure 4. Pathophysiology of Autonomic Neuropathy in Diabetes Mellitus**

***Peripheral arterial disease and poor wound healing***

The process of development of atherosclerosis is accelerated in DM leading to increased morbidity and mortality. Almost all of the large vessels are involved in this process and clinical manifestations are apparent as a result of atherosclerotic narrowing and thrombosis of coronary, cerebral and leg vessels. It impedes

resolution of minor breaks in the skin of the lower limb, allowing them to enlarge and to become infected.

***Abnormal foot biomechanics:***

Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulcerations.

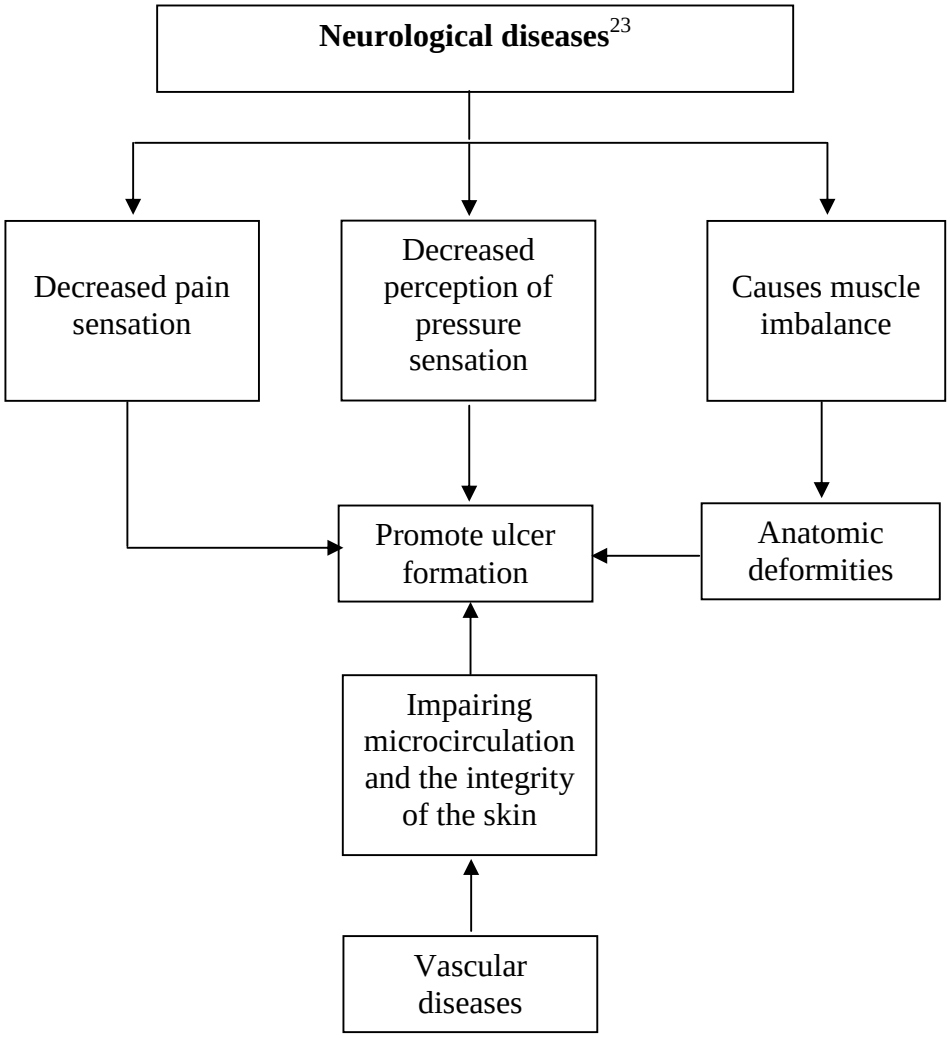



**Figure 5. Pathogenesis of diabetic foot**

**Changes in foot caused by diabetes:**

1. Dryness of skin and callus formation due to peripheral neuropathy.
2. High pressure at bony prominences due to;
    - Decrease plantar tissue thickness
    - Weak intrinsic muscles of foot
    - Imbalances of flexors and extensors leading to clawing of foot
    - Pulling away fat padding from the heads of metatarsals.
3. Limited joint mobility due to;
    - Collagen abnormality
    - Thickening of skin tendons and joint capsule
    - Decreased tissue flexibility
    - Increased plantar pressure

**Recommendations**[24]

- The feet should be examined at least once a year in patients with Type-2 diabetes and in those with Type-1 diabetes existing for more than five years.
- A detailed neurological examination and assessment should be performed for Peripheral vascular disease.
- It is recommended to use the quantitative foot assessment for neurologic symptoms.
- Patients should be considered at high risk for future plantar ulceration if they have[25]
    - A Previous history of foot ulcerations or amputations.

- Neuropathic foot deformities, especially along with overlying bunions or calluses.

***Prophylactic foot care***

It is important that prophylactic advice on foot care should be given to any patient whose feet are at high risk. The recommendations for prophylactic foot care are.

*Avoid:*

- Smoking
- Walking barefoot
- The use of heating pads or hot water bottles
- Stepping into a bath without checking the temperature.

*The feet should be:*

- Washed daily in tepid water.
- Mild soap should be used for cleaning and the feet should be dried by patting gently.
- A moisturizing cream or lotion should be applied to foot.

*Toe Nails:*

The toe nails should be:

- Trimmed to the shape of the toe.
- Filed to remove sharp edges.

*Shoes:*

- The patient's shoes should be snug and not tight,
- Patients who have misshapen feet or have had a previous foot ulcer may benefit from the use of special customized shoes available in foot care centres.

*Socks:*

Socks should be

- Cotton
- Loose fitting
- Should be changed daily

*Inspection of the feet:*

- The feet should be inspected daily. Looking between and underneath the toes and at pressure areas for skin breaks, blisters, swelling or redness. The patient may need to use a mirror or have someone else perform the examination.

*Examination of foot by medical person:*

- A particularly effective strategy is to make specific recommendations to the patient in the form of a 'contract' and to advise the patient that his or her feet are to be examined at every visit to the doctor or nurse.[26]

**Risk factors for foot ulcers or amputation**

- Male sex
- Diabetes> 10 years duration
- Peripheral neuropathy[16-22]
- Abnormal structure of foot [bony abnormalities, callus, thickened nails]
- Peripheral arterial disease
- Smoking
- History of previous ulcer or amputation.[16-22]
- Poor glycemic control. [16-22]

**ULCER:**

**Definition:**

An ulcer is defined as break in the continuity of an epithelial surface, characterised by progressive destruction of the surface epithelium.

***Acute wound***

It is defined as the traumatic loss of normal structure and function to recently uninjured tissue after a noxious insult.[27]

***Chronic wound***

Wounds more than or equal to four weeks duration, is known as chronic wounds. Disruption in the event of healing regulated by process of cellular, humoral , and molecular events and resulting in a time dependent but predictable and orderly pattern of tissue repair.[28]

***Characteristics of chronic wound***

Floor is covered with pale granulation tissue, scanty discharge and indurated base, edge and surrounding skin.

## WOUND HEALING

### Historical background

- Wounds were probably earliest problems of human race.
- Early surgeons like Ambrose Pare, John Hunter and Sir James Paget have given some scientific knowledge to handling of wounds and particularly those resulted from the wars.[29]
- Halsted was curiously interested in wound healing process.
- In the early 1900's, investigation were made by Carrel and his associates with the scientific approach to wound healing. Later Carrel (1916), Harvey and Howe's (1930), studied incised wounds and contributed for the knowledge of wound healing.[29]

### Definition

**"**Body replacement of destroyed tissue by the living tissue" or "Integrated series of cellular and biochemical events which restores the functional integrity and regains the strength of injured tissue".

### Phases of healing

Wound healing and repair are complex processes that involve dynamic series of events.

***Coagulation***

- Helps in preventing blood loss, covering wound surface and holding the wound edges together and thus contributing to the healing process
- It is shown that equivocally that fibrin and platelates play an important role in initiating the wound healing.

***Granulation phase of wound healing***

*Granulation tissue*[30]

"This is a highly vascular tissue, contains largely of;

1. Fibroblast.
2. Endothelial cells lining capillaries of newly spouting blood vessels.
3. Macrophages.
4. Pleuripotent pericytes.

Above all are embedded in a matrix consisting.

1. Fibronectin
2. Proteoglycans rich in Hyaluronic acid and collagen [This collagen is at first mainly of Type-III, changing later to Type I].

The term granulation tissue derived from it, is pink, soft, granular appearance on the surface of wound.[30]

<u>Functions</u>

- Fill the gap of the wound

- Supports the growing and migrating epithelial cells – The nutritive substrate is formed by connective tissue matrix of granulation tissue, over which regenerating epidermis can migrate and is gradually replaced by scar tissue.

Imporant factors for granulation tissue formation

- Chemotactic factor.
- Growth factor.
- Structural molecules.
- Proteases [Digests connective tissue matrix].

***Angiogenesis or neo-vascularisation***

It is most important part of proliferative phase of wound healing and repair.[31]

Without angiogenesis**,** invasion of the wound bed by macrophages and fibroblasts would cease due to lack of oxygen and nutrients.[31]

In the initial stages, these vessels lack basement membrane and have loose cellular junction and are fragile in nature. Because of this even on slightest touch, the vessels bleed profusely which is a characteristic feature of newly formed capillaries. The leakage facilitates the movement of cells and macromolecules into wound site.[31]

There are four steps in angiogenesis:[30,31]

- *Step-1* Proteolytic degradation of basement membrane of parent vessel is to allow formation of capillary sprout and subsequent cell migration.[21]

Angiogenic factors acts on capillary endothelial cells releases collagenase. This enzyme degrades the collagen of basement membrane.[30]

- *Step-2* Fragmentation of the collagen of basement membrane, permits the migration of endothelial cells into peri-vascular spaces.[19]

- *Step-3* Endothelial cells migrate into the peri-vascular spaces where they form buds.[31]

- *Step-4* Maturation of endothelial cells and organisation into capillary loops**.**

    - Functional capillary loops: During dermal repair, these buds grow rapidly towards the free surface and branch at their tips to unite and form **functional capillary loops**.

    - Superficial capillary plexus: On these loops, new buds develop, so that, a **superficial capillary plexus** rapidly forms in the granulation tissue.

    - Canalization: Proliferation and branching of cords of endothelial cells later become canalized to form growing capillary buds of healing wound.

    - Fusion: Capillaries originating from opposite sides of the wound fuse and establish a complete circulation within the wound.

***Remodelling of the vasculature***

There is constant remodelling of the vasculature, which involves obliteration of many of the capillaries.

Each capillary loop becomes functional bringing nutrient and oxygen to nearby cells, enabling the fibroblast to secrete materials for the matrix, through which macrophages and other cells migrate further.

As the scar maturation proceeds, capillaries gradually regress and the red vascular rich wound tissue transforms into a white and relatively avascular poor scar.

The above proliferative and migratory processes are repeated sequentially, until wound bed is filled with granulation tissue.

***Macrophagia***[31]

- It is the point at which protecting and clearing functions of inflammatory response are linked to starting of repair process:

  Macrophagia is;

  1. Migration of Monocyte [from blood] to the site of tissue injury.
  2. Conversion of monocyte to Macrophage after migration to tissue injury site.
     - They are key cells in dermal repair
     - Wound macrophages, which appear subsequent to the cells, play pivotal role in healing by liberating various factors.

*Functions of macrophages:*[32]

- Take over the function of phagocytes that is debridement.
- Release matrix metalloproteinases (MMP).
- Macrophages secrete numerous cytokines.

- Macrophages also release growth factors that stimulate fibroblast, endothelial cells and keratinocyte proliferation.
- Promote angiogenesis by liberating endothelial growth factor [EGF].
- Macrophage-secreted platelet derived growth factor (PDGF) stimulate collagen and proteoglycan synthesis.

***Fibroplasia***[32]

After injury, sparse fibroblasts are chemoattracted to the inflammatory site, divide and produce the components of the extra cellular matrix (ECM). After stimulation by macrophage and platelet derived cytokines and growth factors, the fibroblast which is normally arrested in $G_0$ phase, undergoes replication and proliferation.

The primary function of fibroblsts is to synthesize collagen. The rate of collagen synthesis declines after 4 weeks and eventually balances the rate of collagen destruction by collagenase (MMP-1). At this point the wound enters a phase of collagen maturation. The maturation phase continues for months or even years.

## DIABETIC FOOT

A diabetic foot infection is most simply defined as any inframalleolar infection in a person with diabetes mellitus. These include paronychia, cellulitis, myositis, abscesses, necrotizing fasciitis, septic arthritis, tendonitis, and osteomyelitis. The most common and classic lesion, however, is the infected diabetic “mal perforans” foot ulcer.[33] Wound infection is the deposition and

multiplication of bacteria in tissue with colony count of more than $10^5$ bacteria per gram of tissue with an associated host reaction.[46]

Diabetic foot ulcers occur as a result of various factors, such as mechanical changes in conformation of the bony architecture of the foot, peripheral neuropathy and atherosclerotic peripheral arterial disease, all of which occur with higher frequency and intensity in the diabetic population.

**Anatomy of the foot** [35,36]

The human foot is a marvel of mechanical construction. It acts as a pliable platform to support the body weight in the upright posture as a lever to propel the body forwards in walking, running or jumping. It has 26 bones, 29 joints, 42 intrinsic muscles, various ligaments, 4 mm thick skin, exquisite nerve supply and abundant vascularity with good collaterals. These components work together to provide the body with support and balance with mobility.

**Parts**

Structurally the foot has three main parts;

1. *The fore foot:* It is composed of phalanges and metatarsals. They are connected together by metatarso-phalangeal joint at the balls of the foot. The fore foot bears the half of the body weight and balance pressure on the balls of the foot.
2. *The mid foot:* It is composed of five tarsals bones. It forms the arch of foot and serves as a shock absorber.

3. *The hind foot:* It links the mid foot to ankle. It is composed of two long bones of the lower leg, the tibia and the fibula which forms ankle joint with talus. This subtalar joint is formed between talus and calcaneum which is cushioned inferiorly by a fat layer.

**Arches**

The foot consists of three arches.

1. Medial longitudinal arch

    - It is the highest and the most important arch of the foot.
    - It is composed of calcaneum, talus, navicular, cuneiforms and first three metatarsal bones. The submit of the arch is formed by talus.
    - It acts as a shock absorber.

2. Lateral longitudinal arch

    - It is characteristically low arch.
    - It is composed of calcaneum, cuboid, fourth and fifth metatarsal bones. The submit of the arch is formed by calcaneum.
    - It transmits the body weight and thrust to the ground.

3. Transverse arch

    - It is a continuous structure formed by cuboid, three cuneiforms and the bases of the metatarsal bones.

***Factors responsible for the maintenance of the arches***

1. Ligaments and plantar aponeurosis.
2. Action of extrinsic and intrinsic muscles of the foot.
3. Structure of the bones.

Functions of the arches of the foot

1. They distribute body weight to the weight bearing areas of the sole mainly heel and the base of the toes (first and fifth).
2. They act as springs; chiefly the medial longitudinal arch which helps in walking and running.
3. They also act as a shock absorbers in stepping and jumping.
4. The concavity of the arches protects the soft tissue of the sole against pressure.

**Sole**

The skin of the sole is about 4 mm thick. It is adapted for weight bearing. There are subcutaneous concentrations of the fat over the weight bearing areas such as heel, lateral margin of the sole and across the plantar aspect of the metatarsal heads. Numerous fibrous bands between the skin and the plantar aponeurosis prevent undue movement of sole during walking.

**Muscles**

***Intrinsic***

- Origin and insertion are located within the foot.

- They include plantar flexors, dorsiflexors, abductors and adductors of the toes.
- They also support the arches of the foot.

***Extrinsic***

- Origin of these muscles are in the lower leg.
- They have long tendon that crosses the ankle to insert on the bones of foot except the talus.
- They are responsible for the movement at the ankle, foot and toes.
- They also support the arches of the foot.

**Major joints and movements**

- Ankle joint – Dorsiflexion and plantar flexion.
- Subtalar joint – Inversion and aversion.
- Midtarsal joint – Abduction and adduction.

**Blood supply**

Anterior tibial artery continues as a dorsalis pedis artery in the foot. Dorsalis pedis artery gives off an arcuate artery that along with its branches supplies the outer four toes. The dorsalis pedis artery continues down to supply the great toe. Posterior tibial artery in the sole of the foot divides into two branches, the lateral and medial plantar arteries that supplies the sole of the foot. The peroneal artery descends down and supply posterior and the outer aspect of the heel.

**Nerve supply**

***Sensory nerve supply***

*Dorsum*

- The saphenous nerve: It supplies the medial border of the foot upto the ball of the great toe.
- The superficial peroneal nerve: It supplies entire dorsum of the foot except the lateral border, medial border and the cleft between the first and second toe.
- The sural nerve: It supplies the lateral border of the foot upto the tip of the little toe.
- The deep peroneal nerve: It supplies the cleft between the first and the second toes.
- The digital branch of the medial and lateral plantar nerve supplies the distal part of the dorsum of the toes.

*Sole*

- Medial calcaneal branch of tibial nerve: It supplies posterior and medial portion of the sole.
- Medial plantar nerve: It supplies the anteromedial portion of the sole and medial three and half digits.
- Lateral plantar nerve: It supplies anterolateral portion of the sole and lateral one and half digits.

***Motor nerve supply***

- Deep peroneal nerve.
- Superficial peroneal nerve.
- Tibial nerve - Medial plantar nerve; Lateral plantar nerve.

**Epidemiology**

Approximately 15% of all patients with diabetes will develop a peripheral ulcer. 20% of all patients with diabetes admitted to a hospital will have a skin ulcer. The risk of amputation in a patient with diabetes is 15–40 times higher than that in a patient without diabetes. The presence of an ulcer in a diabetic patient has a profound impact on the quality of life for the patient and on the delivery of care. The cost of care for diabetic ulcers and the associated amputations is staggering. Although the prevalence of chronic ulcers has been estimated to be 120/100,000 people between 45–64 year of age, the prevalence increases to more than 800/100,000 people over the age of 75 year. Persons with diabetes have up to a 40-fold greater risk of lower extremity amputation than their nondiabetic counterparts. There were approximately 86,000 hospital discharges for diabetes-related nontraumatic amputations in the United States in 1996. The 5-year survival rate after amputation of a diabetic limb is less than 50%. These grim statistics reflect an increased prevalence of peripheral lesions in diabetes, but also delayed healing.[37]

**Risk factors**

Risk factors for foot ulcers or amputation include male sex, diabetes >10 years duration, peripheral neuropathy, abnormal structure of foot (bony

abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation and poor glycemic control.

**Etiology**

The etiologies of diabetic ulceration include neuropathy,[38] arterial disease,[39] pressure,[40] and foot deformity.[41] Diabetic peripheral neuropathy, present in 60% of diabetic persons and 80% of diabetic persons with foot ulcers, confers the greatest risk of foot ulceration; which is contributed by microvascular disease and suboptimal glycemic control. Sensory neuropathy involving the feet may lead to unrecognized episodes of trauma due to ill-fitting shoes. Motor neuropathy, causing intrinsic muscle weakness and splaying of the foot on weight bearing, compounds this trauma. The result is a convex foot with a rocker-bottom appearance. Multiple fractures are unnoticed until bone and joint deformities become marked. This is termed a Charcot foot (neuropathic osteoarthropathy) and most commonly is observed in diabetes mellitus, affecting about 2% of diabetic persons. If a Charcot foot is neglected, ulceration may occur at pressure points, particularly the medial aspect of the navicular bone and the inferior aspect of the cuboid bone. Sinus tracts progress from the ulcerations into the deeper planes of the foot and into the bone. Charcot change can also affect the ankle, causing displacement of the ankle mortise and ulceration, which can lead to the need for amputation.

**Microbiologic features of diabetic foot**

Aerobic Gram-positive cocci are the predominant bacteria that colonize and acutely infect breaks in the skin. *Staph aureus* and the hemolytic streptococci (groups A, C, and G, but especially group B) are the most commonly isolated

pathogens. Chronic wounds develop a more complex colonizing flora, including enterococci various Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa*, and nonfermentative Gram-negative rods.[42] Hospitalization, surgical procedures, and, especially, prolonged or broad-spectrum antibiotic therapy may predispose patients to colonization and/or infection with antibiotic-resistant organisms (MRSA or vancomycin-resistant enterococci [VRE]).[43] Although MRSA strains have previously been isolated mainly from hospitalized patients, community associated cases are now becoming common and are associated with poor outcomes in patients with diabetic foot infections.[44]

The impaired host defenses around necrotic soft tissue or bone may allow low-virulence colonizers, such as coagulase-negative staphylococci and *Corynebacterium* species ("diphtheroids"), to assume a pathogenic role. Acute infections in patients who have not recently received antimicrobials are often monomicrobial (almost always with an aerobic Gram-positive coccus), whereas chronic infections are often polymicrobial. Cultures of specimens obtained from patients with such mixed infections generally yield 35 isolates, including Gram-positive and Gram-negative aerobes and anaerobes.[45] The pathogenic role of each isolate in a polymicrobial infection is often unclear.

**Pathogens associated with various clinical foot-infection syndromes**[46]

| Foot- infection syndrome | Pathogens |
|---|---|
| Cellulitis without an open skin wound. | Beta-hemolytic streptococcus* and Staphylococcus aureus |
| Infected ulcer and antibiotic naïve (X). | Staph aureus and beta-hemolytic streptococcus* |
| Infected ulcer that is chronic or was previously treated with antibiotic therapy (Y). | Staphylococcus aureus, beta-hemolytic streptococcus, and Enterobacteriaceae |
| Ulcer that is macerated because of soaking (Y). | Pseudomonas aeruginosa (often in combination with other organisms) |
| Long-duration nonhealing wounds with (Y, Z) prolonged broad-spectrum antibiotic therapy | Aerobic gram-positive cocci (Staph aureus, coagulase-negative staphylococci, and enterococci), diphtheroids, Enterobacteriaceae, Pseudomonas species, nonfermentative gram-negative rods and possibly, fungi. |
| "Fetid foot": extensive necrosis or gangrene or malodorous (Z) | Mixed aerobic gram-positive cocci, including enterococci, gangrene, malodorous Enterobacteriaceae, nonfermentative gram-negative rods, and obligate anaerobes |

*Groups A, B, C, and G; X Often monomicrobial; Y Usually polymicrobial; Z Antibiotic-resistant species (e.g., MRSA, vancomycin-resistant enterococci, or extended-spectrum beta-lactamase–producing gram-negative rods) are common

**Risk Factors for Foot Ulceration and Infection**[46]

| Risk Factor | Mechanism of Injury or Impairment |
|---|---|
| Peripheral motor neuropathy | Abnormal foot anatomy and biomechanics, with clawing of toes, high arch, and subluxed metatarsophalangeal joints, leading to excess pressure, callus formation and ulcers. |
| Peripheral sensory neuropathy | Lack of protective sensation, leading to unattended minor injuries caused by excess pressure or mechanical or thermal injury. |
| Peripheral autonomic neuropathy | Deficient sweating leading to dry, cracking skin. |
| Neuro-osteoarthropathic deformities (i.e., Charcot disease) or limited joint mobility | Abnormal anatomy and biomechanics, leading to excess pressure, especially in the midplantar area. |
| Vascular (arterial) insufficiency | Impaired tissue viability, wound healing, and delivery of neutrophils. |
| Hyperglycemia and other metabolic derangements | Impaired immunological (especially neutrophil) function and wound healing and excess collagen cross-linking. |
| Patients disabilities | Patient reduced vision, limited mobility, and previous amputation(s). |
| Maladaptive patient behaviors | Inadequate adherence to precautionary measures and foot inspection and hygiene procedures, poor compliance with medical care, inappropriate activities, excessive weight-bearing, and poor footwear. |
| Health care system failures | Inadequate patient education and monitoring of glycemic control and foot care. |

**Infections and compromise of the foot vessels**

Puncture or penetrating wounds of the plantar region or the web space infections may go up in the central non expansible plantar space. The inflammatory exudates that collect causes pressure on the small arteries in the tissues and will lead to thrombosis or obliteration. This will lead to gangrene.[47]

**Recognition of wound infection** [48]

The inflammatory response is a protective mechanism that aims to neutralize and destroy any toxic agents at the site of an injury and restore tissue homeostasis. The classic signs of infection include:

- Localised erythema.
- Localised pain.
- Localised heat.
- Oedema.

Further criteria include:

- Abscess.
- Discharge which may be viscous in nature, discoloured and purulent.
- Delayed healing not previously anticipated.
- Discolouration of tissues both within and at the wound margins.
- Unhealthy granulation tissue.
- Abnormal smell.
- Wound breakdown associated with wound pocketing/bridging at base of wound.

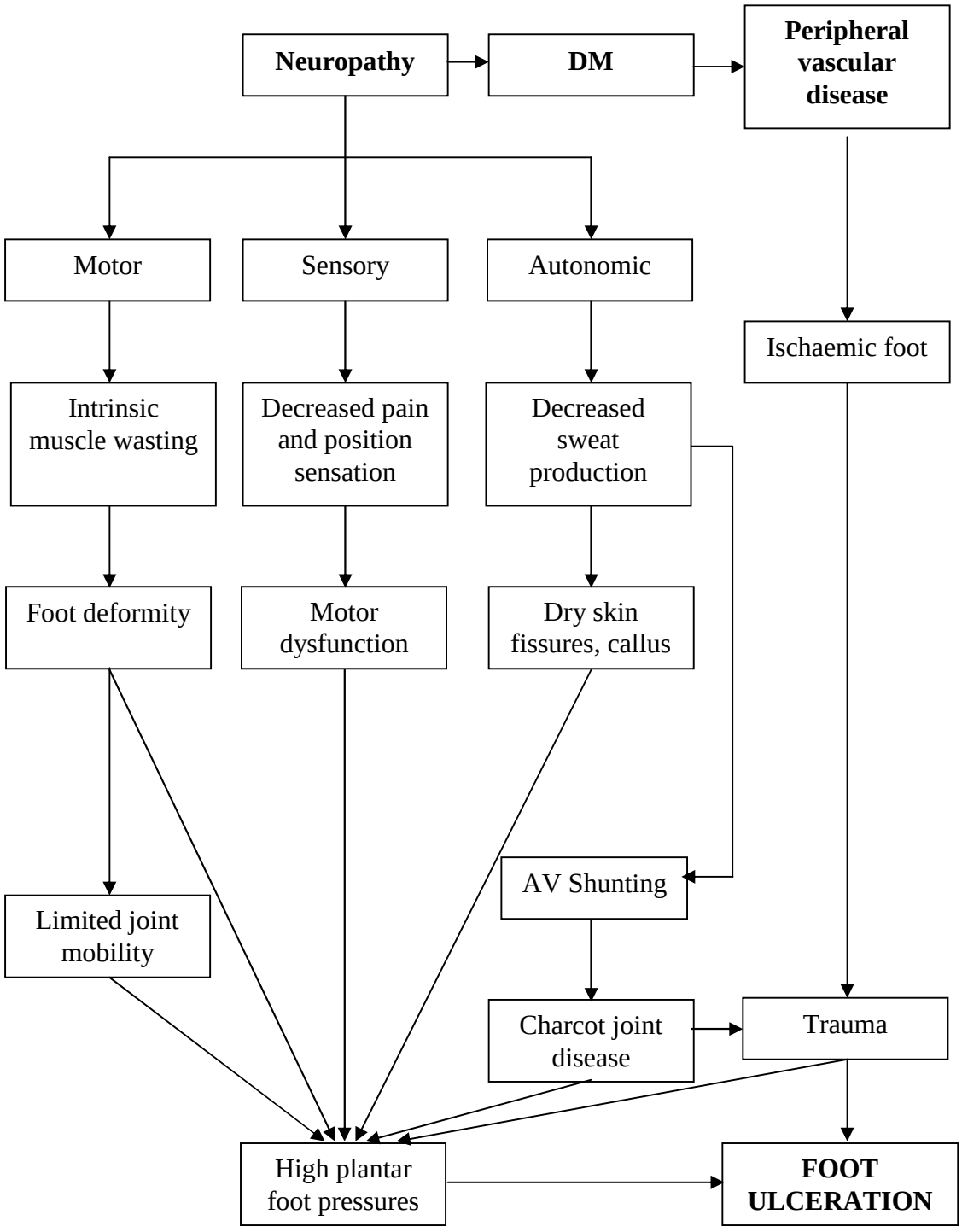



**Figure 6. Clinical pathways leading to foot ulceration**[49]

**Evaluation**

- Characteristics: Size, depth, appearance, discharge and location.
- Etiological assessment: Neuropathic, ischemic, or neuro-ischemic.
- Screening for neuropathy.
    - Pressure of 5.07 (10-g) Semmes Weinstein monofilament.
    - Vibration sensation with the use of standard tuning fork (128 cycles per second)
    - Neurologic reflex hammer.
- Probing of ulcer for underlying osteomyelitis.
- Culture sensitivity of the discharge.
- Radiograph for underlying osteomyelitis.
- Colour Doppler study for vascular pathology.
- MRI for Charcots neuropathy.

**Classification**

The Wagner system has been widely used for 25 years for grading of diabetic foot ulcer.[50]

**Wagner Ulcer Classification System**

| Grade | Lesion |
|---|---|
| 0 | No open lesions; may have deformity or cellulitis. |
| 1 | Superficial diabetic ulcer (partial or full thickness). |
| 2 | Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis. |
| 3 | Deep ulcer with abscess, osteomyelitis, or joint sepsis. |
| 4 | Gangrene localized to portion of forefoot or heel. |
| 5 | Extensive gangrenous involvement of the entire foot. |

Wagner ulcer classification system was developed for the “dysvascular” foot. It was skewed toward severe disease and contains all infections within a single grade.

Consensus is developing that the key issues in classifying a diabetic foot wound are its depth (in particular, which tissues are involved) and whether the wound is complicated by either ischemia or infection. The International Consensus on the Diabetic Foot recently published a preliminary progress report on a diabetic foot ulcer classification system for research purposes.[50,51,52] The key elements are summarized by the acronym PEDIS (perfusion, extent/size, depth/tissue loss, infection and sensation).

**MEDICAL AND SURGICAL MANAGEMENT**[53]

**A Baseline Approach in Managing the Acute Problem of the Diabetic Foot**

1. Appraise problem
    a. Careful inspection with emphasis on webspaces and back of heels.
    b. Record pulses, venous filling time, rubor
    c. Record sensation.
2. Describe lesion
3. Describe Necrotic tissue, probe sinuses with sterile probe to determine the extent of disease.
4. Culture pus for aerobic and anaerobic organisms
5. Begin broad spectrum antibiotic until appropriate antibiotics can be given according to culture and sensitivity.
6. Medical Management of Diabetes — Blood sugar monitoring and anti diabetic measures to achieve good glycemic control, Doppler study of vessels.
7. X - ray both feet to exclude osteomyelitis.
8. No weight bearing
    a. Hospitalize with absolute bed rest when indicated.
    b. Crutches or walker when feasible.
9. Surgical Management of the Problem
    a. No soaks
    b. Antibiotics
    c. Medical Management of diabetes
    d. Dressing change atleast once daily.

e. Surgical debridement, frequently if necessary.

f. Consideration for possible arterial reconstruction

g. Drainage or open amputation.

10. Rehabilitation

a. Podiatrist for patient education, preventive maintenance orthotics, healing sandals and special shoes.

b. Nutritionist to advice on diet needs.

c. Surgeon to ensure proper wound healing and proper prosthetics

d. Physician to make final decision about diabetes management.

e. Psychiatrist to return to normal activity.

**Principles of Medical Management**

1. Pus from ulcers sent for culture and sensitivity.
2. Careful monitoring of the blood glucose levels.
3. Appropriate antidiabetic measures either insulin preparations or oral hypoglycemic drugs.
4. Broad spectrum antibiotics to be started at the onset and change over to other antibiotics depending on the culture and sensitivity report.
5. Patients with limb threatening infections require hospitalization. It is most prudent initially to administer antibiotics parenterally to ensure adequate serum levels.

**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 involved areas.
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.

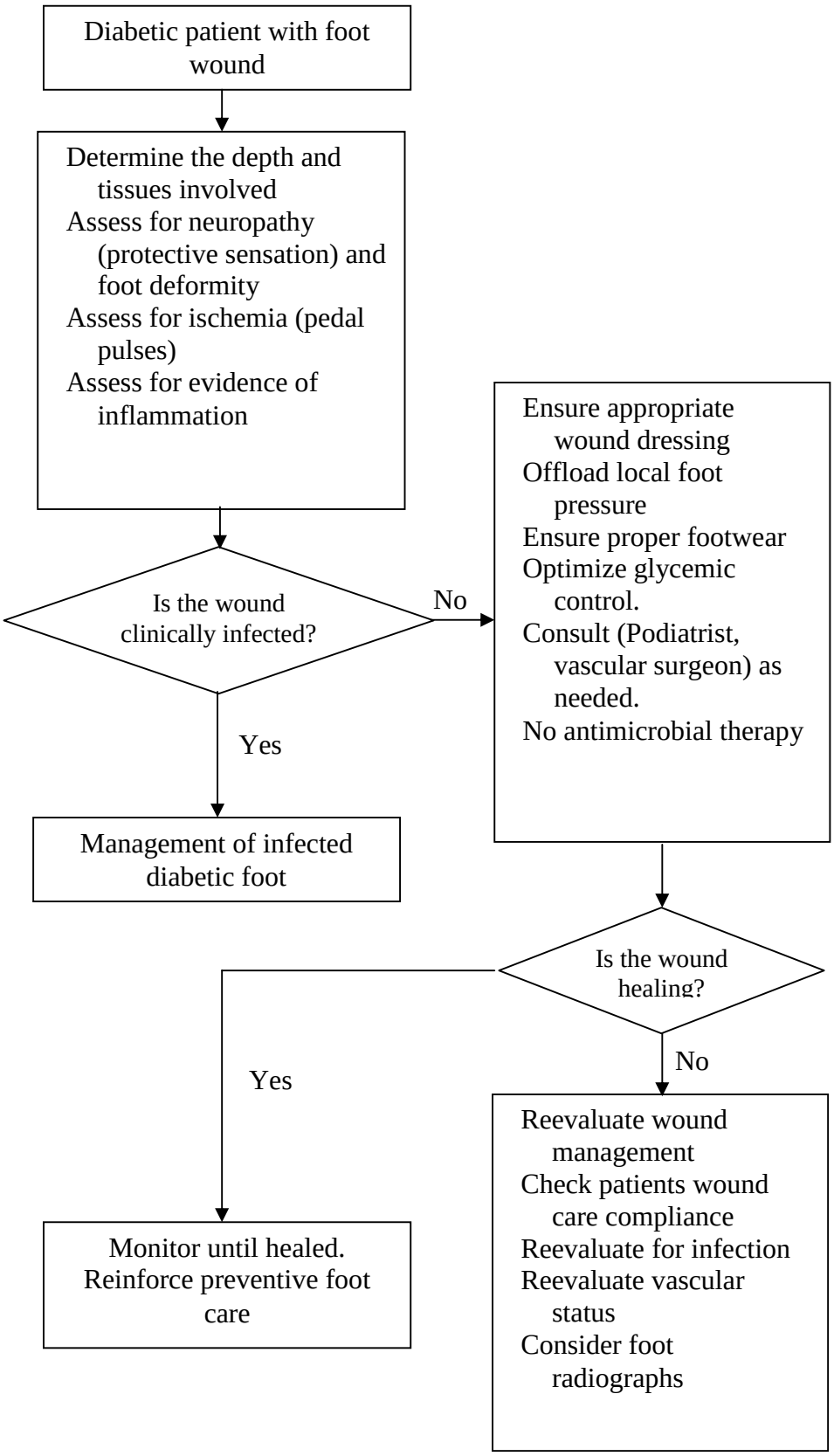



**Figure 7. Approach to treating a patient with diabetic foot wound**[51]

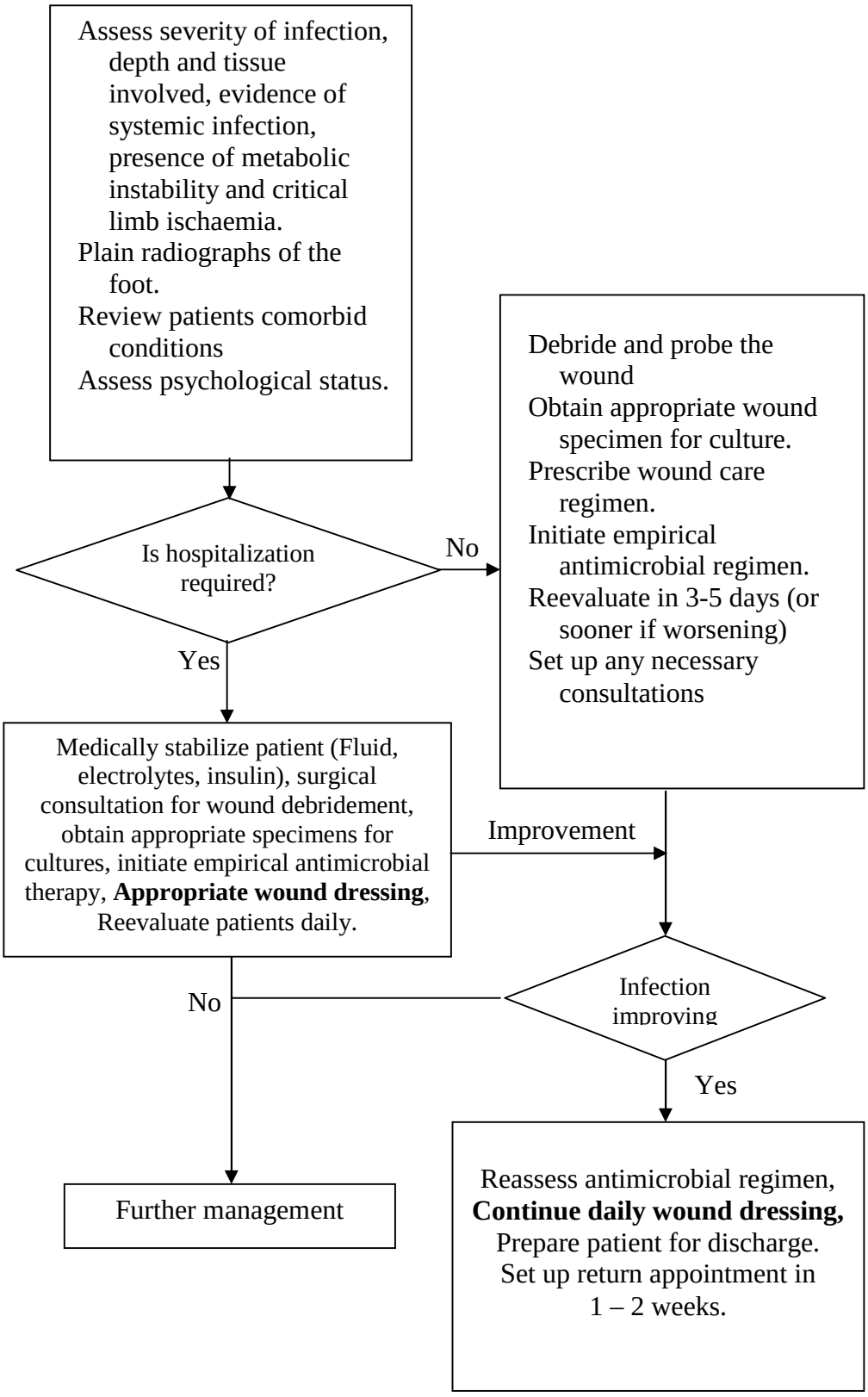



**Figure 8. Approach to the management of infected diabetic foot**[51]

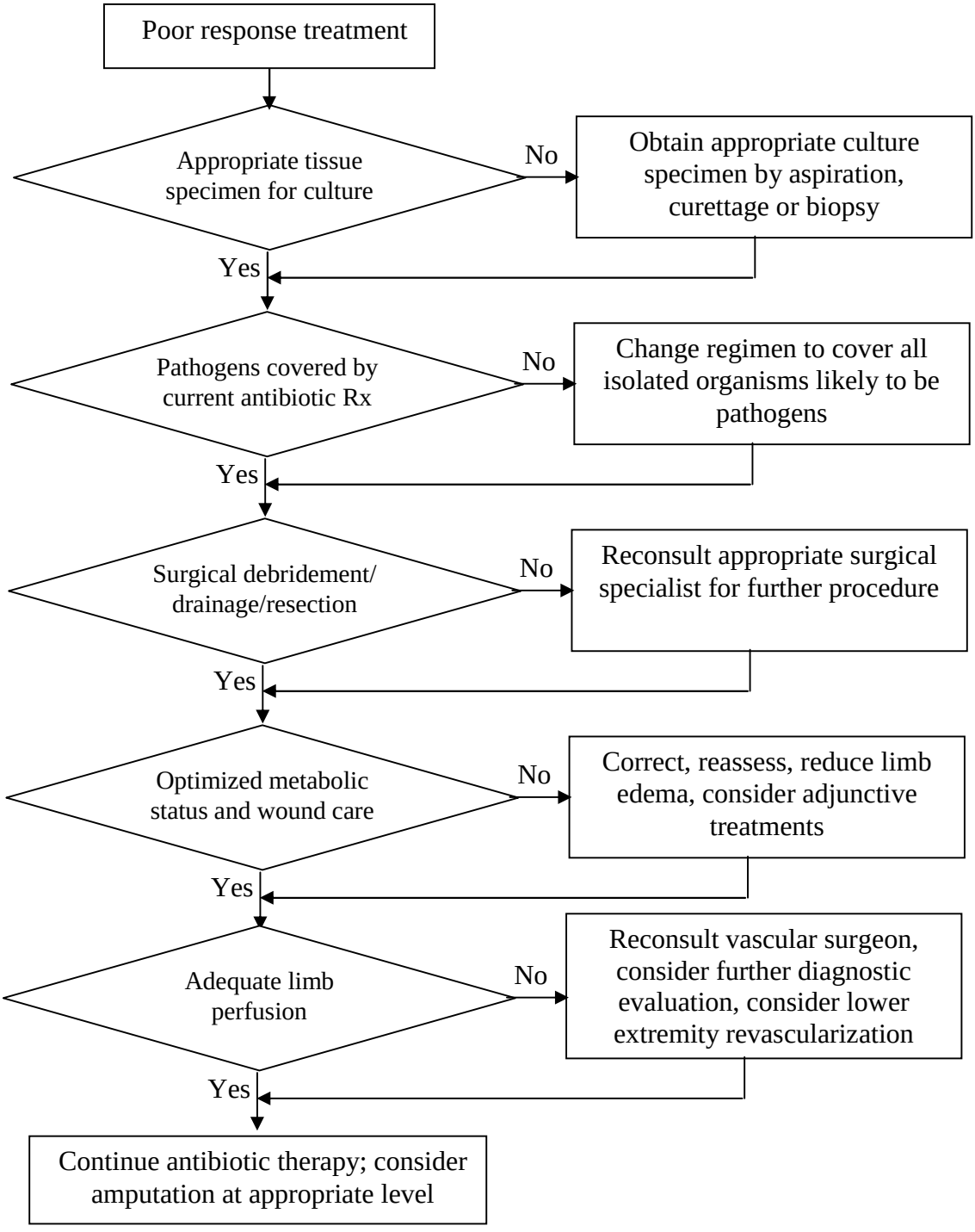



**Figure 9. Approach to the patient of infected diabetic foot not responding to the treatment**[51]

**Wound care management**

Historical aspects

The earliest documentation concerning wound management is found in the Papyrus Ebers, which dates from around BC 1500 indicating crude treatments based on oiled frog skins, honey, lint and animal grease were commonly used by the Egyptians as wound coverings. An early Hindu document, the Susrutu Sanhita reported skin grafts being used as early as BC 700. Jeter and Tintle report that spider webs, new-born puppies boiled in oil of white lilies, and red-hot pokers to cauterize wounds have been used at various times throughout history. George states that the Sumerians were the first to fashion occlusive dressings, which are capable of maintaining a moist environment, using clay.[54]

In the 19th century, Pasteur advocated that wounds should be covered and kept dry because he believed this would keep them 'germ' free. The dressings developed at this time, made from cloth, cotton and gauze, have dominated wound management in recent history and in some countries they continue to be the main products used. The first manufactured dressings were probably Gamgee wadding and tulle gras. Gamgee discovered that degreased cotton wrapped in bleached lint would absorb fluids, and he introduced his first dressing in the 19th century. During the 1914-18 war, Lumiere in France developed a cotton gauze that was impregnated with paraffin to prevent the dressing sticking to the wound. Wound management technology did not progress significantly beyond these early developments until the 1960s, when comparisons were made of wound healing in dry and moist environments. Although initial attempts were made to only alter the moisture at the

surface of a wound, researchers are now investigating the whole wound healing process in order to establish what factors impede wound healing and what characteristics of the environment could be manipulated to accelerate healing.[54]

Physiology of wound healing

When the skin is wounded, a complex series of cellular and chemical events are initiated which act on the damaged tissues – blood vessels, dermis, and epidermis. Wounds that results in limited tissue loss, such as surgical wounds, have a tendency to heal rapidly on the surface as opposing edges of the wound are in close proximity for cellular and structural repair. The wound is healed in about a week, but will continue to mature for a year or more. During this time the structural architecture of the wound changes, the scar usually flattens, and the skin regains most of its pre-wound tensile strength.[54]

In wounds where significant tissue loss occurs the damaged edges are usually unsuitable for primary closure. In this case, the tissue defect must be made up before the wound can heal. To facilitate healing, dressings are applied to try to protect the wound from contamination and keep the wound surface moist to maintain the integrity of the cells present in the defect. In a dry wound environment, dividing cells at the wound edges are unable to migrate into those areas occupied by dry scab material.[54]

Chronic wound occurs where healing is protracted as a result of significant tissue loss (as in deep pressure sores) or due to underlying pathology (venous leg ulcers). Although not initially chronic in nature, both surgical wounds and pilonidal sinuses can develop into chronic wounds if they fail to heal by primary intention.

Wound healing process

The biological mechanism associated with wound healing is complex and still not well understood. Although there is much to learn about the detail of the processes involved, some of the general concepts of healing are understood.[55]

Chronic open wounds, such as leg ulcers and pressure sores, heal by secondary intention or granulation, rather than primary intention (the means by which a surgical incision heals). Platelet aggregation during haemostasis liberates a number of soluble mediators, including platelet-derived growth factor, which initiate the healing process.[55]

Haemostasis is followed by an early inflammatory phase that is characterised by vasodilatation, increased capillary permeability, complement activation and polymorphonuclear (PMN) and macrophage migration into the wound.[55]

PMNs predominate during the first days of post wound occurrence, with the macrophage becoming the predominant inflammatory cell within 3 days. Macrophages are large, mobile and actively phagocytic, engulfing bacteria and devitalized tissue and acting effectively as the body's own debridement system. Additionally, macrophages are considered to play a key role in regulating subsequent events in the healing process. This is achieved by secretion of a number of factors that regulate their own and other cell functions. These factors are responsible for the chemotactic attraction of more macrophages and the migration and induction of proliferation by fibroblasts and endothelial cells. The increasing number of fibroblasts and endothelial cells forming granulation tissue around the fifth day post-injury heralds the 'proliferative phase'.[55]

Fibroblasts are the 'factory cells' of the wound healing module. They are rich in mitochondria, endoplasmic reticulum, and Golgi apparatus essential for protein synthesis. Fibroblasts synthesize collagen and ground substance (proteoglycans and fibronectin), which support new cells, and the fragile capillary buds, which appear around this time (angiogenesis). The endothelial buds become canalised, and are thus able to increase the vascularity and hence oxygen tension of the new tissue, so responding to the large metabolic demand of tissue repair. Epithelialisation requires the migration of epithelial cells across the granulation tissue, to close the epidermal defect.[55]

Collagen synthesis continues for many months after wound closure, but also undergoes continous lysis, so a delicate balance exists between the two processes. This final remodelling phase, accompanied by increasing tensile strength of the wound, and a decreasing cellularity, may continue for up to a year.[55]

Little research has been carried out to investigate the differences between acute and chronic wounds, though this comparison is now becoming the focus of recent work. Most studies of the wound healing process have been undertaken on acute wounds, usually in experimental animals. How closely the healing of a chronic wound follows the healing pattern of an acute wound is not clear. The question of what makes a chronic wound 'chronic' has yet to be answered.[56]

The healing process is considered to be regulated by cytokines and growth factors, and recent studies have demonstrated that the cytokine environment in a healing chronic wound is different from that in a non-healing wound.[57] However, the precise nature of the defect(s) leading to non-healing remain to be defined.

Moisture and wound healing

In 1962, Winter [58] published his seminal text on the effect of occlusion on wound healing. Winter made experimental wounds in Large-White pigs, and covered half with occlusive film and left the other half exposed to the air. The occluded, and hence moist wounds, had an epithelialisation rate twice that of those left to form a scab. Experimental, acute wounds in humans and animals appear to heal more rapidly in a moist environment. The relevance of this to chronic, pathological wounds is unclear.

Role of oxygen in wound healing

Oxygen is essential for cell metabolism, and demand is increased by synthetic processes such as those occurring during wound healing. Shortly after injury, the oxygen tension in a wound falls, so that by day 3, the $pO_2$ in the dead space of a wound is below 10 mmHg. This fall in oxygen tension is accompanied by an increase in the concentration of $CO_2$, and a fall in pH. A low $pO_2$ provides optimal conditions for fibroblast regeneration, possibly stimulating the process and increasing the rate of advance of granulation tissue.[54]

The concept that hypoxia stimulates healing was further supported by Knighton and co-workers[59] who demonstrated a positive relationship between a steep oxygen gradient between capillaries and hypoxic tissue, and angiogenesis.

pH and wound healing

Few studies have examined the effect of pH on wound healing. In 1973, Leveen[60] demonstrated that the acidification of wound surfaces increased healing.

Varghese and co-workers[61] found wound fluid to be more acidic under a Granuflex dressing than under an Opsite dressing, the more acidic pH being compatible with *in vitro* antibacterial activity. However, there are no high-quality randomized controlled trials (RCTs) examining the effects of wound pH on ulcer healing.

Micro-organisms and ulcer healing

The effect of micro-organisms on ulcer healing remains an area of intense debate. That chronic wounds are usually colonised by bacteria is accepted, and an important distinction should be made between colonisation and infection. Infection is characterised by the stigmata of pain, inflammation, purulent exudates and heat by the more objective measures of a PMN response and tissue concentrations of organisms in excess of $10^5$/g. The effect of occlusive dressings on infection rates is controversial.[54]

Local treatment

Uncontrolled diabetes affects infection and infection adversely affects diabetes. The basic rules in treating any foot infection are;[54]

1. Absolute bed rest
2. Regulation of diabetes
3. Adequate culturing of wound
4. Administration of appropriate antibiotics
5. Adequate drainage of all infection
6. Appropriate wound care.

*Drainage*

Drainage means opening all abscesses, probing carefully and laying open all sinus tracts, debriding all necrotic tissue and providing unhindered dependent drainage of pus in the resting foot. The pus must drain down and out. Gas in the tissues can often be felt as crepitus or may be the first detected on x-ray film. This is a serious finding and must be treated immediately by open drainage of all infected spaces and prompt intravenous antibiotics.[54]

Drainage of an infected area may involve amputation of a necrotic toe or toes or even an open amputation. Such amputations are drainage procedures primarily. The avascular joints tolerate infection, badly and ultimately the infected joints in the toes and the feet have to be removed. When an infected area has been enclosed, it is important to plan and attempt to salvage tissue for a possible definitive wound closure.[54]

*Dressings*

Most foot infections do not require extensive incisions and debridement, yet the principles must always be remembered. Dressings are used to serve the following purposes.[54]

1. Contain wound drainage.
2. Debride a wound
3. Protect an area from trauma
4. Protect an area from contamination
5. Promote proper wound healing

The basic equipment necessary for bedside foot care is

1. Sterile debridement set containing
    a. Sharp scissors for debriding
    b. Blunt ended needle wound probe
    c. Smooth forceps
2. Sterile toenail clippers
3. Sterile guaze dressings
4. Tube guaze, paper tape, culture tubes
5. Medicines
    a. Povidone iodine 2.5% - Bactericidal
    b. Dakin's solution (chlorazene 0.25%)
    c. Bacitracin ointment — antibacterial
    d. Vaseline guaze
    e. Normal saline

Patients suffering from diabetic foot ulcers need special care. Infection of the diabetic ulcer can have serious consequences. The challenges in treating diabetic foot ulcers includes prolonged hospital stay, high morbidities, medical expenses and sometime leads to lower limb amputation. Dressing is one of the important part of the treatment of the diabetic ulcer. The types of wound dressing used in diabetic foot ulcer are;[54]

1. Conventional dressing
    a. Gauze dressing
2. Modern wound dressing (Occlusive / moist wound dressing)
    a. Alginate Dressings
    b. Amorphous hydrogels

c. Hydrogel Dressings

d. Hydrocolloid Dressings

e. Composite Dressings

f. Transparent Films

Normal wound healing processes require restoration of epithelisation and collagen formation. The first occurs by migration and proliferation of keratinocytes from the wound edges and by differentiation of stem cells from remaining hair follicle bulbs. The second occurs by influx of growth factors secreted by macrophages, platelets and fibroblasts, by fibroblast proliferation and subsequent synthesis and remodelling of collagen dermal matrix. However, in the case of full-thickness burn injuries and chronic wounds such as pressure ulcers, venous ulcers and diabetic foot ulcers these processes are damaged and new technologies have been developed to improve the healing in these conditions.[62]

The time it takes for a chronic wound to heal varies due to the idiosyncratic nature of each wound and inherent complex factors, which may impede healing. Infection, poor blood supply, immobility, diabetes, medicines, inadequate hydration and nutrition, trauma and poor wound management are causative or contributory factors. Tissue repair research and advances in moist wound healing pharmaceuticals have been pivotal in improving wound dressing technology.[62]

Clinical experience suggests that wound healing is often impaired in the elderly. The elderly have a high prevalence of chronic leg and pressure ulcers and are vulnerable to skin tears that can be slow to heal due to decreased dermal

thickness and the loss of proliferative capacity of the ageing dermis. Chronic wounds represent a significant burden in human and economic costs.[62]

Choosing the appropriate dressing

The decision-making process to select the most appropriate dressing for the treatment of a wound can be complicated and clarity concerning dressing form and function is often a further challenge.[63]

Prior to dressing selection it is important to identify the purpose or principal aim of the proposed treatment. Dressing selection is only one part of a holistic wound management plan with individualized patient goals. It is necessary to assess the whole patient, diagnose underlying disease pathology and assess the patient's concerns before assessing the wound and choosing the dressing.[62]

Effective wound management is not only about the availability and use of new dressings, it requires an understanding of the process of tissue repair and the knowledge of the properties of the dressings available.[62]

Dressings:

Wound management has seen many changes over the past few decades. A myriad of dressings have been applied to wounds since ancient times. The list of naturally occurring materials include spider webs, dung from various animals and insects, leaves, tree bark, honey, vinegar, beer and wine. The 20$^{th}$ century has seen a revolution in wound management. Moist wound healing principles are based on pioneering work by Winter in 1962 and a year later by Hinman and Maibach.[62]

As research and understanding improves at the cellular level we are better able to assist the body not only by covering the wound to protect it but also by providing wound dressings to aid the healing process. Wound dressings can be divided into two broad groups: inert/passive and interactive/bioactive. Inert dressings can be sub classified into absorbing and non- absorbing and interactive dressings as absorbing, non-absorbing and moisture donating. The interactive group has six different dressing types.[62]

Inert/Passive Dressings

For many years the dressings used were of the 'passive' or the 'plug and conceal' concept including gauze, lint, nonstick and tulle. They fulfill very few of the properties of an ideal dressing and have very limited use as primary dressings, but some are useful as secondary dressings. In addition to gauze, lint and cotton dressings, other simple modified absorbent pads covered with a perforated plastic film to prevent adhering to a wound such as Melolin, Cutilin and Telfa are used as primary and secondary dressings. They are used in minimal and low- exudating wounds.[62]

Exudry, a modern inert dressing, has a highly absorbent pad and a nonstick non-shear surface. It can be used as secondary dressing over moderate to highly exudating wounds and over hydrocolloid paste, cadexomer iodine, alginate and other primary dressings. Tulle/paraffin gauze dressings are among the earliest modern dressings. Many variations have been developed over the years by changing the loading of paraffin in the base. These dressings produce a waterproof paraffin cover over the wound, but this may lead to maceration as the water vapour and exudation

may not pass through and be trapped within the wound. These dressings are permeable to bacteria, may adhere to the wound and in some cases may cause trauma on removal and will require a secondary dressing. Use is limited to simple clean superficial wounds and minor burns. They are also used as a primary dressing over skin grafts. There are modern alternative dressings composed of synthetic fibres tightly meshed and impregnated with materials that allow moisture to pass through and thus minimize any maceration of the wound and tissues, e.g. Adaptic, Cuticerin, Atrauman.[64]

First-Line Interactive/Bioactive Dressings

Interactive/bioactive dressings alter the wound environment and interact with the wound surface to optimize healing. The ability to provide a moist, conducive environment for improved healing when compared with traditional passive dressings has meant that new dressing technologies are a better alternative. Interactive dressings use the environment provided by the body to encourage normal healing and stimulate the healing cascade. The first-line dressings are more readily available in acute, subacute and community settings. Other more advanced dressings may be used when the first-line films, foams, alginates, hydrocolloids, hydroactives, and hydrogels are unsuitable or have not achieved successful healing.[62]

*Semi-Permeable Film Dressings*

Film dressings are adhesive, thin transparent polyurethane, which are permeable to gas but impermeable to liquid and bacteria. Films are elastic, conformable and transparent allowing inspection of the wound. As films are non-absorbent they are not suitable for exudating wounds although island dressings with

a central nonstick pad are available and can absorb slightly more exudates that the simple films. Films can also be used as secondary dressings to waterproof a primary dressing such as foam. Incorrect removal of film dressings may cause trauma to surrounding skin.[62]

*Foam Dressings*

Foam dressings are made from polyurethane, which may in some cases have been heat-treated on one side to create a semi-permeable membrane. This allows the passage of exudates through the non-adherent, semi-permeable surface into the insulating foam. Foams are available in sheets or cavity filling shapes. Foams have several advantages they are highly absorbent, cushioning and protective, insulate and conform well to body surfaces. Foams facilitate a moist wound environment and absorb excess exudates to decrease the risk of maceration. Foam dressings are also available with charcoal impregnation for malodorous wounds. Depending on the level of exudates, foams can be left in place for up to seven days.[62]

Foam wound cavity dressings reduce dead space in the wound, conform to wound shape and absorb large amounts of exudates, therefore reducing the need for frequent dressing changes although cavity foam dressings require secondary dressings and that adds to cost. Foams are generally non- adhesive and require a secondary dressing or tape/bandage to keep in place. Care is needed when adhesives are used to fix dressings in the elderly, as their skin is often fragile and prone to breakdown. Tubular retention bandages to fix dressing in place are a safer option in the elderly.[62]

*Alginate Dressings*

Alginates (calcium or calcium/sodium) are highly absorbent, biodegradable dressings derived from seaweed. An active ion exchange of calcium ions for sodium ions at the wound surface forms soluble sodium alginate gel that provides a moist wound environment. Calcium dressings need moisture/exudate from the wound to function, therefore they are not suitable for dry wounds or wounds with hardened eschar. The fibrous nature of most alginates can leave residual fibres in the wound if there is insufficient wound exudate to gel the fibres. This may precipitate an inflammatory reaction as it stimulates a foreign body response. Caution is also needed when using alginate rope dressings in very deep or narrow sinuses, as complete removal can be difficult. Studies have shown that some calcium alginate dressings promote haemostasis in bleeding wounds due to the active release of calcium ions that aid the clotting mechanism.[65] Alginate dressings are available in sheet, ribbon or rope form in various sizes and require a secondary dressing.

*Hydrocolloid Dressings*

Hydrocolloids are moisture-retentive dressings, which contain gel-forming agents such as sodium carboxymethyl cellulose and gelatin. Many dressings combine the gel-forming properties with elastomers and adhesives which are applied to a carrier such as foam or film to form an absorbent, self-adhesive, waterproof wafer. In the presence of wound exudates, hydrocolloids absorb liquid and form a gel, the properties of which are determined by the nature of the formulation. In sheet form the polymer outer layer can be either semi-occlusive or occlusive. Hydrocolloid interaction debride by autolysis and can reduce dressing frequency to

up to seven days wear time depending on the amount of exudates and the type of hydrocolloid dressing.[62]

Hydrocolloids are also available in paste and powders for increased absorption and to decrease dead space in the wound cavity. Generally, hydrocolloids with a waterproof backing are not recommended on clinically infected wounds due to the semi-occlusive nature of the dressing. There have been reports of hypergranulation with prolonged use of hydrocolloids in moderate to highly exudating wounds so wound tissue assessment is paramount when applying hydrocolloids for long periods. Hydrocolloids should be discontinued before hypergranulation occurs.[62]

Hydrogel Dressings As the name implies, hydrogels are designed to hydrate wounds, rehydrate eschar and aid in autolytic debridement. Hydrogels are insoluble polymers that expand in water and are available in sheet, amorphous gel or sheet hydrogel-impregnated dressings. They provide a moist environment for cell migration and absorb some exudate. Autolytic debridement without harm to granulation or epithelial cells is another advantage of hydrogel dressings. Hydrogels have marked cooling and soothing effect on the skin, which is valuable in burns and painful wounds. The viscosity varies between dressings. Purilon and IntraSite are two of the thickest gels available which helps them stay in the cavity of the wound. Solugel and Solosite are two of the thinnest, allowing easy spread over a large area. Some amorphous gels contain propylene glycol that can cause allergic reactions in elderly skin. Amorphous hydrogels are applied liberally onto or into a wound and covered with a secondary dressing such as foam or film. Hydrogels can remain in situ for up to three days. For easy removal of hydrogels the wound is irrigated. In

addition to their use in wounds the thin hydrogels are helpful in the management of lesions such as chicken pox and shingles.[62]

*Hydroactive Dressings*

These multilayered highly absorbent polymer dressings, some with a surface adhesive and a waterproof outer layer, are similar to hydrocolloids. However, instead of forming a gel in contact with exudates, the fluid is trapped within the dressing, to maintain a moist environment.[62]

**Collagen granule dressing**

Proteins are natural polymers and make up almost 15% of the human body. The building blocks of all proteins are amino acids. Collagen is the major protein of the extracellular matrix (ECM) and is the most abundant protein found in mammals, comprising 25% of the total protein and 70% to 80% of skin (dry weight). Collagen acts as a structural scaffold in tissues. The central feature of all collagen molecules is their stiff, triple-stranded helical structure. Types I, II, and III are the main types of collagen found in connective tissue and constitute 90% of all collagen in the body.[66]

Function of Collagen in Wound Healing

Previously, collagens were thought to function only as a structural support; however, it is now evident that collagen and collagen-derived fragments control many cellular functions, including cell shape and differentiation, migration and synthesis of a number of proteins. Findings suggest that cell contact with precise extracellular matrix molecules influence cell behavior by regulating the quantity and quality of matrix deposition. Type I collagen is the most abundant structural

component of the dermal matrix; migrating keratinocytes likely interact with this protein. Collagenase (via formation of gelatin) may aid in dissociating keratinocytes from collagen-rich matrix and thereby promote efficient migration over the dermal and provisional matrices. Cellular functions are regulated by the ECM. The information provided by ECM macromolecules is processed and transduced into the cells by specialized cell surface receptors.[66]

Evidence demonstrates that the receptors play a major function in contraction of wounds, migration of epithelial cells, collagen deposition, and induction of matrix-degrading collagenase. Although keratinocytes will adhere to denatured collagen (gelatin), collagenase production is not turned on in response to this substrate. Keratinocytes have been known to recognize and migrate on Type I collagen substratum, resulting in enhanced collagenase production. Collagen plays a key role in each phase of wound healing.[66]

Hemostasis (Duration = Minutes).

Platelets aggregate around exposed collagen. Platelets then secrete factors, which interact with and stimulate the intrinsic clotting cascade, which strengthens the platelet aggregate into a stable hemostatic "plug." Blood platelets also release αa-granules, which release a variety of growth factors (GFs) and cytokines, such as platelet derived GF (PDGF), insulin-like GF (IGF-1), epidermal GF (EGF), and transforming GF-beta (TGF-b), which "call" a variety of inflammatory cells (neutrophils, eosinophils, and monocytes) to the wound site and initiate the inflammatory phase.[66]

Inflammation (Duration = Days).

Proteolytic enzymes are secreted by inflammatory cells that migrate to wound sites, notably neutrophils, eosinophils, and macrophages. The action of proteolytic enzymes on the macromolecular constituents of the ECM (such as collagen) gives rise to many peptides (protein fragments) during wound healing. These degradation products have a chemotactic effect in the recruitment of other cells, such as mononuclear cells, additional neutrophils, and macrophages. Activated macrophages secrete TNF-a, which among other things, induces macrophages to produce IL-1b. IL-1bβ is mitogenic for fibroblast and up-regulates matrix metalloproteinase (MMP) expression. TNF-α and IL-1bβ are key pro-inflammatory cytokines, which directly influence deposition of collagen in the wound by inducing synthesis of collagen via fibroblasts and down regulation of tissue inhibitors of matrix metalloproteinases (TIMPs). Inflammatory cells also secrete growth factors including TGF-b, TGF-b, bHB-EGF, and bFGF.[67]

These GFs continue to stimulate migration of fibroblasts, epithelial cells and vascular endothelial cells into the wound. As a result, the cellularity of the wound increases. This begins the proliferative phase.[66]

Proliferation (Duration = Weeks).

Cleavage products resulting from collagen degradation stimulate fibroblast proliferation. Fibroblasts secrete a variety of GFs (IGF-1, bFGF, TGF-b, PDGF, and KGF), which guide the formation of the ECM. The collagen cleavage products also stimulate vascular endothelial cell proliferation. These cells secrete a variety of GFs (VEGF, βFGF, PDGF), which promote angiogenesis. With a vascularized ECM,

granulation is achieved. Collagen cleavage products also stimulate keratinocyte migration and proliferation. Keratinocytes secrete a variety of GFs and cytokines, such as TGF-b, TGF-b, and IL-1. As keratinocytes migrate from the edge of the wound across the newly formed granulation tissue, re-epithelization is achieved.[12]

Remodeling (Duration = 1 Year +).

A balance is reached between the synthesis of new components of the scar matrix and their degradation by MMPs, such as collagenase, gelatinase, and stromelysin. Fibroblasts are the major cell type that synthesizes collagen, elastin, and proteoglycans. They are also the major source of MMPs and TIMPs. In addition, they secrete lysyl oxidase, which cross-links components of the ECM. Angiogenesis ceases and the density of capillaries in the wound site decreases as the scar matures. The result is the creation of a stronger scar, though the skin only regains almost 75% of its original tensile strength.[66]

The epidermis is the upper layer of the skin and provides the first barrier of protection from the invasion of foreign substances into the body. The principal cell of the epidermis is called keratinocyte. The dermis (the layer just below the epidermis) assumes the important functions of the thermoregulation and supports the vascular network to supply the avascular epidermis with nutrients. The dermis contains mostly fibroblasts, which are responsible for secreting collagen, elastin, and ground substance that give support and elasticity to the skin. Immune cells are also present and defend against foreign invaders that pass through the epidermis. The hypodermis, also called the hypoderm, subcutaneous tissue, or superficial fascia, is the lowest layer of the skin. Types of cells found in the hypodermis are fibroblasts,

adipose (fat) cells, and macrophages. Upon injury, a series of biochemical events are initiated. These activities are generally grouped into 4 overlapping phases (hemostasis, inflammation, proliferation, and remodeling).[66]

This shows the wound bed and key cells involved in wound healing. The macrophage (green-colored cells) is just one of the inflammatory cells involved. Initially, macrophages act to remove the cell debris and bacteria. However, macrophages also secrete cytokines and growth factors, which guide the wound through the inflammatory phase into the proliferative phase. Endothalial cells (tan-colored cells) create new blood vessels. Fibroblasts are depicted here as the purple colored cells. Collagen is also a key component of the extracellular matrix (ECM). Fribroblasts secrete matrix metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs), and glycosaminoglyacans (GAGs). Glycosaminoglyacans bind with water to create a gel medium, which aids in cell movement.[66]

Macrophages have secreted pro-inflammatory cytokines (eg, TNF-α and IL-1β), which have signaled the fibroblasts to secrete MMPs (the orange colored cells), TIMPs (purpe-colored cells), and GAGs. The MMPs are degrading the nonviable collagen in order to prepare the wound bed for granulation. The degradation products are chemotactic agents, which stimuate migration of fribroblasts, epithelial cells, and vascular endothelial cells in the wound. TIMPs inhibit MMPs to a certain extent to assure the level of activity of the MMPs remains at the optimal level for wound healing.[66]

Fibroblasts have secreted new fibrous proteins, such as collagen and GAGs. The fibrous proteins act as a scaffold upon which cells can migrate. Glycosaminoglycans and the fibrous proteins make up the ECM. In addition, endothelial cells are creating new capillaries. Thus the cells in the wound bed have created ciable granulation tissue. Keratinocytes (epidermal cells) will also start migrating from the wound edge.[66]

A layer of keratinocytes has moved across the viable granulation tissue initiating re-epithelization. Re-epithelization will continue until the epidermis is full. The next phase of healing is the remodeling phase; wherein, fibroblasts will remodel and cross-link the collagen fibers to make a stronger scar.[66]

The Role of MMPs in Wound Chronicity

Wound bed preparation (WBP) can be described as the management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures.[68,69]

The 4 basic aspects of WBP can be represented by the acronym: TIME. T = tissue (nonviable or deficient); I = infection or inflammation; M = moisture control; E = epidermal margin.[70]

Focusing on the "E" in TIME, collagen dressings possess properties, which lend themselves to creating a wound environment favorable to the migration of cells from the epidermal margin across granulation tissue, encouraging wound closure. Due to a number of potential stimuli (local tissue ischemia, bioburden, necrotic tissue, repeated trauma, etc.), the wound has stalled in the inflammatory phase contributing to the chronicity of the wound. As a result of the aforementioned pro-

inflammatory stimuli, the wound is over stimulated and inflammatory cells, such as macrophages, are present in higher numbers and are more active than they typically would be in an acute wound. In addition, the cells, such as fibroblasts and endothelial cells, are senescent and unable to function properly as they would in an acute wound. With the overabundance of macrophages, there is an overabundance of key pro-inflammatory cytokines, such as TNF-b and IL-1b, secreted by the macrophages. These pro-inflammatory cytokines signal the fibroblasts to secrete MMPs, but due to the overabundance of pro-inflammatory cytokines the fibroblasts secrete elevated levels of MMPs.[66]

At this level, MMPs not only degrade nonviable collagen, but also viable collagen laid down by the fibroblasts themselves. Additionally, the fibroblasts are unable to secrete tissue inhibitors of MMPs (TIMPs) at an adequate level to control the activity of the MMPs. These events prevent the formation of the scaffold needed for cell migration and ultimately prevent the formation of the ECM. In addition, cells in a chronic wound tend to be senescent, thus unable to communicate with other cells and unable to function properly. One result of this is a lack of endothelial cell activity slowing the formation of blood vessels. Without an adequate blood supply, tissue can die and as a result, there is an increase in wound size. All of the aforementioned phenomena impede the formation of viable granulation tissue and thus inhibit re-epithelization (ie, wound closure).[67]

One of the key contributors to wound chronicity is an overabundance (and/or activity) of MMPs in the wound; the ability to inhibit or deactivate a number of excess MMPs may help create an environment more conducive to the formation of granulation tissue, and eventual wound closure.[66]

Collagen-based Wound Dressings

There are a number of different collagen dressings available, which employ a variety of carriers/combining agents such as gels, pastes, polymers, oxidized regenerated cellulose (ORC), and ethylene diamine tetraacetic acid (EDTA). The collagen within these products tends to be derived from bovine, porcine, equine, or avian sources, which is purified in order to render it non-antigenic. The collagen in a given collagen dressing can vary in concentration and type. Certain collagen dressings are comprised of Type I (native) collagen; whereas, other collagen dressings contain denatured collagen as well. A given collagen dressing may contain ingredients, such as alginates and cellulose derivatives that can enhance absorbency, flexibility, and comfort, and help maintain a moist wound environment. Collagen dressings have a variety of pore sizes and surface areas, as well. All of these attributes are meant to enhance the wound management aspects of the dressings. Many collagen dressings contain an antimicrobial agent to control pathogens within the wound. Collagen dressings typically require a secondary dressing.[66]

Mechanism of action (MOA).

Research has shown that some collagen-based dressings produce a significant increase in the fibroblast production; have a hydrophilic property that may be important in encouraging fibroblast permeation; enhance the deposition of oriented, organized collagen fibers by attracting fibroblasts and causing a directed migration of cells; aid in the uptake and bioavailability of fibronectin; help preserve leukocytes, macrophages, fibroblasts, and epithelial cells; and assist in the maintenance of the chemical and thermostatic microenvironment of the wound.[66]

The MOA of several collagen dressings includes the inhibition or deactivation excess MMPs. As mentioned, excess MMPs are a key contributor to wound chronicity.[66]

**The role of collagen dressings in chronic wound care**

Here, a traditional collagen based wound dressing has been placed into the chronic wound. Being a chronic wound, there is an overabundance of MMPs and a decrease in the number of TIMPs. The effects of collagen-based wound dressing MMP activity. Since MMPs attack and break down collagen, a portion of them migrate toward the collagen based dressing and start to degrade it. Other cells such as fibroblasts and endothelial cells are necessary for the formation of granulation tissue. MMPs degrade collagen-based wound dressings. However, as the collagen dressing is degraded by the MMPs, it is broken down and releases active MMPs back into the wound.[66]

**The role of collagen and EDTA in chronic wound care**

Here, a collagen based wound dressing containing EDTA has been placed into the chronic wound. Being a chronic wound, there is an overabundance of MMPs and a decrease in the number of TIMPs. The effects of collagen and EDTA on MMP activity. EDTA (a chelating agent depicted here in blue) permanently deactivates a portion of the MMPs preventing them from degrading collagen, and since MMPs attack and break down collagen, a portion of them migrate toward the collagen based dressing and start to degrade it. As the collagen dressing is degraded, MMPs are released back into the wound, a portion of which has been deactivated by EDTA. MMPs degrade collagen-based wound dressings. The degradation products call in

other cells, such as fibroblasts and endothelials, necessary for the formation of granulation tissue.[66]

An overview of the role of fibroblasts and endothelial cells during granulation. As a result, the level of active MMPs is reduced to a level that allows fibroblasts to proliferate, lay down new collagen (and other fibrous proteins), and to secrete glycosaminoglycans (GAGs), resulting in a functional ECM. The collagen fragments have also activated endothelial cells to propogate and create new blood vessels. With a functional ECM and a blood supply, granulation is achieved.[66]

Overview of the role of keratinocytes in wound closure. Keratinocytes (red colored cells) from the wound margin migrate across the functional granulation tissue initiating the process of re-epithelization. Re-epithelization will continue until the epidermis is full. The next phase of healing is the remodeling phase; wherein, fibroblasts will remodel and cross-link the collagen fibers to make a stronger scar.[66]

Collagen: Native Versus Denatured

In addition to the various sources of collagen (bovine, porcine, etc.), collagen dressings can also contain different types of collagen. These types of collagens may result in unique activity in the wound bed as they have different substrate specificity. For example, Type I (native) collagen attracts MMP-1.[71]

Denatured collagen (gelatin) attracts MMP-2 and MMP-9.[72] Gelatin also attracts stromelysin and matrilysin.[72] These MMPs (among others) are found in excess in chronic wounds and contribute to a wound's chronicity (see Appendix II for a breakdown of collagen source/type per collagen dressing).[66]

Biochemistry of Collagen Types.

When a migrating cell (such as a keratinocyte) encounters Type I collagen, the cell secretes MMPs in order to denature the Type I collagen to gelatin. A critical reason for this is that once Type I collagen is converted into gelatin, many active sites (RGD sequences) are made accessible to the cells. RGD (Arg-Gly-Asp) sequences are attachment sites and are chemotactic for a variety of cells responsible for creating granulation tissue. Thus, a collagen dressing containing gelatin could provide enhanced signaling to the cells responsible for creating granulation tissue. A collagen-dressing containing only Type I collagen requires MMP-1 to initially convert collagen to gelatin, so cells in the wound must first release MMP-1 to change the Type I collagen into gelatin to get this benefit.[66]

Pore Size and Surface Area.

Pore size of collagen dressings is important to allow cells to enter the dressing and concentrate therein. In addition, surface area plays a role in managing exudates. Typically the larger the surface area, the more exudates is absorbed.[66]

**Recent studies**

A study conducted by Vaves A et al. in 2002, A randomized controlled trial, comparing the collagen dressing vs standard treatment in diabetic foot ulcers showed result that, collagen granules have wound healing property.[73]

A study conducted by Wollina U et al. in 2005 in Germany, Some effects of a topical collagen-based matrix on the microcirculation and wound healing in patients with chronic venous leg ulcers: preliminary observations; showed that

topical collagen improves microcirculation which is a key parameter of granulation tissue formation.[74]

A study conducted by Lobmann R et al in 2006 Germany, Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing showed that the local treatment with a protease inhibitor dressing/collagen dressing has a beneficial effect on wound healing.[75]

Similarly, a study by. Lazaro-Martinez JL, in 2007 Spain, Randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers, showed that protease-modulating dressings in patients with neuropathic diabetic foot ulcers leads to better tissue regeneration than good wound care.[76]

Also a study conducted by Ulrich D et al in Netherland in 2011, Effect of oxidized regenerated cellulose/collagenmatrix on proteases in wound exudates of patients with diabetic foot ulcers, showed significant reduction in protease, size and greater reduction in wound size.[77]

# METHODOLOGY

This randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period, from January 2013 to December 2013.

**Study design:** A randomized controlled trial.

**Study period and duration:** This study was performed for the duration of one year from January 2013 to December 2013.

**Place:** The present study was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum attached to KLE University's Jawaharlal Nehru Medical College, Belgaum.

**Source of Data:** Patients having diabetic foot ulcers measuring more than 1cms, with slough, foul smell and minimal granulation tissue were included in the study.

**Sample size:** The present study was comprised of 60 cases divided into two groups of 30 each.

**Sampling procedure:** Applying thumb rule, a total of 60 cases were planned for this study.

**Randomization:** The patients were divided into two groups of 30 each based on computer generated random numbers.

**Selection criteria**

Inclusion

- Patients having diabetic foot ulcers measuring more than 1cm, with slough, foul smell and minimal granulation tissue.
- Diabetic patients with age more than 20 years.
- Patients with controlled diabetes with fasting blood glucose levels less than 127 mg/dl.
- Patients with grade 1 and grade 2 of Wagners classification

Exclusion

Patients with/who have;

- Grade 3, 4, 5 Wagners classification.
- Absent peripheral pulses.
- Immunocompromised patients
- Malnourished status of patients
- Associated malignancies and metabolic disorders.

**Ethical clearance**

The study was approved from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

**Informed Consent**

The eligible patients who fulfilled the selection criteria were informed in detail about the study and a written informed consent was obtained (Annexure I).

**Method of collection of data**

The demographic data and ulcer characteristics were gathered through an interview. Patients were asked for the past history, ulcer duration, diabetic history and treatment history. Further these patients were subjected to clinical examination. The findings were noted on a predesigned and pretested proforma (Annexure II).

**Investigations**

The patients underwent following investigations.

- Complete blood count.
- Fasting blood sugar
- Culture and antibiotic sensitivity.
- Blood Urea and Serum Creatinine
- Protein levels
- X-Ray foot –AP and Lateral view.

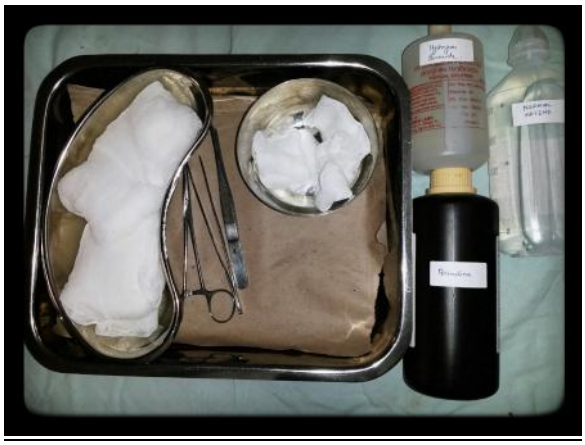
**Intervention**

The patients were divided into two groups of 30 each based on computer generated random numbers and treated accordingly.

- Group A – Patients underwent dressing with topical Collagen granules dressing.
- Group B – Patients underwent dressing with conventional dressing.


**Photograph 1. Collagen granule vial**

**Photograph 2.Dressing material for collagen granule dressing**



**Photograph 3. Dressing material for conventional dressing**

Assessment of wound

Ulcer size was assessed at the end of every second and fourth week. Ulcer mapping was made and the size recorded by superimposing a gauze over the ulcer and thus assessing the largest dimensions of the ulcer. Size was measured twice and the mean of the both measurements were considered as the size of the wound. Wound was also observed for granulation, tissue quality, discharge and control of infection at the end of second and fourth week.

**Statistical analysis**

The data obtained was coded and entered in Microsoft Excel Spreadsheet. The categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test and Fisher's exact test. Continuous data was expressed as mean ± standard deviation and the independent sample 't' test was used for comparison. A 'p' value of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

# RESULTS

The present one year randomized controlled trial was carried out under Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period, from January 2013 to December 2013. A total of 60 patients having diabetic foot ulcers measuring more than 1 cms, with slough, foul smell and minimal granulation tissue were divided into two groups of 30 each as;

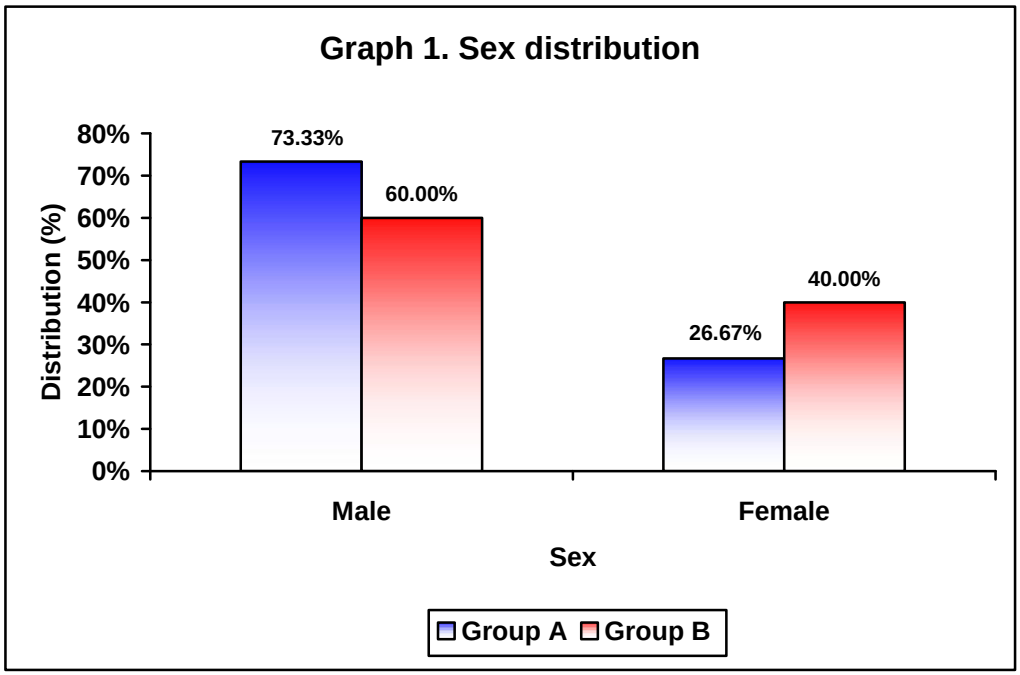
- Group A – Patients underwent dressing with topical Collagen granules dressing.
- Group B – Patients underwent dressing with conventional dressing.

The data obtained was analysed and the final results and observations were tabulated as below.

**Table 1. Sex distribution**

| Sex | Group A (n=30) | | Group B (n=30) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| Male | 22 | 73.33 | 18 | 60.00 |
| Female | 8 | 26.67 | 12 | 40.00 |
| **Total** | **30** | **100.00** | **30** | **100.00** |

**p = 0.273**

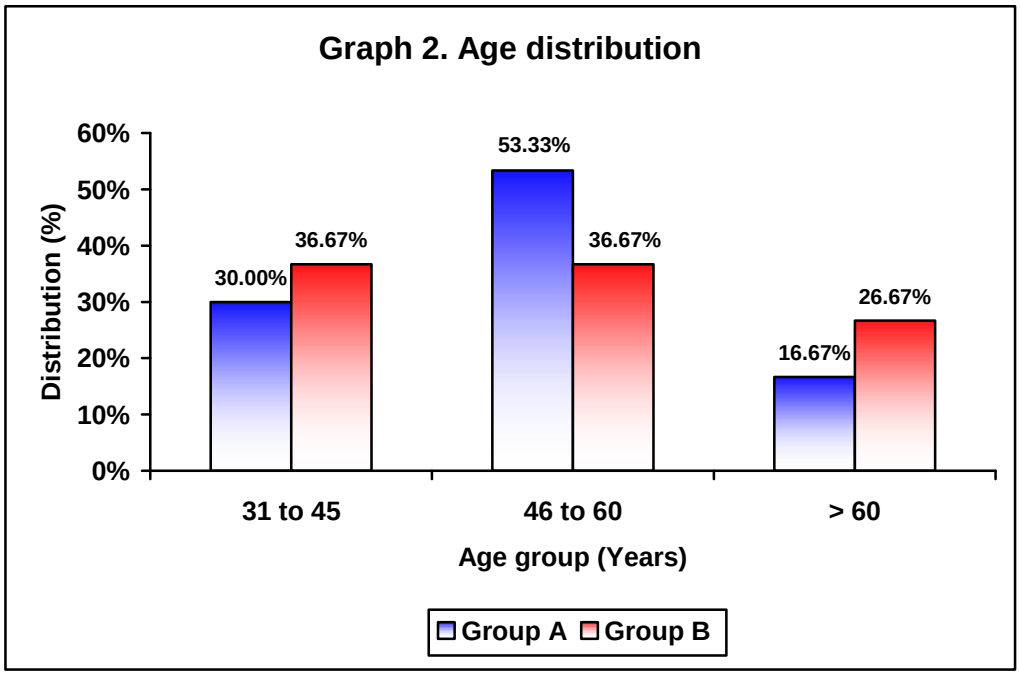



In the present study most of the patients in group A (73.33%) and group B (60%) were males. The male to female ratio in group A was 2.75:1 and in group B it was 1.5:1. However the difference was statistically not significant (p=0.273).

**Table 2. Age distribution**

| Age group (Years) | Group A (n=30) | | Group B (n=30) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| 31 to 45 | 9 | 30.00 | 11 | 36.67 |
| 46 to 60 | 16 | 53.33 | 11 | 36.67 |
| > 60 | 5 | 16.67 | 8 | 26.67 |
| **Total** | **30** | **100.00** | **30** | **100.00** |

**p = 0.403**




In this study 53.33% of the patients in group A were aged between 46 to 60 years compared to 36.37% in group B. However the difference was statistically not significant (p=0.403).

**Table 3. Mean age**

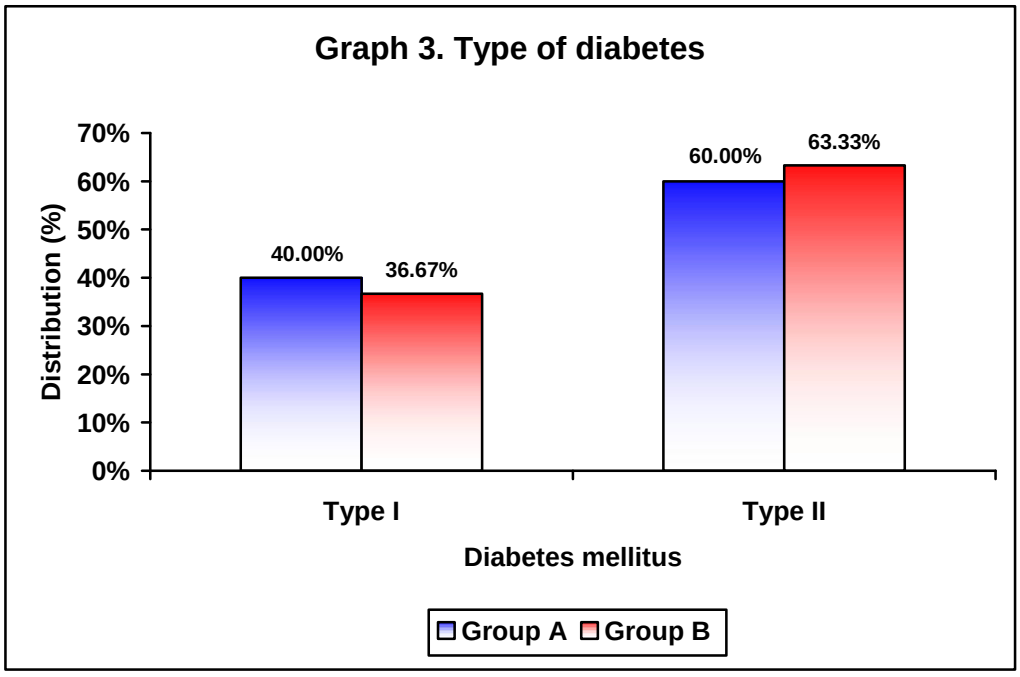
| Variables | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | |
| Age (Years) | 49.00 | 8.15 | 49.60 | 10.39 | 0.804 |

In the present study the mean age in group A was 49.00 ± 8.15 years compared to 49.60 ± 10.39 in group B but the difference was statistically not significant (p=0.804)

**Table 4. Type of diabetes**

| Diabetes mellitus | Group A (n=30) | | Group B (n=30) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| Type I | 12 | 40.00 | 11 | 36.67 |
| Type II | 18 | 60.00 | 19 | 63.33 |
| **Total** | **30** | **100.00** | **30** | **100.00** |

**p = 0.791**

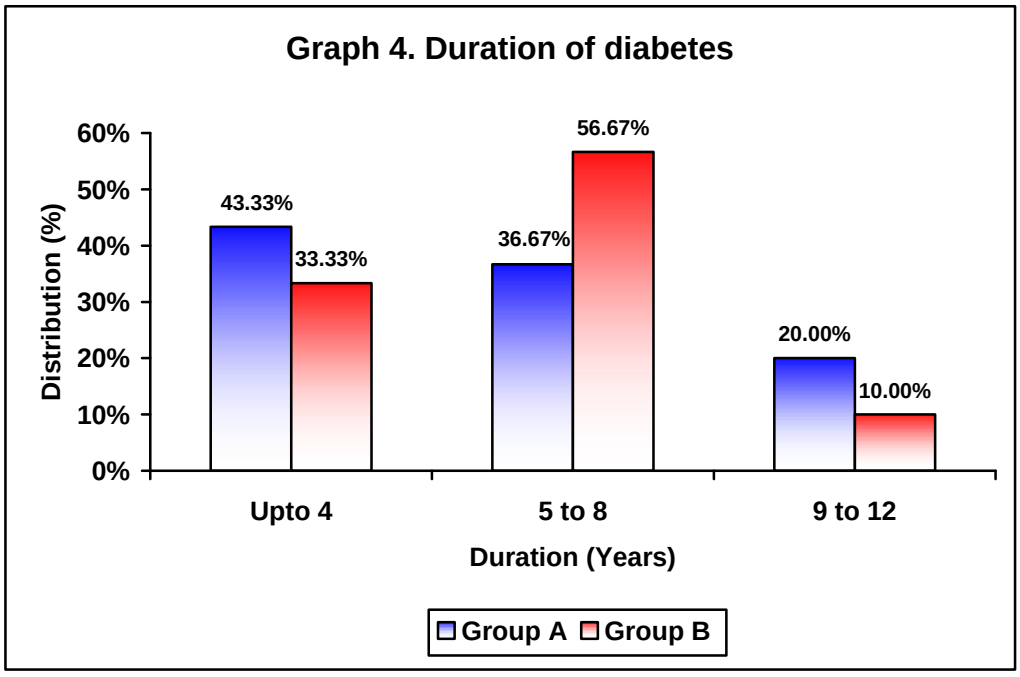



In this study most of the patients in group A and B had type II diabetes (60.00% and 63.33% respectively; p=0.791)

**Table 5. Duration of diabetes**

| Duration (years) | Group A (n=30) | | Group B (n=30) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| Upto 4 | 13 | 43.33 | 10 | 33.33 |
| 5 to 8 | 11 | 36.67 | 17 | 56.67 |
| 9 to 12 | 6 | 20.00 | 3 | 10.00 |
| **Total** | **30** | **100.00** | **30** | **100.00** |

**p = 0.282**




In the present study most of the patients (36.67%) in group A presented with a duration of diabetes between five to eight years and the same duration was noted among 56.67% of the patients in group B (p=0.282).

**Table 6. Mean duration of diabetes**

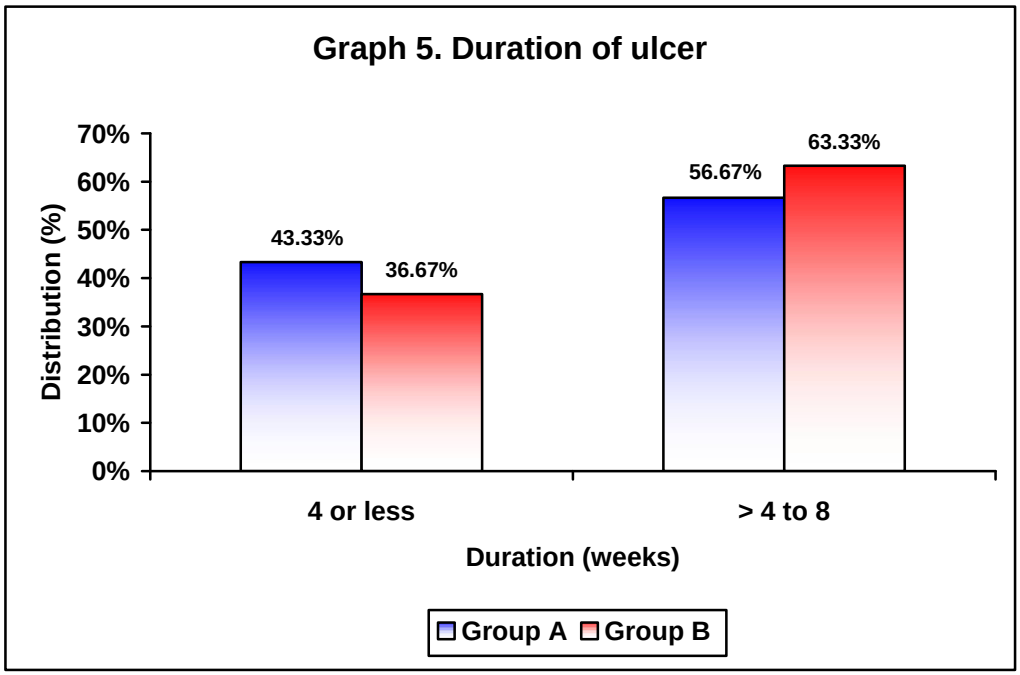
| Variables | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Duration (years) | 5.58 | 2.91 | 5.77 | 2.40 | 0.791 |

In this study the mean duration of diabetes was 5.58 ± 2.91 years in group A compared to 5.77 ± 2.40 years in group B but difference was statistically not significant (p=0.791).

**Table 7. Duration of ulcer**

| Duration (weeks) | Group A (n=30) | | Group B (n=30) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| 4 or less | 13 | 43.33 | 11 | 36.67 |
| > 4 to 8 | 17 | 56.67 | 19 | 63.33 |
| **Total** | **30** | **100.00** | **30** | **100.00** |

**p = 0.598**




In the present study most of the patients in group A (56.67%) and in group B (63.33%) presented with more than four to eight weeks duration of ulcer (p=0.598).

**Table 8. Mean duration of ulcer**

| Variables | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Duration (weeks) | 4.72 | 1.34 | 5.50 | 1.69 | 0.052 |

In this study the mean duration of ulcer was comparable in group A and B (4.72 ± 1.34 weeks vs 5.50 ± 1.69 weeks; p=0.052).

**Table 9. Mean size of ulcer**

| Variables | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Size (sq mm) | 51.83 | 17.44 | 53.60 | 18.44 | 0.704 |

In this study the mean size of ulcer in group A was found to be 51.83 ± 17.44 sq mm compared to 53.60 ± 18.44 sq. mm in group B. However this difference was statistically not significant (p=0.704).

**Table 10. Ulcer characteristics before treatment**

| Characteristics | Findings | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| **Site** | LLL | 9 | 30.00 | 12 | 40.00 | 0.289 |
| | RLL | 21 | 70.00 | 18 | 60.00 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Shape** | Irregular | 24 | 80.00 | 22 | 73.33 | 0.598 |
| | Oval | 6 | 20.00 | 8 | 26.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Discharge** | Present | 26 | 86.67 | 25 | 83.33 | 0.500 |
| | Absent | 4 | 13.33 | 5 | 16.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Slough/necrotic tissue** | Present | 24 | 80.00 | 17 | 56.67 | 0.052 |
| | Absent | 6 | 20.00 | 13 | 43.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |

The characteristics of ulcer before the treatment are as shown in Table 10. It was observed that, the ulcer characteristics site of ulcer, shape, discharge and slough / necrotic tissue were comparable between group A and B ($p>0.050$).

**Table 11. Mean fasting blood sugar levels**

| Variables | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Fasting blood sugar (mg/dL) | 178.47 | 47.00 | 172.27 | 33.27 | 0.558 |

In the present study the fasting blood sugar levels were comparable in group A and B (178.47 ± 47.00 mg/dL vs 172.27 ± 33.27 mg/dL; p=0.558).

**Table 12. Ulcer culture, organisms and sensitivity before dressing**

| Pus culture | Findings | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| **Culture** | Positive | 11 | 36.67 | 12 | 40.00 | 0.500 |
| | Negative | 19 | 63.33 | 18 | 60.00 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Organisms** | Absent | 19 | 63.33 | 18 | 60.00 | 0.798 |
| | Klebsiella | 3 | 10.00 | 3 | 10.00 | |
| | Proteus | 3 | 10.00 | 2 | 6.67 | |
| | Staph aureus | 3 | 10.00 | 6 | 20.00 | |
| | Staph epi. | 2 | 6.67 | 1 | 3.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Sensitivity** | Yes | 11 | 36.67 | 12 | 40.00 | 0.500 |
| | No | 19 | 63.33 | 18 | 60.00 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |

The ulcer characteristics before dressing are as shown in table 12. It was observed that, 36.67% of the patients in group A and 40% in group B had positive culture (p=0.500). The commonest organism in group B was staph aureus (20%) and in group A Klebsiella, proteus and staph aureus were noted in 10% of the patients each (p=0.798). Further 36.67% in of the ulcers in group A and 40% in group B were sensitive (p=0.500)

**Table 13. Ulcer culture, organisms and sensitivity after 10 days of dressing**

| Pus culture | Findings | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| **Culture** | Positive | 1 | 3.33 | 2 | 6.67 | 0.500 |
| | Negative | 29 | 96.67 | 28 | 93.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Organisms** | Absent | 29 | 96.67 | 28 | 93.33 | 0.492 |
| | Proteus | 1 | 3.33 | 0 | 0.00 | |
| | Staph aureus | 0 | 0.00 | 2 | 6.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Sensitivity** | Yes | 1 | 3.33 | 2 | 6.67 | 0.500 |
| | No | 29 | 96.67 | 28 | 93.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |

The ulcer characteristics after 10 days of dressing are as depicted in table 13. Positive culture was noted in 3.33% of the patients in group A and proteus was the organism. In group B, 6.67% of the patients had positive culture and staph aureus was the organism. Both the organisms were sensitive. However, no statistically significant difference was noted with regard to culture, organisms and sensitivity between group A and B after 10 days of dressing.

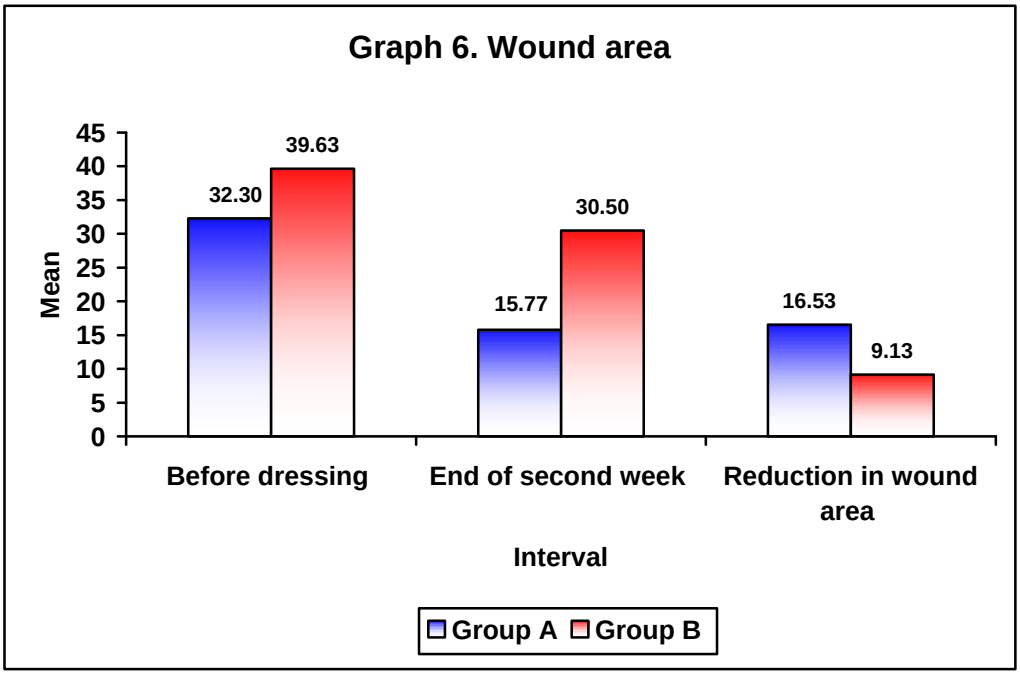
**Table 14. Wound observation at end of second week**

| Variables | Findings | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| **Floor** | Pale | 1 | 3.33 | 25 | 83.33 | < 0.001 |
| | Pink | 29 | 96.67 | 5 | 16.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Discharge** | Present | 29 | 96.67 | 26 | 86.67 | 0.112 |
| | Absent | 1 | 3.33 | 4 | 13.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Slough/necrotic** | Present | 2 | 6.67 | 17 | 56.67 | < 0.001 |
| **tissue** | Absent | 28 | 93.33 | 13 | 43.33 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |

In the present study wound observation at end of second week revealed significantly lower number of patients with pale floor (3.33%) and slough / necrotic tissue (6.67%) in group A compared to group B (83.33% and 56.67% respectively) ($p<0.001$). However, discharge was comparable in group A and B (96.67% vs 86.67%; $p=0.112$).

**Table 15. Wound area**

| Interval | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Before dressing | 32.30 | 13.75 | 39.63 | 14.69 | 0.051 |
| End of second week | 15.77 | 8.44 | 30.50 | 13.58 | <0.001 |
| Reduction in area | 16.53 | 6.60 | 9.13 | 4.10 | <0.001 |




In the present study the mean wound area before dressing was comparable in group A (32.30 ± 13.75 sq mm) and group B (39.63 ± 14.69 sq mm) (p=0.051). At the end second week the mean wound area was significantly less in group A and B (p<0.001). The reduction in wound area at the end of second week was significantly high in group A (16.53 ± 6.60 sq mm) compared to group B (9.13 ± 4.10 sq mm) (p<0.001).

**Table 16. Wound observation at end of fourth week**

| Variables | Findings | Group A (n=30) | | Group B (n=30) | | p value |
|---|---|---|---|---|---|---|
| | | No. | % | No. | % | |
| **Floor** | Pale | 0 | 0.00 | 11 | 36.67 | < 0.001 |
| | Pink | 1 | 3.33 | 17 | 56.67 | |
| | Red | 29 | 96.67 | 2 | 6.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Discharge** | Present | 0 | 0.00 | 7 | 23.33 | 0.005 |
| | Absent | 30 | 100.00 | 23 | 76.67 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |
| **Slough/necrotic** | Present | 0 | 0.00 | 3 | 10.00 | 0.119 |
| **tissue** | Absent | 30 | 100.00 | 27 | 90.00 | |
| | **Total** | **30** | **100.00** | **30** | **100.00** | |

In this study wound observations at the end of fourth week revealed none of the patient with pale floor and discharge in group A compared to 36.67% and 23.33% in group B and this difference was statistically significant ($p<0.001$ and $p=0.005$ respectively).

**Photograph 4. Wound before collagen granule dressing**

**Photograph 5. Wound after collagen granule dressing**

# DISCUSSION

An ideal dressing used in wound management should be economical, easy to apply, readily available dressing or method or coverage that will provide good pain relief, protect wound from infection, keep moisture, be elastic, non – antigenic, adhere well to the wound, promote healing and healthy granulation tissue.[78]

In 150 A.D the Greek surgeon, Galen of Pergamum while working with a Roman gladiator cuts, first addressed the fact that the wound should be kept moist to ensure adequate healing.[79] Among newer type of wound dressings - Biological dressings like collagen create the most physiological interface between the wound surface, environment and impermeable to bacteria.[62]

Collagen is an endogenous substance, which forms an important structural component in connective tissue and is of special importance in the skin. The importance of collagen in healing has been appreciated for many years for the simple reason that, the result of repair in wound healing is always a scar, which is composed of collagenous fibers. It is now evident that collagen and collagen-derived fragments control many cellular functions, including cell shape and differentiation, migration, and synthesis of a number of proteins;[15] so collagen plays a key role in each phase of wound healing. The present study was aimed to compare the efficacy of collagen granule dressing over the conventional dressing in healing of diabetic foot ulcers.

This one year randomized controlled trial was done from January 2013 to December 2013 in the Department of General Surgery, KLES Dr. Prabhakar Kore

Hospital and Medical Research Centre, Belgaum. A total of 60 patients presenting with diabetic foot ulcers measuring > 1 cm, with slough, foul smell and minimal granulation tissue were enrolled. The patients were divided into two groups of 30 each as Group A (Dressing with topical collagen granules) and Group B (Dressing with conventional dressing).

The occurrence of diabetic foot ulcers mostly in males has been reported by several researchers14,15 In the present study male preponderance was observed. In patients with group A, 73.33% and in group B 60% were males and the male to female ratio was 2.75 in group A compared to 1.5:1 in group B. However the difference was statistically not significant (p=0.273). The male preponderance observed in the present study is consistent with an epidemiological study from Varanasi to determine risk factors for foot ulceration where 71.13% of the patients were males and 28.86% were females.[80]

In this study the commonest age group was 46 to 60 years comprised of 53.33% of the patients in group A while in group B, 36.37% of the patients each were aged between 46 to 60 years and 31 to 45 years. The mean age in group A was found to be 49.00 ± 8.15 years and in group B the same was found as 49.60 ± 10.39 years. However, the comparison of age distribution and mean age showed no statistically significant difference between group A and B (p>0.050). The occurrence of diabetic foot ulcers mostly in middle aged subjects has been reported by several researchers.[37] A study[80] from Varanasi to determine risk factors for foot ulceration reported mean age of the patients with diabetic foot ulcers as 55.25 years.

In this study with regard to diabetic history, type of diabetes (p=0.791), duration of diabetes (p=0.282) and mean duration of diabetes (p=0.791) were comparable in group A and B. The fasting blood sugar levels were comparable in group A and B (178.47±47.00 mg/dL vs 172.27±33.27 mg/dL; p=0.558). Further, both group A and B were comparable in terms of ulcer characteristics including duration of ulcer (p=0.598), mean duration of ulcer (p=0.052), mean size of ulcer (p=0.704), ulcer shape, discharge and slough / necrotic tissue (p>0.050). With regard to culture, positive culture for bacteria was noted in 36.67% of the patients in group A and 40% in group B. The commonest organism in group B was staphylococcus aureus (20%) and in group A, Klebsiella, proteus and staphylococcus aureus were noted in 10% of the patients each. Further 36.67% of the ulcers in group A and 40% in group B were sensitive (p>0.050)

Overall these findings suggest that, the demographic characteristics of the study population, history of diabetes, ulcer characteristic in patients with group A and B were comparable ruling out bias in the outcome.

In this study wound observation at end of second week revealed significantly lower number of patients with pale floor (3.33% vs 83.33%; p<0.001) and slough / necrotic tissue (6.67% vs 56.67%; p<0.001) in group A compared to group B. Wound observations at the end of fourth week showed none of the patient with pale floor and discharge in group A compared to 36.67% and 23.33% in group B and this difference was statistically significant (p<0.001 and p=0.005 respectively). On tenth day after dressing positive culture was noted in only 3.33% of the patients in group A and 6.67% of the patients in group B. In group A, proteus was the organism and in group B, staph aureus was the organism (p>0.050). The present study showed

significantly higher reduction in mean wound area (16.53 ± 6.60 sq mm vs 9.13 ± 4.10 sq mm; p<0.001) from baseline (32.30±13.75 sq mm vs 39.63 ± 14.69 sq mm) to end to second week (15.77 ± 8.44 sq mm vs. 30.50 ± 13.58) in patients with group A compared to group B. These findings suggest that, topical collagen granules dressing accelerates the wound healing process compared to conventional dressing in patients with diabetic foot ulcers.

Studies comparing the effect of topical collagen granules dressing in diabetic foot ulcers are scarce. Vaves A et al. in his randomized controlled trial to compare collagen dressing vs standard treatment in diabetic foot ulcers reported that collagen granules have wound healing property.[73] Similarly another randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers by Lazaro-Martinez JL[76] showed that protease-modulating dressings in patients with neuropathic diabetic foot ulcers leads to better tissue regeneration than good wound care.

Another study by Lobmann R et al[75] in 2006 reported that, expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing showed that the local treatment with a protease inhibitor dressing/collagen dressing has a beneficial effect on wound healing. Effect of oxidized regenerated cellulose/collagen matrix on proteases in wound exudate of patients with diabetic foot ulcers, showed significant reduction in protease size and greater reduction in wound size.[77] Wollina U et al.[74] reported some effects of a topical collagen-based matrix on the microcirculation and wound healing in patients with chronic venous leg ulcers. The preliminary observations showed that topical

collagen improves microcirculation which is a key parameter of granulation tissue formation. Findings of the present study were consistent with these studies.

Collagen granule dressing has better advantage over conventional dressing in terms of collagen formation with greater reduction in inflammatory cells during healing days resulting in decreased days of healing, where as conventional dressing has minimal collagen formation, high grade of inflammation during the healing days with maximum exudates formation resulting in increased days of healing. A collagen granule dressing has another advantage over conventional dressing in terms of non-immunogenic, non-pyrogenic, being natural, easy application, hypo allergic and pain free.[73]

Overall the present study showed that diabetic foot ulcers treated with collagen granule dressing are efficacious in terms of reduction in wound area, slough / necrotic tissue, discharge and increase in granulation tissue resulting in early wound healing.

# CONCLUSION

Based on the results of this study it may be concluded that, diabetic foot ulcers treated with collagen granule are efficacious in terms of reduction in wound area, slough / necrotic tissue and discharge resulting in early wound healing compared to conventional dressing.

# SUMMARY

Diabetic foot problems are the commonest reason for hospitalization of diabetic patients. It is reported that, collagen granule has an advantage over conventional dressing in terms of collagen formation with greater reduction in inflammatory cells during healing days resulting in decreased days of healing. The present study was aimed to compare the efficacy of collagen granule dressing over the conventional dressing in the healing of diabetic foot ulcers.

This one year randomized controlled trial was carried out under the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients having diabetic foot ulcers measuring more than 1 cm, with slough, foul smell and minimal granulation tissue from January 2013 to December 2013 were studied. Patients were divided into two groups of 30 each as group A (Dressing with topical collagen granules dressing) and group B (Dressing with conventional dressing).

In this study male preponderance was noted with male to female ratio of 2.75:1 in group A and 1.5:1 in group B (p=0.273). The commonest age group was 46 to 60 years (53.33% in group A and 36.37% in group B; p=0.403). The mean age in group A was 49.00 ± 8.15 years compared to 49.60 ± 10.39 in group B (p=0.804). Most of the patients in group A and B had type II diabetes (60.00% and 63.33% respectively; p=0.791) The duration of diabetes in group A was between five to eight years in 56.67% of the patients compared to 36.67% in group B (p=0.282). The mean duration of diabetes was 5.58 ± 2.91 years in group A compared to 5.77 ± 2.40 years in group B (p=0.791). Most of the patients in group A (56.67%) and in group

B (63.33%) presented with four to eight weeks duration of ulcer (p=0.598). The mean duration of ulcer was comparable in group A and B (4.72 ± 1.34 vs 5.50 ± 1.69 weeks; p=0.052). The mean size of ulcer in group A was 51.83 ± 17.44 sq mm compared to 53.60 ± 18.44 sq. mm in group B (p=0.704). The ulcer characteristics including site of ulcer, shape, discharge and slough / necrotic tissue were comparable between group A and B (p>0.050). Fasting blood sugar levels were comparable in group A and B (178.47 ± 47.00 mg/dL vs 172.27 ± 33.27 mg/dL; p=0.558). Before dressing culture was positive in 36.67% of the patients in group A and 40% in group B (p=0.500) and commonest organism in group B was staphyloccus aureus in group B (20%) and in group A, Klebsiella, proteus and staph aureus (10%) (p=0.798). Further 36.67% in of the ulcers in group A and 40% in group B were sensitive (p=0.500) After 10 days of dressing, positive culture was noted in 3.33% of the patients in group A and proteus was the organism. In group B, 6.67% of the patients had positive culture and staph aureus was the organism and both these organisms were sensitive (p>0.050). Wound observation at end of second week revealed significantly lower number of patients with pale floor (3.33%) and slough / necrotic tissue (6.67%) in group A compared to group B (83.33% and 56.67% respectively) (p<0.001). Discharge was comparable in group A and B (96.67% vs 86.67%; p=0.112). At the end of fourth week none of the patient had pale floor and discharge in group A compared to 36.67% and 23.33% in group B (p<0.001 and p=0.005 respectively). The reduction in wound area at the end of second week was significantly high group A (16.53 ± 6.60 sq mm) compared to group B (9.13 ± 4.10 sq mm) (p<0.001).

Treatment of diabetic foot ulcers with collagen granule helps in reduction in wound area, slough / necrotic tissue and discharge leading to early wound healing compared to conventional dressing.

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# ANNEXURE I – CONSENT FORM

## A RANDOMISED CONTOL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH COLLAGEN GRANULES VERSUS CONVENTIONAL DRESSING IN MANAGEMENT OF DIABETIC FOOT ULCERS.

Principal Investigator:-
Dr. **** ***** ******
Post Graduate Student
Department Of General surgery,
J. N. Medical College, Belgaum.

Co-investigator:-
Dr. **** *******
Professor,
Department Of General Surgery,
J. N. Medical College, Belgaum.

You are requested to participate in a study which is an attempt to find out the efficacy of dressings with collagen granules as compared to conventional dressing in management of diabetic foot ulcers.

The diabetic foot ulcers are a common complication of diabetes mellitus and treatment of which is a major challenge. Presently these ulcers are being managed by local dressings with agents like Povidine Iodine, Eusol, etc… which have their own limitations. Collagen granules may represent an alternative to the currently available antiseptics and may answer the quest for better control of wound infection in diabetic patients. So, the study has been undertaken to compare the efficacy of dressings with collagen granules with conventional dressing in the management of diabetic foot ulcers.

This study will be conducted by Dr. **** *******, Post Graduate in Department of Surgery, under the direct supervision and guidance of Dr. **** ******, Professor, Department of Surgery, J. N. Medical College, Belgaum.

You need to be eligible, meeting all the selection criteria to participate in this study. You should be willing to provide information about yourself. Sixty subjects

will be enrolled in this study that will then be randomized in either of 2 groups (details given below).

If you agree to participate in this study, you will be randomly allotted into a group (A or B) and accordingly receive either the standard management (conventional dressing) or the newer management (dressing with collagen granule). The ulcer size will be assessed once for every two weeks for healing. There is no observable risk associated with this study.

No financial incentives are being offered to enrolled subjects. It is purely being done with the idea of research purpose and all cost of the study will be borne by the investigator. In the event that you become injured as a results of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum., or your will be given information about where to receive medical care in which case you/your insurance company will be responsible for the costs. However, no reimbursement, compensation or free medical care will be given.

Every effort will be made to protect the confidentiality of the information you provide. Only Dr. ***** ***** and Dr. **** ***** will have access to the information provided by you. Results of this study may be published but your identity will not be revealed. Taking part in this study is voluntary; you may choose not to enroll in this study. Your decision will not change the present or future health care services offered to you at KLES Dr. Prabhakar Hospital, Belgaum. The alternative that you have is to undergo the traditional procedure that is carried out in KLES Hospital.

If you have any queries about the study, you may contact Principal investigator, Dr. **** ***** ***** (Mob. ***** *****) / Dr. **** ******, (Mob. **** ******) Professor, Department of Surgery, J. N. Medical College, Belgaum., without any hesitation. In case you need any further information regarding your rights as a study participant, you may contact Dr. **** *****., Chairman of Institutional Dissertation and Thesis Ethical Committee on human subject research.

**CONSENT TO PARTICIPATE IN A RESEARCH STUDY:**

I, Mr./Mrs. _____

voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having been explained to me in my vernacular language including risks and the benefits and having all queries cleared.

Subject Name: _____

Signature of the participant

Or Left thumb print _____

Witness name: _____

Signature: _____

Investigator's name: _____

**Place**: _____

**Date:**_____ **Signature of the investigator**

# ANNEXURE II – PROFORMA

## I. PATIENT IDENFICIATION DATA

GROUP :

CASE NO. :

I.P/ O.P.D NO.:

D.O.A:

NAME :

D.O.S:

SEX :

D.O.D:

OCCUPATION:

ADDRESS :

## II. CHIEF COMPLAINTS:

## III. MEDICAL HISTORY

| | | | |
|---|---|---|---|
| Peripheral neuropathy | : | (YES/NO) | ☐ |
| Nephropathy | : | (YES/NO) | ☐ |
| Retinopathy | : | (YES/NO) | ☐ |
| PVD | : | (YES/NO) | ☐ |
| CVD | : | (YES/NO) | ☐ |

## IV. DIABETIC STATUS

Type : Duration :

Medication : ☐

Oral Hypoglycemics : (YES/NO)

Insulin : (YES/NO) ☐

**V. ULCER DETAIL**

1. Mode of onset

Traumatic : (YES/NO) ☐

Spontaneous : (YES/NO) ☐

Pressure : (YES/NO) ☐

Others : (YES/NO) ☐

2. Duration :

3. Progress :

**VI. WOUND OBSERVATIONS:**

| | **Before dressing** | **End of second week** | **End of fourth week** |
|---|---|---|---|
| 1. Site | | | |
| 2. Size | | | |
| 3. Shape | | | |
| 4. Edge | | | |
| 5. Margin | | | |
| 6. Floor / Granulation tissue | | | |
| 7. Base | | | |
| 8. Discharge | | | |
| 9. Surrounding Skin | | | |
| 10. Slough /necrotic tissue | | | |

**VII. NEUROLOGICAL EXAMINATION :**

a. Motor System-

b. Sensory System-

**VIII. VASCULAR EXAMINATION**

| | Right | Left |
|---|---|---|
| Popliteal artery | | |
| Ant. Tibial artery | | |
| Post Tibial artery | | |
| Dorsalis Pedis artery | | |

**IX. ANY FOOT DEFORMITY PRESENT**

Toe deformity : (YES/NO) ☐

Charcots foot : (YES/NO) ☐

Foot drop: (YES/NO) ☐

**X. IF DEBRIDEMENT HAS BEEN DONE**

Specify, Date :

Side :

Type of anaesthesia :

No of debridements :

**XI. INVESTIGATIONS :**

**CBC :**

**Hb- ( )**

**TLC- ( )**

**DC- ( N- , L- , M- ,E- )**

**FBS : ( ) Date Time**

**Blood Urea** **( )**

**Sr. Creatinine** **( )**

**Urine** :

Routine

Microscopy

**X-ray**

AP view

Lat. View

**Tissue culture/ sensitivity:**

Before dressing :

10 days after dressing :

# ANNEXURE III – KEY TO MASTER CHART

| | | |
|---|---|---|
| - | - | Absent |
| + | - | Present |
| A | - | Collagen granule dressing |
| AP | - | Antero posterior |
| B | - | Conventional dressing |
| F | - | Female |
| I.D. Number | - | Identification number |
| IR | - | Irregular |
| KL | - | Klebsiella |
| LLL | - | Left lower limb |
| M | - | Male |
| mg/dL | - | Milligram per deciliter |
| N | - | No |
| n | - | Normal |
| PR | - | Proteus |
| RLL | - | Right lower limb |
| SA | - | Staphylococcus aureus |
| SE | - | Staphylococcus epidermis |
| SL | - | Slanting edge |
| sq cms | - | Square centimeters |
| Y | - | Yes |

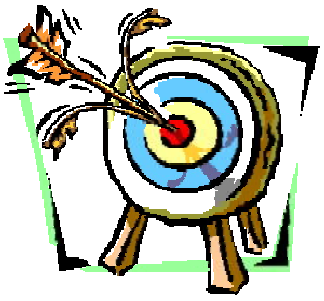
## ANNEXURE III - MASTER CHART

| | | | | History | | | | | Diabetic history | | | Ulcer details | | | | | | | | | | Systemic examination | | Vascular examination | | | | deformity | | Debridement | | Investigations | | | | | | | | Observation | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Urine | | X-ray foot | | Culture before | | Pus culture after 10 days of dressing | | | End of second week | | | | End of fourth week | | | |
| I.D. Number | Group | Sex | Age (Years) | Peripheral neuropathy | Nephropathy | Retinopathy | PVD | CVD | Type of DM | Duration | Medication | Duration (weeks) | Site | Size (sq cms) | Shape | Edge | Margin | Floor / granulation tissue | Discharge | Surrounding skin | Slough/necrotic tissue | Sensory system | Motor system | Popliteal artery | Anterior tibial artery | Post tibial artery | Dorsalis pedis artery | Deformity | Site | Debridement | Number of debridements | Fasting blood sugar (mg/dL) | Routine | Microscopy | AP | Lateral | Organism | Sensitivity | Organism | Culture | Sensitivity | Wound area | Floor | Discharge | Slough | Wound area | Floor | Discharge | Slough |
| 1 | A | M | 52 | N | N | N | N | N | II | 10 | Y | 4 | LLL | 58 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 132 | n | n | n | n | - | N | - | - | N | 42 | PINK | Y | N | 28 | RED | N | N |
| 2 | A | M | 48 | N | N | N | N | N | II | 1.5 | Y | 3 | RLL | 34 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 128 | n | n | n | n | SA | Y | - | - | N | 22 | PINK | Y | N | 9 | RED | N | N |
| 3 | A | M | 45 | N | N | N | N | N | I | 8 | Y | 2.5 | RLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 141 | n | n | n | n | - | N | - | - | N | 18 | PINK | Y | N | 8 | RED | N | N |
| 4 | A | M | 50 | N | N | N | N | N | II | 4 | Y | 5 | LLL | 84 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 138 | n | n | n | n | - | N | - | - | N | 58 | PINK | Y | N | 22 | RED | N | N |
| 5 | B | M | 62 | N | N | N | N | N | I | 6 | Y | 8 | RLL | 68 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 142 | n | n | n | n | - | N | - | - | N | 56 | PALE | Y | Y | 48 | PINK | N | N |
| 6 | B | M | 54 | N | N | N | N | N | I | 3 | Y | 6 | RLL | 72 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 139 | n | n | n | n | - | N | - | - | N | 66 | PALE | Y | Y | 60 | PINK | N | N |
| 7 | A | M | 52 | N | N | N | N | N | II | 3.5 | Y | 7 | RLL | 48 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 158 | n | n | n | n | SA | Y | - | - | N | 32 | PINK | Y | N | 18 | RED | N | N |
| 8 | B | F | 48 | N | N | N | N | N | I | 4 | Y | 8 | RLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 148 | n | n | n | n | SE | Y | - | - | N | 28 | PALE | Y | Y | 24 | PALE | Y | N |
| 9 | A | M | 46 | N | N | N | N | N | II | 5.5 | Y | 4.5 | RLL | 28 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 137 | n | n | n | n | - | N | - | - | N | 14 | PINK | Y | N | 4 | RED | N | N |
| 10 | A | M | 61 | N | N | N | N | N | I | 5 | Y | 5 | LLL | 30 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 168 | n | n | n | n | - | N | - | - | N | 16 | PINK | Y | N | 6 | RED | N | N |
| 11 | B | M | 63 | N | N | N | N | N | II | 6 | Y | 3.5 | LLL | 26 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 141 | n | n | n | n | SA | N | - | - | N | 22 | PALE | Y | Y | 16 | PALE | Y | N |
| 12 | A | F | 54 | N | N | N | N | N | II | 3 | Y | 5 | RLL | 42 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 143 | n | n | n | n | - | N | - | - | N | 26 | PINK | Y | N | 12 | RED | N | N |
| 13 | A | M | 64 | N | N | N | N | N | II | 6 | Y | 4 | RLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 168 | n | n | n | n | - | N | - | - | N | 18 | PINK | Y | N | 10 | RED | N | N |
| 14 | A | M | 38 | N | N | N | N | N | I | 5.5 | Y | 6 | LLL | 36 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 138 | n | n | n | n | - | N | - | - | N | 22 | PINK | Y | N | 8 | RED | N | N |
| 15 | B | F | 41 | N | N | N | N | N | I | 6 | Y | 5.5 | RLL | 28 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 181 | n | n | n | n | SA | Y | - | - | N | 20 | PALE | Y | N | 16 | PINK | N | N |
| 16 | B | F | 49 | N | N | N | N | N | II | 5 | Y | 4 | LLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 138 | n | n | n | n | - | N | - | - | N | 26 | PALE | Y | N | 22 | PINK | N | N |
| 17 | A | M | 57 | N | N | N | N | N | II | 4 | Y | 4 | LLL | 42 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 158 | n | n | n | n | SE | Y | - | - | N | 26 | PINK | NIL | N | 8 | RED | N | N |
| 18 | B | M | 57 | N | N | N | N | N | II | 3 | Y | 4 | RLL | 70 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 132 | n | n | n | n | - | N | - | - | N | 62 | PALE | Y | N | 42 | PINK | N | N |
| 19 | B | M | 49 | N | N | N | N | N | II | 5 | Y | 3 | LLL | 78 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 128 | n | n | n | n | SA | Y | - | - | N | 48 | PALE | Y | N | 32 | PINK | N | N |
| 20 | B | M | 41 | N | N | N | N | N | I | 7 | Y | 5 | RLL | 42 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 141 | n | n | n | n | KL | Y | - | - | N | 32 | PALE | Y | N | 22 | PINK | N | N |
| 21 | A | F | 38 | N | N | N | N | N | II | 3 | Y | 2.5 | RLL | 68 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 148 | n | n | n | n | - | N | - | - | N | 42 | PINK | Y | N | 18 | RED | N | N |
| 22 | B | M | 61 | N | N | N | N | N | II | 2 | Y | 8 | RLL | 72 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 152 | n | n | n | n | PR | Y | - | - | N | 38 | PINK | Y | N | 20 | RED | N | N |
| 23 | A | M | 63 | N | N | N | N | N | I | 1.5 | Y | 6 | RLL | 81 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 153 | n | n | n | n | KL | Y | - | - | N | 62 | PINK | Y | N | 32 | RED | N | N |
| 24 | A | F | 62 | N | N | N | N | N | I | 2 | Y | 7 | RLL | 60 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 161 | n | n | n | n | - | N | - | - | N | 38 | PINK | Y | N | 20 | RED | N | N |
| 25 | B | F | 53 | N | N | N | N | N | II | 3 | Y | 6 | LLL | 38 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 139 | n | n | n | n | - | N | - | - | N | 28 | PINK | Y | Y | 19 | PINK | N | N |
| 26 | B | M | 41 | N | N | N | N | N | II | 4 | Y | 4 | LLL | 40 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 194 | n | n | n | n | SA | Y | SA | + | Y | 30 | PALE | Y | Y | 22 | PINK | N | N |
| 27 | A | M | 49 | N | N | N | N | N | II | 5 | Y | 5 | RLL | 61 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 213 | n | n | n | n | PR | Y | PR | + | Y | 36 | PALE | Y | Y | 18 | RED | N | N |
| 28 | B | M | 38 | N | N | N | N | N | II | 12 | Y | 6 | LLL | 48 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 208 | n | n | n | n | - | N | - | - | N | 29 | PINK | Y | Y | 19 | PINK | N | N |
| 29 | A | M | 39 | N | N | N | N | N | II | 11 | Y | 3 | RLL | 36 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 139 | n | n | n | n | SE | Y | - | - | N | 20 | PINK | Y | N | 8 | RED | N | N |
| 30 | A | F | 48 | N | N | N | N | N | II | 7 | Y | 5 | RLL | 71 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 162 | n | n | n | n | - | N | - | - | N | 39 | PINK | Y | N | 14 | RED | N | N |
| 31 | B | M | 54 | N | N | N | N | N | II | 9 | Y | 8 | RLL | 48 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 191 | n | n | n | n | - | N | - | - | N | 38 | PALE | Y | Y | 28 | PINK | N | N |
| 32 | A | M | 62 | N | N | N | N | N | I | 10 | Y | 4 | LLL | 62 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 189 | n | n | n | n | - | N | - | - | N | 38 | PINK | Y | N | 20 | RED | N | N |
| 33 | A | M | 39 | N | N | N | N | N | I | 5 | Y | 4 | RLL | 42 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 219 | n | n | n | n | - | N | - | - | N | 19 | PINK | Y | N | 10 | RED | N | N |
| 34 | A | F | 49 | N | N | N | N | N | II | 3 | Y | 3 | LLL | 40 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 200 | n | n | n | n | - | N | - | - | N | 17 | PINK | Y | Y | 10 | PINK | N | N |
| 35 | A | M | 52 | N | N | N | N | N | II | 10 | Y | 7 | RLL | 72 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 138 | n | n | n | n | - | N | - | - | N | 38 | PINK | Y | N | 20 | RED | N | N |
| 36 | A | M | 48 | N | N | N | N | N | I | 3 | Y | 5 | LLL | 68 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 194 | n | n | n | n | SA | Y | - | - | N | 38 | PINK | Y | N | 18 | RED | N | N |

## ANNEXURE III - MASTER CHART

| I.D. Number | Group | Sex | Age (Years) | History | | | | | Diabetic history | | | Ulcer details | | | | | | | | | | Systemic examination | | Vascular examination | | | | deformity | | Debridement | | Investigations | | | | | | | | Observation | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Fasting blood sugar (mg/dL) | Urine | | X-ray foot | | Culture before | | Pus culture after 10 days of dressing | | | End of second week | | | | End of fourth week | | | |
| | | | | Peripheral neuropathy | Nephropathy | Retinopathy | PVD | CVD | Type of DM | Duration | Medication | Duration (weeks) | Site | Size (sq cms) | Shape | Edge | Margin | Floor / granulation tissue | Discharge | Surrounding skin | Slough/necrotic tissue | Sensory system | Motor system | Popliteal artery | Anterior tibial artery | Post tibial artery | Dorsalis pedis artery | Deformity | Site | Debridement | Number of debridements | | Routine | Microscopy | AP | Lateral | Organism | Sensitivity | Organism | Culture | Sensitivity | Wound area | Floor | Discharge | Slough | Wound area | Floor | Discharge | Slough |
| 37 | A | M | 42 | N | N | N | N | N | I | 7 | Y | 4 | RLL | 39 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 215 | n | n | n | n | KL | Y | - | - | N | 22 | PINK | Y | N | 8 | RED | N | N |
| 38 | A | M | 48 | N | N | N | N | N | II | 4 | Y | 3.5 | RLL | 42 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 194 | n | n | n | n | PR | Y | - | - | N | 28 | PINK | Y | N | 14 | RED | N | N |
| 39 | B | F | 61 | N | N | N | N | N | II | 5 | Y | 4 | LLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 181 | n | n | n | n | - | N | - | - | N | 24 | PALE | Y | Y | 17 | PALE | N | N |
| 40 | B | M | 33 | N | N | N | N | N | II | 7 | Y | 7 | RLL | 68 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 148 | n | n | n | n | - | N | - | - | N | 48 | PINK | Y | Y | 38 | PINK | N | N |
| 41 | A | F | 46 | N | N | N | N | N | II | 8 | Y | 6 | RLL | 52 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 215 | n | n | n | n | KL | Y | - | - | N | 32 | PINK | Y | N | 18 | RED | N | N |
| 42 | B | F | 38 | N | N | N | N | N | I | 4 | Y | 5 | LLL | 38 | OVAL | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 280 | n | n | n | n | PR | Y | - | - | N | 28 | PALE | Y | Y | 20 | PINK | N | N |
| 43 | A | M | 52 | N | N | N | N | N | I | 3 | Y | 6 | RLL | 53 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 290 | n | n | n | n | - | N | - | - | N | 38 | PINK | Y | N | 18 | RED | N | N |
| 44 | A | F | 41 | N | N | N | N | N | II | 2 | Y | 4 | RLL | 62 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 230 | n | n | n | n | PR | Y | - | - | N | 40 | PINK | Y | N | 22 | RED | N | N |
| 45 | B | M | 38 | N | N | N | N | N | II | 11 | Y | 3 | RLL | 78 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 180 | n | n | n | n | KL | Y | - | - | N | 42 | PALE | Y | N | 28 | PALE | N | N |
| 46 | A | M | 32 | N | N | N | N | N | II | 9 | Y | 4.5 | RLL | 90 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 171 | n | n | n | n | - | N | - | - | N | 68 | PINK | Y | N | 42 | RED | N | N |
| 47 | A | F | 48 | N | N | N | N | N | I | 8 | Y | 5 | LLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 332 | n | n | n | n | - | N | - | - | N | 20 | PINK | Y | N | 8 | RED | N | N |
| 48 | A | M | 45 | N | N | N | N | N | I | 10 | Y | 7 | RLL | 58 | OVAL | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 182 | n | n | n | n | - | N | - | - | N | 40 | PINK | Y | N | 22 | RED | N | N |
| 49 | B | F | 61 | N | N | N | N | N | II | 7 | Y | 8 | RLL | 64 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 210 | n | n | n | n | - | N | - | - | N | 52 | PALE | Y | Y | 38 | PALE | N | N |
| 50 | B | F | 60 | N | N | N | N | N | I | 6 | Y | 6 | LLL | 52 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 138 | n | n | n | n | SA | Y | SA | + | Y | 42 | PALE | Y | Y | 34 | PINK | N | N |
| 51 | B | M | 32 | N | N | N | N | N | II | 5 | Y | 6 | LLL | 38 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 181 | n | n | n | n | - | Y | - | - | N | 20 | PINK | Y | N | 8 | RED | N | N |
| 52 | B | M | 62 | N | N | N | N | N | II | 8 | Y | 4 | RLL | 84 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 210 | n | n | n | n | - | N | - | - | N | 68 | PALE | N | N | 50 | PALE | N | N |
| 53 | B | M | 32 | N | N | N | N | N | II | 4 | Y | 6 | RLL | 32 | IR | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 184 | n | n | n | n | - | N | - | - | N | 24 | PALE | N | N | 20 | PINK | N | N |
| 54 | B | F | 48 | N | N | N | N | N | I | 3 | Y | 3 | RLL | 68 | IR | SL | n | PALE | - | n | - | n | n | n | n | n | n | - | - | - | - | 178 | n | n | n | n | - | N | - | - | N | 60 | PALE | Y | N | 48 | PALE | Y | N |
| 55 | B | M | 58 | N | N | N | N | N | II | 8 | Y | 4 | LLL | 70 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 164 | n | n | n | n | SA | Y | - | - | N | 60 | PALE | Y | N | 52 | PALE | Y | Y |
| 56 | B | M | 62 | N | N | N | N | N | I | 7 | Y | 7 | RLL | 58 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 209 | n | n | n | n | KL | Y | - | - | N | 48 | PALE | N | Y | 42 | PINK | N | N |
| 57 | B | F | 45 | N | N | N | N | N | I | 8 | Y | 5 | LLL | 76 | IR | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 181 | n | n | n | n | - | N | - | - | N | 60 | PALE | Y | Y | 52 | PALE | Y | Y |
| 58 | B | M | 38 | N | N | N | N | N | II | 7 | Y | 8 | RLL | 42 | OVAL | SL | n | PALE | + | n | + | n | n | n | n | n | n | - | - | - | - | 169 | n | n | n | n | - | N | - | - | N | 32 | PALE | N | N | 24 | PINK | N | N |
| 59 | B | F | 48 | N | N | N | N | N | II | 5 | Y | 6 | RLL | 38 | OVAL | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 178 | n | n | n | n | - | N | - | - | N | 26 | PALE | Y | Y | 22 | PALE | Y | Y |
| 60 | B | F | 61 | N | N | N | N | N | I | 3 | Y | 4 | RLL | 76 | OVAL | SL | n | PALE | + | n | - | n | n | n | n | n | n | - | - | - | - | 203 | n | n | n | n | - | N | - | - | N | 62 | PALE | Y | Y | 52 | PALE | Y | N |

# *Introduction*



# *Objectives*

# *Review of Literature*

# *Methodology*

# Results

# *Discussion*

# Conclusion

# Summary

# *Bibliography*

# *Annexure-I*

# *Annexure-II*

# *Annexure-III*