“A CLINICAL STUDY ON ROLE OF COLLAGEN DRESSINGS IN DIABETIC ULCER MANAGEMENT”

A DISSERTATION SUBMITTED TO THE TAMILNADU

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In partial fulfillment of the requirement for the degree of

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BRANCH – I

Register No: 221711363

DEPARTMENT OF GENERAL SURGERY

TIRUNELVELI MEDICAL COLLEGE

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DECLARATION

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

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PROTOCOL TITLE: A CLINICAL STUDY ON ROLE OF COLLAGEN DRESSINGS IN DIABETIC ULCER MANAGEMENT
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DESIGNATION OF PRINCIPAL INVESTIGATOR: DR.S.PAUL SOLOMAN, MBBS.,
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Dear Dr.S.PAUL SOLOMAN, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during The IEC meeting Held on 01.09.2017.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of The Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
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8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, These must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
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   g. Any deviation/violation/waiver in the protocol must be informed.

STANDS APPROVED UNDER SEAL

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CERTIFICATE – II

This is to certify that this dissertation work title "**A CLINICAL STUDY ON ROLE OF COLLAGEN DRESSINGS IN DIABETIC ULCER MANAGEMENT**" of the candidate **Dr. S. PAUL SOLOMAN** with registration Number **221711363** for the award of M.S. Degree in the branch of **GENERAL SURGERY (I).** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **21 percentage** of plagiarism in the dissertation.

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INTRODUCTION

Diabetic foot is one of the most significant and devastating complications of diabetes, and is defined as a foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. It is estimated that about 5% of all patients with diabetes present with a history of foot ulceration, while the lifetime risk of diabetic patients developing this complication is 15%. The majority (60–80%) of foot ulcers will heal, while 10–15% of them will remain active, and 5–24% of them will finally lead to limb amputation within a period of 6–18 months after the first evaluation. 40–70% of all nontraumatic amputations of the lower limbs occur in patients with diabetes. Furthermore, many studies have reported that foot ulcers precede approximately 85% of all amputations performed in diabetic patients. The prevention of diabetic foot is crucial, considering the negative impact on a patient's quality of life and the associated economic burden on the healthcare system.

DFU can lead to infection, gangrene, amputation, and even death if necessary care is not provided[1]. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than patients without diabetes[2]. It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU[2]. In addition, it is reported that every 30 s one leg is amputated due to DFU in worldwide[3].

Collagen components, such as fibroblast and keratinocytes, are a major part of skin development. Collagen may be harvested from living and nonliving bovine, porcine, and equine skin. Once harvested, a native collagen bioscaffold matrix is created that stabilizes the vascular and cellar components, which become incorporated into the wound bed[4]. Cullen et al [5] reported that after using the (oxygenised regenerated cellulose)ORC/collagen dressing, researchers analyzed wound fluid and found a significant decrease in collagenase-like activity; gelatinase, matrix metalloproteinase (MMP)-2, and MMP-9 levels; and increased scavenged free radicals and binding of growth factors. Normal wound healing maintains a balance of extracellular matrix degradation and formation. Nonhealing diabetic foot wounds maintain a chronic inflammatory state with lack of extracellular matrix formation[5]. Bacteria are believed to play a role in chronic extracellular matrix degradation. Analysis of wound fluid has found increased levels of proteases, inflammatory cytokines, and decreased growth factors[6]. Many grampositive pathogens commonly found in diabetic foot ulcers, such as Staphylococcus aureus, Enterococcus faecalis, and Streptococcus equi, are able to bind to collagen by utilizing collagen-binding adhesins of the microbial surface component recognizing adhesive matrix molecules family.[7–9]

AIMS AND OBJECTIVES

- To estimate the efficacy of Collagen dressing in patients with diabetic foot ulcer.

- To estimate the rate of healing of the diabetic ulcer after collagen dressings and to finally assess whether SSG was required or not.

REVIEW OF LITERATURE

Definition of diabetic foot

Diabetic foot is defined as the presence of infection, ulceration and/or destruction of deep tissues associated with neurologic abnormalities and various degrees of peripheral arterial disease in the lower limb in patients with diabetes.

ULCER

Definition An ulcer is a break in the continuity of the covering epithelium, either skin or mucous membrane due to molecular death.

Parts of an Ulcer

a. Margin: It may be regular or irregular. It may be rounded or oval.
b. Edge: Edge is the one which connects floor of the ulcer to the margin.
c. Floor: It is the one which is seen. Floor may contain discharge granulation tissue or slough.
d. Base: Base is the one on which ulcer rests. It may be bone or soft tissue.

Stages of ulcer healing

1. Stage of extension: Ulcer floor is covered with slough, purulent discharge and inflamed edge and margin.
2. Stage of transition: Floor shows separated slough; healthy granulation tissue; serous discharge.
3. Stage of repair: Fibrosis, collagen deposition, scar formation.

WOUND HEALING

Wound healing is complex method to achieve anatomical and functional integrity of disrupted tissue by various components like neutrophils, macrophages, lymphocytes, fibroblasts, collagen; in an organised staged pathways—haemostasis → inflammation → proliferation → matrix synthesis (collagen and proteoglycan ground substance) → maturation → remodelling → epithelialisation → wound contraction (by myofibroblasts).

Phases of Wound Healing

Inflammatory phase (Lag or Substrate or Exudative Phase)

It begins immediately after formation and lasts for 72 hours. There is initial arteriolar vasoconstriction, thrombus formation, platelet aggregation due to endothelial damage and release of adenosine diphosphate (ADP).

Later vasodilatation and increased vascular permeability develops. Here haemostasis, coagulation and chemotaxis occur.

Note: Coagulation begins at wound haematoma → formation of platelet fibrin thrombus → release of cytokines, PDGF (platelet-derived growth factor), epidermal growth factor (EGF), transforming growth factor β (TGF – β), platelet activating factor and platelet factor IV, fibrin, serotonin. Chemotaxis causes first neutrophil migration, and then activation of macrophages, lymphocytes leading into phagocytosis, wound debridement, matrix activation, angiogenesis. Chemotaxis factors are complement factors, interleukin-1, TNF-α (tumour necrosis factor-α) TGF–β and platelet factor. Activated macrophages

produce free radicals and nitric oxide; release cytokine to activate lymphocytes which release interferon and interleukin (called as lymphokines). These factors attract polymorphonuclear leucocytes (PMN—polymorphonuclear cells–neutrophils) in 48 hours secreting inflammatory mediators and bactericidal oxygen derived-free radicals. Injured tissues and platelet release histamine, serotonin and prostaglandins which increases the vascular permeability by vasodilatation. These actions are reduced in diabetes mellitus, Cushing's syndrome and immunosuppression increasing the sepsis rate.

All these cause features of acute inflammation—rubor, calor, tumour, dolor and loss of function.

Proliferative phase (Collagen/fibroblastic phase)

It begins from 3rd day and lasts for 3–6 weeks. There will be formation of granulation tissue and repair of the wound. Granulation tissue contains fibroblasts, neocapillaries, collagen, fibronectin and hyaluronic acid.

(1) Initial angiogenesis (growth of new blood vessels) occurs by release of vascular endothelial cell growth factor (VEGF) by keratinocytes; by release of TNF-α, TGF–β, PDGF, FGF by macrophages.

(2) Eventual fibroplasia develops by fibroblast activity with formation of the collagen and ground substance/ glycosaminoglycans. Type III collagen is deposited initially in a random fashion.

(3) Later re-epithelialisation of the wound surface occurs by migration of basal layer of the retained epidermis which proliferates, differentiates and stratifies to form wound closure.

Remodelling phase (Maturation Phase)

It begins at 6 weeks and lasts for 6 months to 1 or 2 years. There is maturation of collagen by cross linking and realignment of collagen fibers along the line of tension, which is responsible for tensile strength of the scar. There is reduced wound vascularity. Fibroblast and myofibroblast activity causes wound contraction. Type III collagen is replaced by type I collagen causing maturation of the collagen. Ratio of type I collagen to type III collagen becomes 4:1. Early extracellular matrix contains fibronectin and collagen type III; eventually it contains glycosaminoglycans and proteoglycans; final matrix contains type I collagen.

Scar strength is 3% in 1 week; 20% in 3 weeks; 80% in 12 weeks.

Final matured scar is acellular and avascular.

Note: Initially fibrin, fibronectin, proteoglycans deposition occurs; later collagen protein develops to form scar. Normal dermal skin contains 80% type I (20% type III) collagen; granulation tissue contains mainly type III collagen; scar contains both type I and III collagen, initially in equal proportion, later becomes 4:1. Basic essential components of collagen are proline and lysine. Hydroxylation of lysine and later glycosylation of this hydroxylysine decides

the type of collagen molecule. Hydroxylation of both proline and lysine as essential step needs adequate concentration of vitamin C, iron and α ketogluteric acid. Collagen deposition in the wound is assessed by quantity of hydroxyproline excreted in urine. There is a balanced activity of collagen production and degradation of collagen (collagenolysis). Collagen is broken down by collagenase and MMPs (matrix metalloproteinases). Procollagen through procollagenase → collagen fibril → cross linking → collagen fiber → deposition. Deposited collagen → through collagenase → degradation and collagenolysis.

Factors affecting Wound Healing

Local factors

- Infection
- Presence of necrotic tissue and foreign body
- Poor blood supply
- Venous or lymph stasis
- Tissue tension
- Haematoma
- Large defect or poor apposition
- Recurrent trauma
- X-ray irradiated area

Site of wound, e.g. wound over the joints and back has poor healing

Underlying diseases like osteomyelitis and malignancy

Mechanism and type of wound—incised/lacerated/crush/avulsion

Tissue hypoxia locally reduces macrophage and fibroblast activity

General Factors

- Age, obesity, smoking, alcohol, stress
- Malnutrition, zinc, copper, manganese
- Vitamin deficiency (Vit C, Vit A)
- Anaemia, hypoxia
- Malignancy
- Uraemia
- Jaundice
- Diabetes, metabolic diseases
- HIV and immunosuppressive diseases
- Steroids and cytotoxic drugs
- Neuropathies of different causes

Etiopathogenesis of Foot Problems

The major risk factors for foot ulceration are a loss of protective sensation due to neuropathy, PAD and trauma. Diabetic neuropathy or PAD alone does not cause foot ulceration; it is the combination of these factors with trauma that leads to foot problems. Trauma and loss of protective sensation or PAD are the

major contributors to foot ulceration, and diabetic neuropathy is the common denominator in almost 90% of diabetic foot ulcers. Trauma initially causes minor injuries, which are not perceived by the patient with a loss of protective sensation. As the patient continues his or her activities, a small injury enlarges and may be complicated by infection.

Data on the prevalence and incidence of PAD vary considerably in population-based studies depending on the method used for the assessment. PAD is 2–8 times more common in patients with diabetes in comparison to the general population, with a prevalence of 10–20% and an annual incidence of 6–13.5 per 1000 patients with diabetes. In addition, it starts at an earlier age and progresses more rapidly, is usually more severe in extent and affects the segments between the knee and ankle more commonly in comparison to patients without diabetes.

It is also in itself an independent factor for increased mortality due to associated cardiovascular disease. PAD is a major contributory factor for foot ulceration and a major predictor of outcome. Even a minor injury, especially if complicated by infection, increases the demand for blood supply and may eventually result in ulceration and amputation.

A diagnosis of PAD can be easily made by a history, clinical examination and determination of the ankle– brachial pressure index (ABI). Smoking cessation, tight blood pressure control, use of antiplatelets, and management of dyslipidemia can reduce the risk for PAD in diabetes.

Neuropathies are common in diabetes, affect different parts of the nervous system and may present with diverse clinical manifestations. Most common among neuropathies are chronic sensorimotor distal symmetric polyneuropathy and peripheral autonomic neuropathy. Peripheral sensorimotor neuropathy is defined – according to the International Consensus Group on Neuropathy– as ”the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after exclusion of other causes.”

The average prevalence of peripheral sensorimotor neuropathy in diabetes is about 30%, irrespective of gender or type of diabetes. Diabetic neuropathy shows a positive association with both age and duration of diabetes and is very common (a prevalence of up to 60%) in older patients with type 2 diabetes. It should be emphasized that the prevalence of symptomatic neuropathy (burning sensation, pins and needles or allodynia, shooting, sharp and stabbing pain or muscle cramps in the legs) is less common (20–30%) among patients with neuropathy; thus, most of the patients with neuropathy are asymptomatic. Often, the first sign of peripheral neuropathy is a neuropathic ulcer. Other patients have neuropathic pain and on examination are found to have a severe loss of sensation. This combination is described as ”painful–painless feet,” and these patients are at increased risk for foot ulceration.

Peripheral neuropathy, beyond a loss of protective sensation, leads to small muscle wasting, foot deformities and gait disturbances, all of which are associated with increased plantar pressures and callus formation.

Peripheral autonomic neuropathy affects the distal parts of the lower limbs and leads to reduced sweating, dry skin, fissures and callus formation. Cross-sectional data show that reduced sweating and dryness of the skin of the feet is associated with an increased risk for foot ulceration. With opening of the arteriovenous shunts in the skin, in the absence of severe PAD, the feet may be warm with distended dorsal veins. The warm, insensitive and dry foot is at risk for ulceration partly because the patient has a false sense of security, as most patients perceive vascular disease as the main cause of foot problems.

Trauma, either internal (from calluses, ingrown nails and foot deformities) or external (from ill-fitting shoes and insoles, burns and foreign bodies), is a sufficient cause for skin breakdown. The pathways to foot ulceration are depicted in Figure All patients with diabetes should be examined at least annually for peripheral neuropathy, so that those at risk for ulceration can be identified. A diagnosis of peripheral neuropathy should be based on the history and clinical examination and can be made easily in a few minutes.

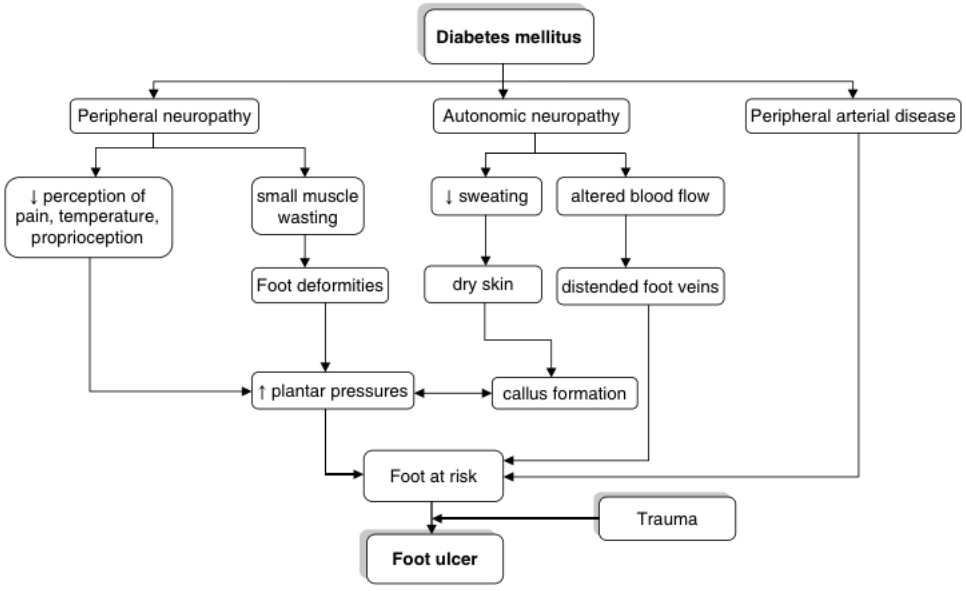


Figure: 1

Other Risk Factors of Foot Ulceration

Beyond neuropathy and PAD, a history of previous foot ulceration or amputation, foot deformities, calluses, neuro-osteoarthropathy (Charcot arthropathy) and high plantar pressures have been associated with an increased risk for foot ulceration. Limited joint mobility may result in high plantar pressures. In addition, poor vision, diabetic nephropathy and especially dialysis, and social factors including low social position, poor access to healthcare services, poor education and living alone have all been associated with foot ulceration. Cigarette smoking is also considered a risk factor for foot ulceration because it is associated strongly with both PAD and neuropathy. Another important factor for foot ulceration is poor compliance of the patient with medical instructions and neglectful behaviour. Edema may impair the blood supply to the foot, particularly in patients with PAD.

The risk factors for foot ulceration are summarized below

- Previous amputation
- Past foot ulcer
- Peripheral neuropathy
- Foot deformity
- Peripheral arterial disease
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)
- Poor glycemic control
- Cigarette smoking

Classification of Foot Problems

Classically, diabetic foot ulcers are neuropathic in the presence of neuropathy but no ischemia, ischemic if they are due to ischemia in the absence of neuropathy, and of mixed etiology (neuro-ischemic) if neuropathy and ischemia coexist. However, this is a rather crude classification for the initial evaluation. Many efforts have been made, for both clinical and research purposes, to categorize foot ulcers according to extension, size and depth, location, presence of infection and ischemia.

The Meggitt-Wagner classification is the best known and validated system for foot ulcers and is described as below.

Meggitt-Wagner classification of foot ulcers.

Grade 0 Pre- or post-ulcerative lesion completely epithelialized

Grade 1 Superficial, full-thickness ulcer limited to the dermis, not extending to the subcutis

Grade 2 Ulcer of the skin extending through the subcutis with exposed tendon or bone and without osteomyelitis or abscess formation

Grade 3 Deep ulcers with osteomyelitis or abscess formation

Grade 4 Localized gangrene of the toes or the forefoot

Grade 5 Foot with extensive gangrene

Advantages and Disadvantages of the Meggitt-Wagner Classification System

Advantages

- It is simple in use and has been validated in many studies
- Higher grades are directly related to increased risk for lower limb amputation
- It provides a guide to plan treatment
- It is considered the gold standard against which other systems should be validated

Disadvantages

- Although the presence of infection and ischemia are related to poor outcome, ischemia is not taken into account in patients with grades 1–3 and infection in grades 1, 2 and 4
- The location and size of the ulcer are not evaluated
- Neuropathy status is not evaluated

The University of Texas classification system for diabetic foot wounds.

The University of Texas classification system for diabetic foot wounds has been proposed and validated by the University of Texas. This system evaluates both the depth of the ulcer – as in the Meggitt- Wagner classification system – and the presence of infection and ischemia. Uncomplicated ulcers are

classified as stage A, infected ulcers as stage B, ulcers with ischemia as stage C and ulcers with both infection and ischemia as stage D. Grades 1 and 2 are similar to the Meggitt-Wagner classification. Grade 3 ulcers are those penetrating to bone or joint.

This system has been evaluated prospectively, showing that the greater the grade and stage of an ulcer, the greater the risk for non-healing and amputation. Thus, the healing rate of foot ulcers was 90% for stage A, 89% for stage B, 69% for stage C and only 36% for stage D. The advantages and disadvantages of the University of Texas system are shown below. The system can be used in every day clinical practice.

Grade					
Stage		0	1	2	3
	A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
	B	With infection	With infection	With infection	With infection
	C	With ischemia	With ischemia	With ischemia	With ischemia
	D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

Table: 1

Advantages and Disadvantages of the University of Texas Classification System for Diabetic Foot Wounds

Advantages

- It is simple in use and more descriptive
- It has been evaluated and has shown greater association with the outcome of an ulcer, healing or amputation, compared with the Meggitt-Wagner classification

- Cases with infection and/or ischemia are classified
- It provides a guide to plan treatment

Disadvantages

- The location and size of the ulcer are not evaluated
- Neuropathy status is not evaluated

In 2003, the International Working Group on the Diabetic Foot proposed the PEDIS system (P, perfusion; E, extent/size; D, depth/tissue loss; I, infection; S, sensation) to classify foot ulcers for prospective research. The PEDIS system is more complex and classifies foot ulcers into five categories. It also includes subcategories (grades) according to the severity of ischemia (grades 1–3), depth/tissue loss (grades 1–3) and infection (grades 1–4), as well as taking into consideration the dimensions of the ulcer. Modifications of the PEDIS system have been used and evaluated prospectively. One study showed that a modified PEDIS system predicted foot ulcers and outcome better than the original PEDIS system.

The PEDIS System

Perfusion

Grade 1: No symptoms or signs of PAD in the affected foot in combination with:

- palpable foot arteries or
- ABI 0.9–1.1 or
- TBI>0.6 or
- tcpO2>60 mmHg

Grade 2: Symptoms or signs of PAD, but not of CLI:

- presence of intermittent claudication or
- ABI <0.9 but with ankle pressure> 50 mmHg or
- TBI <0.6 but with systolic toe blood pressure> 30 mmHg or
- TcPO2 30–60 mmHg or
- other abnormalities of non-invasive testing, compatible with PAD but not with CLI

Grade 3: CLI, as defined by:

- systolic ankle blood pressure< 50 mmHg or
- systolic toe blood pressure< 30 mmHg or
- TcPO2< 30 mmHg

Extent/Size

Wound size (in square centimeters determined by multiplying the largest diameter by the second largest diameter), preferably after debridement

Depth/Tissue Loss

Grade 1: Superficial full-thickness ulcer, not penetrating any structure deeper than the dermis

Grade 2: Deep ulcer, penetrating below the dermis to subcutaneous structures, involving fascia, muscle or tendon

Grade 3: All subcutaneous layers of the foot involved, including bone and/or joint (exposed bone, probing bone)

Infection

Grade 1: No symptoms or signs of infection

Grade 2: Infection involving the skin and the subcutaneous tissue only (without involvement of deeper tissues and without systemic signs, as described below). At least two of the following items are present:

- local swelling or induration
- erythema >0.5–2 cm around the ulcer
- local tenderness or pain
- local warmth
- purulent discharge (thick, opaque to white or sanguineous secretion)

- Other causes of inflammatory response of the skin should be excluded (trauma, gout, acute Charcot neuro-arthropathy, fracture, thrombosis, venous stasis)

Grade 3: Erythema >2 cm plus one of the items described above (swelling, tenderness, warmth, discharge) or infection involving structures deeper than skin and subcutaneous tissue such as abscess, osteomyelitis, septic arthritis or fasciitis. No systemic inflammatory response signs, as described below

Grade 4: Any foot infection with the following signs of a systemic inflammatory response syndrome. This response is manifested by two or more of the following conditions:

- temperature> 38 or< 36°C
- heart rate>90 beats minutes−1
- respiratory rate>20 breaths minutes−1
- PaCo2<32 mmHg
- white blood cell count >12 000 or<4000 mm−3
- greater than 10% immature (band) forms

Sensation

Grade 1: No loss of protective sensation on the affected foot detected, described as the presence of the sensory modalities described below

Grade 2: Loss of protective sensation defined as the absence of perception of the one of the following tests in the affected foot:

- Absent pressure sensation, determined with a 10 g monofilament, on two out of three sites on the plantar surface of the foot, as described by the International Working Group on the Diabetic Foot
- Absent vibration sensation (determined with a 128 Hz tuning fork) or vibration perception threshold >25 V (using semi-quantitative techniques), both tested on the hallux.

ABI, ankle–brachial index; CLI, critical limb ischemia; PaCo2, arterial partial pressure of carbon dioxide; PAD, peripheral arterial disease; TBI; toe–brachial index; TcPo2, transcutaneous oxygen pressure(atlas).

Anatomic Risk Factors for Diabetic Foot Ulceration

Pes Planus or Adult-Acquired Flatfoot Deformity (Flatfoot)

Pes planus is characterized by diminished longitudinal and transverse concavities of the foot.

Bunion

A bunion is an enlargement of bone or tissue around the first metatarsophalangeal joint, or a swollen bursal sac and/or osseous (bony) deformity that has grown on this joint. Hallux valgus is the deformity most commonly associated with a bunion.

Hallux Valgus and Convex Triangular Foot

Hallux valgus is considered to be a medial deviation of the first metatarsal and a lateral deviation and/or rotation of the hallux, with or without medial soft tissue enlargement of the first metatarsal head. Hallux valgus and the associated varus posture of the first metatarsal bone cause various deformities of the other toes, such as varus, clawing and valgus formation A convex triangular foot is characterized by convergence of the first and fifth toes, and claw deformities of the central three toes.

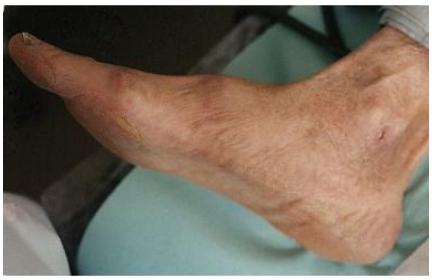


Figure:2 Pes planus

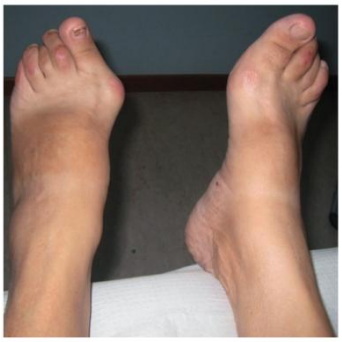


Figure:3 Traingular forefeet with overriding toe. Hallux valgus and a bunion of the left foot, as well as claw toes, can be seen. Corns are present on the phalangophalangeal joints

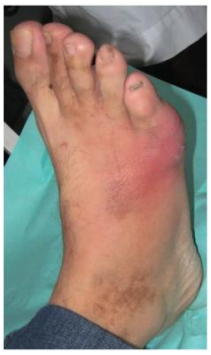


Figure:3 Quintus varus and bunionette with an infected neuropathic ulcer and cellulitis.

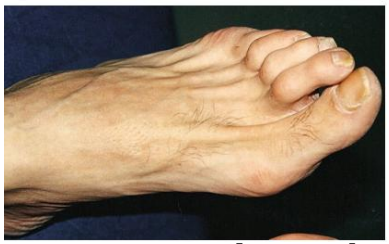


Figure:4 Muscle atrophy with claw toes and hallux valgus with quintus varus and bunionette.

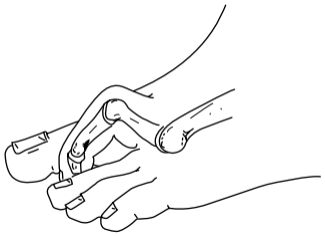


Figure:5 Claw toe.

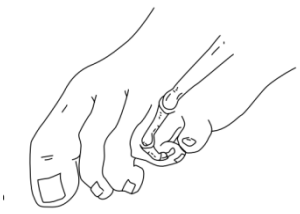


Figure:6 Curly fourth toe.

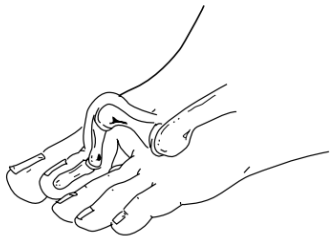


Figure:7 Hammer toe

Figure:8 Mallet toe

• Bunionette (Tailor‘s Bunion)

A bunionette is an acquired lesion of the lateral aspect of the fifth metatarsal head. The name ”tailor‘s bunion” originates from the traditional cross-legged sitting posture of tailors, pressing the lateral aspects of their fifth metatarsal heads onto sturdy benches.

• Protruding Interphalangeal Joints

A callus over a tuberosity of a phalanx of the great toe , or a painful end-corn on the crown of a protruding interphalangeal joint of a lesser toe, a consequence of chronic pressure in the shoe, is a frequent complication even in feet with normal sensation. The corn leads to ulceration in neuropathic feet.

• Claw Toes

Severe atrophy of the intrinsic foot muscles (lumbrical and interossei), due to motor neuropathy, results in an imbalance of the foot muscles and cock-up toes. This is a typical appearance of a neuropathic foot.

• Prominent Metatarsal Heads

Claw toe deformities may cause prominence of the metatarsal heads with subsequent callus formation and ulceration. Ulcers and eventual osteomyelitis

may develop under the metatarsal heads or at the tips of the claw toes, since they are abnormally exposed to pressure during walking.

• Pes Cavus

The spectrum of associated deformities observed with pes cavus includes clawing of the toes, posterior hindfoot deformity (described as an increased calcaneal angle), contracture of the plantar fascia, and cock-up deformity of the great toe.

• Curly Toe

A curly toe consists of a neutral position or plantar flexion of the metatarsophalangeal joint, and plantar flexion of the proximal interphalangeal and distal interphalangeal joints, of more than 5° each A curly toe is a common congenital malformation (with the third or fourth toe overlapping the adjacent toe). Inward or outward rotation may be present.

Other anatomical risk factors are:

• Varus Deformity of the Toes

• Talipes Equinus (Clubfoot)

• Hammer Toe Deformity

• Overriding Toe

• Mallet Toe

• Charcot Foot

Methods of Prevention

Preventing foot complications begins with identifying those at risk, that is, those with previous foot ulcers, prior lower extremity amputations, a long duration (over 10 years) of diabetes, poor glycemic control, impaired vision, structural abnormalities of the lower extremities (calluses, hammer or claw toes, flat feet, bunions, etc.), reduced joint mobility, dry or fissured skin, tinea or onychomycosis and also improperly fitting footwear. Callus must be removed regularly.

First, the patient should be informed about the possible symptoms and signs of foot problems, so that he or she can identify them at their onset, notify the healthcare provider about their existence and seek ways of management. For example, some simple clues can point to circulatory problems: poor pulses, cold feet, thin or blue skin, and lack of hair signal that the feet are not getting enough blood.

Nerve damage may lead to unusual sensations in the feet and legs, including pain, burning, numbness, tingling and fatigue. Patients should describe these symptoms if they occur, including the timing, whether the feet, ankles or calves are affected, and what measures relieve the symptoms. Nerve damage may cause no symptoms as the foot and leg slowly lose sensation and become numb. This can be very dangerous because the person may be unaware that they have improperly fitting shoes, a stone or other irritant in a shoe, or other problems that could cause damage.

Other recommendations to consider are:

- Controlling blood sugar levels can reduce the blood vessel and nerve damage that often leads to diabetic foot complications, and is a vital part of patient care.
- The patients should avoid smoking.
- The use of heating pads or hot water bottles, and stepping into a bath without checking the temperature, should be avoided.
- The toenails should be trimmed to the shape of the toe and filed to remove sharp edges. The patient should be advised never to cut (or allow a manicurist to cut) the cuticles. Patients should never open blisters, try to free ingrown toenails or otherwise break the skin of the feet. A healthcare provider or podiatrist should be consulted for even minor procedures.
- 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, if his or her vision is impaired, have someone else perform the examination. Foot inspection may be the single most important precaution against ulceration that a patient can take.
- The feet should be washed daily in tepid water. Mild soap should be used, and the feet should be dried by gentle patting. A moisturizing cream or

lotion should then be applied. This is even more important in the case of dry or cracked skin.

- The patient should avoid walking barefoot at any time, both indoors and outdoors, even for short periods of time. Shoes should not be worn without socks, even for a short period. New shoes should not be worn for more than one hour a day, and the feet should be inspected after taking off new shoes; if there is any foot irritation, the patient should inform the healthcare provider. Patients should change their shoes at noon and, if possible, again in the evening; this prevents high pressures remaining on the same area of the foot for a prolonged time. Inspect and palpate the inside of the shoes before wearing them.
- Inappropriate footwear is a major cause of ulceration. The aim of providing special shoes and insoles (preventive footwear) to diabetic patients at risk for foot ulceration is to reduce peak plantar pressures over areas ”at risk,” and to protect the feet against injuries from friction.

Methods of Ulcer Healing

1 Chronic Diabetic Wounds

Recent data described that local concentrations of growth factors such platelet-derived growth factor, vascular endothelial growth factor, epidermal and fibroblast growth factor and transforming growth factor-β are not necessarily low in patients with chronic diabetic wounds; however, in the

environment of chronic wounds there is an imbalanced tuning between local neuropeptides, proinflammatory cytokines, and the down-stream proliferative response as well as fragmentation of heparan sulfate, which is a major component of the extracellular matrix in the dermis, as a result of the imbalanced production of serine proteases and matrix metalloproteinases, leading eventually to retardation in wound healing. Experimental data has shown that mast cells participate in wound healing process. Wound microbiota seems to play an important role in wound healing and may serve as prognostic biomarker. Additionally, chronic wounds exudate and biofilm has proved to degrade many of natural and synthetic substrates and derive from inflammatory cells, lytic cells, and local bacteria. Thus, diabetic chronic wounds microenvironment is hostile for local growth factors stability, chemical integrity, bioavailability, and ultimately to their physiological role as major drivers for the healing process. Thus, patients with diabetic foot ulcers who fail to heal by 53% over a 4-week period or if the reduction in ulcers ‘size is less than 0.7mm per week have limited chances to achieve complete wound healing over a 12-week period.

2 Wound Bed Preparation

The term ”wound bed preparation” applies to facilitation of the healing process by optimizing the base and edges of the wound. Management of the infection by the systematic or local use of antibiotics, revascularization when

indicated, debridement and reduction of edema are prerequisites for wound healing.

3 Debridement

Debridement should be employed to all chronic wounds to remove surface debris and necrotic tissues. Debridement can be achieved by different means, namely surgically, enzymatically, biologically and by autolysis.

3.1 Surgical Debridement

Surgical (sharp) debridement is rapid and effective, and can remove large volumes of hyperkeratosis and dead tissue. Wide excision of the wound has been proposed as a method of changing the biology of the chronic ulcer for that of an acute one. Care should be taken during repeated surgical debridement to protect healthy tissue, which has a red or deep pink (granulation tissue) or pink appearance at the wound borders, or isolated pink islets on the surface (epithelial tissue).

Sharp debridement can be performed using, instead of scalpels, modern technology based on ultrasound or hydrosurgery such as Versajet. These devices are expensive and are indicated for the debridement of necrotic areas or when debridement with other methods is not possible.

3.2 Enzymatic Debridement

Enzymatic debridement can be achieved using of a variety of enzymatic agents including crab-derived collagenase, collagen from krill, papain, a combination of streptokinase and streptodornase, and dextrans. These can remove necrotic and sloughy material without damaging healthy tissue. Enzymatic debridement is expensive and requires skill for its application. It is indicated specifically for neuro-ischemic and ischemic ulcers because surgical debridement may be extremely painful.

3.3 Biologic Debridement

This type of debridement has been developed in recent years using sterile maggots. Maggots, when applied to the wound, can digest surface debris, bacteria and necrotic tissues, while respecting healthy tissue. Recent reports suggest that they are particularly effective in the eradication of drug-resistant pathogens such as methicillin-resistant Staphylococcus aureus from wound surfaces. Larval therapy is suitable for the debridement of infected ulcers, ulcers with heavy exudate and dry gangrenous areas.

3.4 Autolytic Debridement

This technique involves the use of dressings that permit a moist wound environment, so that host defense mechanisms (neutrophils, macrophages) will clear devitalized tissue using the body‘s own enzymes. Autolysis is augmented in the moist wound environment with the use of proper dressings such as hydrocolloids, hydrogels, and films. Autolysis is highly selective, with no damage to the surrounding skin.

4 Dressings

Ulcers heal more quickly and are complicated less often by infections in the moist environment of the wound. The only exception to this rule is dry gangrene, where the necrotic area should be kept dry to avoid infection and wet gangrene.

Management of the wound environment by proper dressings, in addition to off-loading, can augment healing and prevent infections. The characteristics for optimal wound dressings have been described as follows. Dressings should:

- Be free from particulate or toxic contaminants,
- Remove excess exudates and toxic components,
- Maintain a moist environment at the wound–dressing interface,
- Be impermeable to microorganisms, thus protecting against secondary infection,
- Allow gaseous exchange,
- Be easily removal without trauma,
- Be transparent or changed frequently, thus allowing monitoring of the wound,
- Be acceptable to the patient, be conformable and not take up too much space in the shoe,
- Be cost-effective,
- Be available in hospital and in the community.

Type of dressing	Necrotic/ gangrenous	Infection	No exudate	Low exudate	Moderate exudate	High exudate	Cavity without sinus	Cavity with sinus tract
Gauzes	+	+	+	+	+			
Dry enzymatic debriders	+							
Films			+	+				
Foams		+		+	+	+		
Hydrogels	+		+	+			+	+
Hydrocolloids				+	+		+	
Alginates		+		+	+	+	Alginate rope or gel	Alginate rope or gel
Dressings with active charcoal		+		+	+	+		
Hydrofibers		+			+	+		
Dressings with honey		+		+	+	+	+ (ointment)	+ (ointment)
Sucrose octasulfate dressing	+			+	+			
Dressings with antimicrobial properties (Sorbact)		+			+	+	+	+ (rope)

Table: 2 Properties of and indications for available dressings

Appearance of the wound	Type of dressing
Healthy granulous tissue	Film, hydrocolloid, foam if exudate is present
Sloughy base, exudate	Alginate, foam, microfibers, Sorbact
Sloughy base, necrosis	Hydrogels, enzymatic debriders
Sloughy base, infection	Alginates, Sorbact, dressings with active charcoal, honey, or silver. Consider dressings with active charcoal if odor is present
Dry gangrene	Keep the gangrenous area dry. Use alcohol solution or local povidone-iodine
Neuroischemic ulcers	Sucrose octasulfate dressing

Table: 3 Selection of dressings according to the characteristics of the ulcers.

Type of dressing	Advantages	Disadvantages
Gauzes	Cheap and widely available. Appropriate for gangrenous lesions	Adhere to the wound bed and may cause bleeding on removal. Do not create a moist environment. Limited absorbing capacity. Provide little protection against bacterial contamination. Fibers can be incorporated into the wound tissue
Films	Semi-permeable. Allow inspection of the wound. Form a bacterial barrier. Durable. Require changing every 4–five days	Useful on flat or superficial wounds only. Some patients are allergic to the adhesive in the dressing
Foams	Appropriate for ulcers with low-to-high volumes of exudate. Provide thermal insulation. Easily conformable. May be used to fill cavities without sinus tracts	Variability of absorbency of different foams. Limited published data
Hydrogels	Effective, versatile and easy to use. Very selective, with no damage to the surrounding skin. Safe process, using the body's own defense mechanisms. Promote autolysis and healing. Decrease risk of infection. Useful in removing slough and necrosis from wounds. May be used to fill cavities with sinus tracts	Effect difficult to quantify. Not as effective and rapid as surgical debridement. Not appropriate for neuro-ischemic ulcers, which produce minimal exudate. Wound must be monitored closely for signs of infection
Hydrocolloids	Safe and selective process, using the body's own defense mechanisms. Good for necrotic lesions with low-to-moderate exudate. May be used to fill cavities without sinus tracts. Can be easily used with a shoe. Adhesive surface prevents slippage. Do not require daily dressing changes. Cost-effective	Their occlusive and opaque nature prevents daily observation of the wound. Wounds must be monitored closely for signs of infection. May promote anaerobic growth and cover a secondary infection
Alginates	Useful as absorbents of exudates. Good for infected ulcers. Some products have hemostatic properties, and some reduce bacterial load	Not appropriate for neuro-ischemic ulcers, which produce minimal exudate. Some researchers think they may traumatize the wound bed and predispose to infections. May dry out and form a plug within the wound bed. Require painstaking removal using large amounts of saline
Enzymatic debriders	Good for any wound with a large amount of necrotic debris, and for eschar formation. Promote autolysis and fast healing. Decrease maceration of the skin and risk of infection	Costly. Application must be performed carefully and only to the necrotic tissue. May require a specific secondary dressing. Irritation and discomfort may occur
Sucrose octasulfate dressing	Efficacy proven for neuro-ischemic ulcers in a large randomized-double blind, placebo controlled clinical trial	Costly. No proven efficacy in neuropathic and no indication for infected ulcers. Proper for ulcers with low-to-moderate exudate
Dressings with antimicrobial properties (Sorbact)	Bind wound bacteria rapidly and effectively. Reduce the bacterial load and support the natural wound healing process. Wide range of formats. No development of bacterial resistance. Indication for infected or heavily contaminated ulcers with a sloughy base	Costly. Limited published data
Dressings with honey	Anti-inflammatory and bactericidal properties. Reduce the formation of reactive oxygen species. Enzymatic debridement; accelerate all phases of healing. Indicated for all types of ulcer except gangrenous	Dressings proper for superficial ulcers only. For deep ulcers, ointment and additional dressing are required. Limited published data
Dressings with active charcoal	Bactericidal activity. Reduce odor. Indicated for infected/heavily contaminated ulcers	Costly. Secondary dressing may be required when the volume of exudate is large. For ulcers with little exudate, a paraffin dressing on the wound surface is recommended to prevent dryness
Microfibers	High absorption capacity. Assure a moist environment. Absorb and retain microorganisms	Costly. Limited published data

Table 4: Advantages and disadvantages of available types of dressing

5 Offloading

The use of offloading techniques, commonly known as pressure modulation, is considered the most important component for the management of neuropathic ulcers in patients with diabetes[10, 11]. Recent studies have provided evidence indicating that proper offloading promotes DFU healing [12-14]. Although many offloading modalities are currently in use, only a few studies describe the frequency and rate of wound healing with some of the methods frequently used clinically. The choice of these methods is determined by patient physical characteristics and abilities to comply with the treatment along with the location and severity of the ulcer[11].

The most effective offloading technique for the treatment of neuropathic DFU is total contact casts (TCC)[11,15,16]. TCC is minimally padded and moulded carefully to the shape of the foot with a heel for walking. The cast is designed to relieve pressure from the ulcer and distribute pressure over the entire surface of the foot; thus, protecting the site of the wound[11]. Mueller et al[16] conducted an RCT that showed TCC healed a higher percentage of plantar ulcers at a faster rate when compared with the standard treatment. In addition, a histologic examination of ulcer specimens has shown that patients treated with TCC before debridement had better healing as indicated by angiogenesis with the formation of granulation tissue than for patients treated with debridement alone as indicated by a predominance of inflammatory elements[17]. The contributory factors to the efficacy of TCC treatment are

likely to be due to pressure redistribution and offloading from the ulcer area. In addition, the patient is unable to remove the cast, which thereby forces compliance, reduces activity levels, and consequently improves wound healing[13]. However, the frequency of side effects referred to in the literature and minimal patient acceptance make this approach inappropriate for wide applications[18,19]. Fife et al[20] has shown that TCC is vastly underutilized for DFU wound care in the United States. Based on this study, only 16% of patients with DFU used TCC as their offloading modalities. The main disadvantage of TCC was the need for expertise in its application. Most centers do not have a physician or cast technician available with adequate training or experience to safely apply TCC. In addition, improper cast application can cause skin irritation and in some cases even frank ulceration. Also, the expense of time and materials (the device should be replaced weekly), limitations on daily activities (e.g., bathing), and the potential of a rigid cast to injure the insensate neuropathic foot are considered other disadvantages. Furthermore, TCC does not allow daily assessment of the foot or wound, which is often contraindicative in cases of soft tissue or bone infections[12]. In some cases, it is suggested to use other kinds of offloading techniques such as a removable cast walker (RCW) or Instant TCC (iTCC).

An RCW is cast-like device that is easily removable to allow for self-inspection of the wound and application of topical therapies that require frequent administration[11,19]. The application of this method allows for

bathing and comfortable sleep. In addition, because RCW is removable, they can be used for infected wounds as well as for superficial ulcers[11]. However, in a study that compared the effectiveness of TCC, RCW, and half-shoe, this method did not show equivalent healing time (mean healing time: 33.5, 50.4, and 61.1 d, respectively), and a significantly higher proportion of people with DFU were healed after 12 wk wearing a TCC compared with the two other widely used offloading modalities[10].

iTCC, which involves simply wrapping a RCW with a single layer of cohesive bandage, Elastoplast or casting tape, is another offloading technique that is shown to be more effective than TCC [21] and RCW [22]. This technique forces the patient to adhere to advice to immobilize the foot while allowing for ease of application and examination of the ulcer as needed. A preliminary randomized trial of TCC vs iTCC in the management of plantar neuropathic foot ulcers has confirmed equivalent efficacy of the two devices and that iTCC is cheaper, quicker to apply, and has fewer adverse effects than traditional TCC[22]. As this device does not require a skilled technician to apply it, it could revolutionize the future management of plantar neuropathic ulcers. It has been suggested that iTCC will dramatically change the treatment of non-ischemic, neuropathic, diabetic plantar ulcers, and has the potential to replace TCC as the gold standard for offloading plantar neuropathic ulcers[21].

Regardless of the modality selected, patients should return to an unmodified shoe until complete healing of the ulcer has occurred. Furthermore, any shoe that resulted in the formation of an ulcer should not be worn again[23].

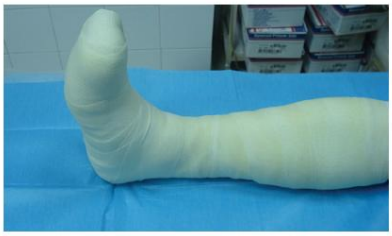


Figure:9 Total contact cast

Figure:10 A removable cast walker

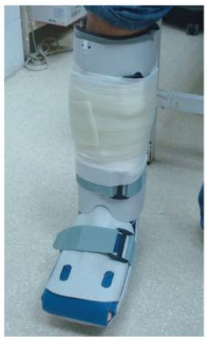


Figure:11 An instant total contact cast

Figure:12 An open toe total contact cast

Figure:13 A half shoe off loading the forefoot

Figure: 14 A half shoe for off loading the rearfoot

6 Growth Factors

6.1 Platelet-Derived Growth Factor-β

Platelet-derived growth factor-β has been developed as a safe and effective topical therapy for the treatment of non-infected diabetic foot ulcers. It is applied by the patient as a gel to the ulcer surface once daily, while the ulcer is debrided on a weekly basis. A dose of 100 μg has been demonstrated to be the most effective.

6.2 Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an autologous product that concentrates a high number of platelets in a small volume of plasma. It mimics the last step of the coagulation cascade, leading to the formation of a fibrin clot, which consolidates and adheres to the application site in a short period of time. Absorption of the fibrin clot is achieved during wound healing within days to weeks following application. Factors secreted from platelets are serotonin, fibronectin, adenosine diphosphate, thromboxane A, platelet factor-4, PDGF-β, and platelet activating factor.

6.3 Granulocyte-Colony Stimulating Factor

The effect of the subcutaneous administration of granulocyte-colony stimulating factor (GCSF) in patients with infected foot ulcers was assessed in five randomized controlled trials. The results indicated a faster resolution of the infection and faster healing in four of the trials. Larger controlled studies are needed to evaluate the efficacy and safety of GCSF in the treatment of infected foot ulcers.

6.4 Basic Fibroblast Growth Factor

Basic fibroblast growth factor (bFGF) is known to be beneficial to the formation of granulation tissue and normal healing.

6.5 Epidermal Growth Factor

Epidermal growth factor (EGF) acts on epithelial cells, fibroblasts and smooth muscle cells to promote healing.

6.6 The LeukoPatch System

The LeukoPatch is a single-use medical device used to generate an autologous platelet and leucocyte-rich fibrin wound dressing. A LeukoPatch is produced from the patient‘s own venous blood by centrifugation, but without the addition of any reagents. The final product comprises a thin, circular patch composed predominantly of fibrin together with living platelets and leucocytes. The yield of platelets is close to 100% and varies minimally from patient to patient. The content and release of growth factors of this product is equal to, or higher, than other reported preparations. The product differs from other autologous platelet products by containing a high concentration of fibrin as well as both platelets and leucocytes.

6.7 Other Growth Factors

In a case study of the topical application of nerve growth factor (NGF) to chronic leg or foot ulcers that had failed to respond to standard treatment, healing was achieved after 5–14 weeks ‘treatment. This effect was ascribed to a stimulation of keratinocyte growth and new vessel formation by NGF. Accelerated cutaneous healing by means of topically administered vascular endothelial growth factor has been described in mice.

7 Bioengineered Skin Substitutes

Tissue-engineered skin substitutes are classified into allo- genic cell-containing (Apligraf, Dermagraft, OrCel), autol- ogous cell-containing (Hyalograft 3D, Laserskin Autograf, TranCell) and acellular (OASIS, GRAFTJACKET) matri- ces. The former contains living cells such as keratinocytes or fibroblasts within a matrix, whereas the latter are free from cells and act by releasing growth factors to stimulate neovascularization and wound healing. Both represent promising therapeutic adjuncts in the management of foot ulceration. All products are indicated for ulcers free of infection.

8 Extracellular matrix proteins

8.1 Hyaff

Hyaff is a semi-synthetic ester of hyaluronic acid. As an essential component of the wound matrix, hyaluronic acid facilitates the growth and movement of fibroblasts and controls hydration. So far, it has been used in the treatment of neuropathic ulcers with promising results.

8.2 Collagen

There are many products on the market containing lyo- philized collagen from various sources (bovine, porcine) alone or in combination with alginates, cellulose or anti- biotics. Collagen seems to induce the production of endogenous collagen and to promote platelet adhesion and aggregation; is also acts as a chemotactic factor for macrophages.

8.3 Regenerating Agents

ReGeneraTing Agents (RGTAs) are a family of polymers bioengineered to stabilize heparin-binding growth factors by mimicking Heparan Sulphate (HS) thereby protecting them and promoting tissue repair and regeneration. In inflammation, destruction of HS exposes the ExtraCellular Matrix–ECM (structural and cellular proteins within) to the actions of proteases and glycanases which break them down and act on cytokines and growth factors to prevent adequate repair. In injured tissue, RGTAs would replace destroyed HS by binding to the structural proteins and reconstruct the ECM scaffold. Growth factors will also bind to RGTA and resume position and organization resembling that of non-injured tissue. Experimental data have shown that RGTAs induce a regeneration process by restoring -the proper cellular micro-environment.

8.4 MMP Modulators

MMPs have an active role in the regulation of extracellular matrix components. During normal wound heal‑ ing, there is a balance between the ”construction” and ”destruction” of extracellular matrix. In chronic wounds, a high expression of MMP-2 in fibroblasts and endothelium is detected and is believed to favor destruction. Experimental data suggest that a down regulation of MMP-2 expression may augment the healing process.

9 Other Agents

9.1 Stem Cell Therapy

There is great interest in delivery of stem or progenitor cells, either applied topically or recruited from the circulation. Some preliminary work suggests that topically applied autologous bone-marrow cultured cells can heal human chronic wounds that are recalcitrant to other treatments, including growth factors and bioengineered skin. Transplantation of stem cells derived from bone marrow, peripheral blood, umbilical cord blood, or adipose tissue have been examined in various studies.

9.2 Negative-Pressure Wound Therapy

Negative-pressure wound therapy (NPWT) has emerged as a new treatment for diabetic foot ulcers. This therapy involves the use of intermittent or continuous subatmospheric pressure through a special pump (vacuum-assisted closure; e.g. V.A.C.) connected to a resilient open celled foam surface dressing covered with an adhesive drape to maintain a closed environment. The pump is connected to a canister to collect wound discharge and exudate. The optimal sub atmospheric pressure for wound healing appears to be approximately 125 mmHg, utilizing an alternative pressure cycle of five minutes of suction followed by two minutes off suction.

Experimental data suggest that NPWT optimizes blood flow, decreases tissue edema and removes exudate, proinflammatory cytokines and bacteria from the

wound area. These physiologic changes promote the development of a moist wound environment, and may increase the rate of cell division and the formation of granulation tissue.

NPWT should be delivered after debridement and should be continued until there is the formation of healthy granulation tissue at the surface of the ulcer. Two randomized controlled trials have demonstrated that the rate of ulcer healing and the time to granulation tissue formation were in favor of V.A.C. Moreover, treatment with V.A.C. resulted in lower amputation rates in comparison to the standard therapy. NPWT is well tolerated, and the device can be portable.

This therapy is contraindicated for patients with an active bleeding ulcer. Care should also be taken in patients on anticoagulant therapy as there is a risk for bleeding. Currently, NPWT is indicated for complex diabetic foot wounds.

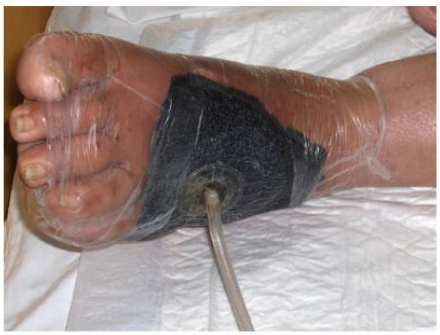


Figure:15 Application of negative pressure wound therapy using vacuum assisted closure system.

Figure: 16 A multiplace chamber to treat multiple individuals with hyperbaric oxygen.

9.3 Hyperbaric Oxygen

There is strong evidence suggesting that fibroblasts, endothelial cells and keratinocytes are replicated at higher rates in an oxygen-rich environment. Moreover, leukocytes kill bacteria most effectively when supplied with oxygen. It is also known that fibroblasts from individuals with diabetes show diminished cell turn-over in comparison with those from non-diabetic controls. Based on these data, the idea was that the administration of oxygen at high concentrations might accelerate wound healing in diabetes.

Treatment with hyperbaric oxygen therapy is the intermittent administration of 100% oxygen at a pressure greater than that at sea level. It is delivered in a chamber with the patient breathing 100% oxygen intermittently while the atmospheric pressure is increased to 2–3 atm absolute. This lasts for one to two hours. A full course typically involves 30–40 of these sessions. The technique can usually be implemented in multiplace chambers compressed to depth with air while the patient breaths 100% oxygen via a face mask or head tent.

COLLAGEN – AN OVERVIEW:

Structure Of Collagen:

About 15% of the human body is made up of proteins which are natural polymers. Collagen comprises the major protein of the extracellular matrix. In mammals, collagen is the most abundant protein as it constitutes about 25% of the total protein. About 70% to 80% of the skin (dry weight) is comprised of collagen.

The unique feature of collagen is the triple stranded helical structure. Collagen serves as a structural scaffold in various tissues. The main types of collagen found in connective tissue include Types I, II and III. Among the collagen found in the human body, 90% is comprised of these types.

FUNCTION OF COLLAGEN IN WOUND HEALING

Collagen not only functions as a structural support but along with the collagen derived fragments control many important cellular mechanisms such as synthesis of numerous proteins, cell shape and differentiation and migration.

The most abundant structural constituent of the dermal matrix is the Type I collagen. Through the formation of gelatin, collagenase helps in the dissociation of keratinocytes from the collagen rich matrix. Extracellular matrix regulates the cellular functions. Various specialized cell surface receptors process and transduce the information into the cells which is provided by the extracellular matrix macromolecules [24] .

The major functions of these receptors include initiation of migration of epithelial cells, deposition of collagen, contraction of wounds and induction of matrix degrading collagenase.

A polypeptide with the repeating sequence (Gly – X – Y) forms the basic unit of collagen. Gly, X and Y represent Glycine, proline and hydroxyproline.

The molecule thus formed twists into a left-handed helix. A triple helix is formed, when these left handed helices wrap around each other. The molecule may be made up of either 2 or 3 different alpha chains, or 3 identical alpha chains, depending on the type of collagen. There may be a continuous stretch of triple helix or it may be interrupted by non-collagenous segments.

Every third position in the repeating amino acid sequence is occupied by glycine, within the triple helical domain. As larger amino acids will not fit into the structure of the triple helix, Glycine is very essential for the triple helical conformation. X and Y positions are usually occupied by proline. Y position may be occupied by hydroxyproline, which are unique amino acids present in the collagen. Numerous lysine derived inter and intramolecular cross-links are present which stabilizes the collagen molecule.

Types Of Collagen:

Collagen constitutes a group of proteins and about 19 different types of collagen have been studied. These collagen types have been classified into three groups, based on the ability of the collagens to form fibils. The first group of

collagens is called fibril forming collagens. They form banded fibrils and they are the most easily recognized forms of collagens. The collagens belong to this group include Type I, II, III, V and XI collagens. In the proteins present in the second group of collagens, noncollagenous sequences interrupt the collagenous domains. The collagens belong to this group include Types IX, XII, XIV and XIV collagens. These collagen types are unique because they contain glycosaminoglycans covalently linked to the protein.

The third group called non-fibrillar collagens, which include Types IV, VI, VII and X. They also include network forming collagens, anchoring fibrils and invertebrate cuticle collagens. With short triple helical collagen domains, these collagens constitute to form sheets of proteins.

Tissue Distribution Of Collagen:

A mixture of collagen types is present in all the tissues. Different collagen types are present in variable proportions and also differ in their structural organization [25].

Type of collagen	Site
Type I	The most abundant collagen, which is present in scar tissue and tendons
Type II	Cartilage
Type III	Granulation tissue
Type IV	Basal lamina
Type V	Interstitial tissue
Type VI	Interstitial tissue
Type VII	Epithelia
Type VIII	Endothelial cells
Type IX	Cartilage
Type X	Hypertrophic and mineralizing cartilage
Type XI	Cartilage
Type XII	Interacts with types I and III

Table : 5 Types of collgen

Collagen‘s Role In Wound Healing:

1.Hemostasis

Platelet membrane has specific receptor sites on which binding of collagen occurs. This initiates the release of certain substances which cause adhesion and aggregation of platelets.

2. Wound debridement

Collagen has chemotactic effect on neutrophils and monocytes. Macrophages are formed from monocytes which act as scavengers and phagocytose foreign bodies.

3. Granulation and angiogenesis

Collagen releases substances which help in the growth of new capillaries. These new capillaries are responsible for the deposition of new fibres.

4. Fibroblastic activity

Collagen has a chemotactic effect on fibroblasts thereby stimulating their migration and proliferation. Collagen also promotes fibrillogenesis and governs the restoration of new tissue by organized fibers.

5. Re-epithelialisation

Keratinocytes migration, differentiation and their growth are influenced by collagen. Collagen arranges a provisional matrix for the migration of the keratinocytes by binding with fibronectin.

6. Wound remodeling

The formation of scar tissue is reduced by collagen by means of deposition of oriented and organized fibers. Collagen also determines the amount of collagenase produced by keratinocytes.

MATERIALS AND METHODS

Source of data:

The study was carried out at Tirunelveli medical college hospital for a period of two years, from September 2017 to August 2019.

Study design:

Cross sectional study.

Sample:

80 patient with diabetic foot ulcer.

INCLUSION CRITERIA:

Patient with diabetic foot ulcer less than 150 sq.cm.

EXCLUSION CRITERIA:

1. Critically ill patients

2. Any evidence of underlying bone osteomyelitis or Malignancy

TECHNIQUE:

The study was conducted on total eighty patients with diabetic foot ulcer, patients who reported at Tirunelveli medical college hospital. All diabetic foot ulcer patients, with ulcer size less than 150 sqcm attending the Surgery Department were invited to participate in the study and written informed consent was taken. All patients underwent a standard clinical and laboratory evaluation. Briefly, information about age, known DM duration, smoking habits, arterial blood pressure, and anthropometric measurements were collected. Critically ill patients and patients with underlying bone osteomyelitis

or malignancy were excluded. In all patients, wound size was measured before treatment initiation.

A collagen dressing was applied to wound, and all patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every 3 to 4 days until wound healing or for maximum period of **12 weeks.** Changes in wound size was recorded when the dressing was removed; and at 4 and 12 weeks. Healing time, follow up period was noted. All patients were followed up for adverse events. All the data was captured in the pre-printed pro-forma (given below).

DATA ENTRY AND STATISTICAL ANALYSIS:

Data was presented as mean and standard deviation.

Independent student t tests was used to compare the difference between mean and standard deviation.

Wilcoxon signed rank test was used to compare the non parametric data.

Pearson correlation test was used to find the correlation of two continuable variables. Significance was defined by P values less than 0.05 using a two-tailed test.

Statistical analysis was performed with the help of statistical package **SPSS** (Statistical Package for the Social Sciences) version 21.

END POINTS

PRIMARY ENDPOINTS:

ULCER HEALING: Time required to achieve a 60% reduction in ulcer size, compared to the pre collagen therapy ulcer size.

SECONDARY ENDPOINTS:

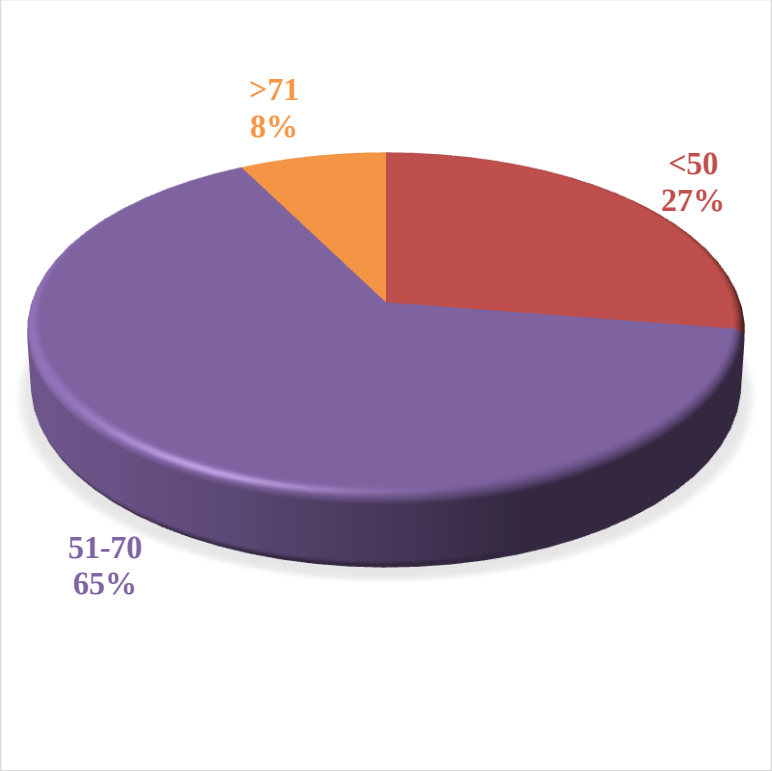
Dressing period: For a maximum of 12 weeks.

RESULTS

Table : 6 Age distribution

Age	Frequency	Percent
<50	22	27.5
51-70	52	65.0
>71	6	7.5
Total	80	100.0

Chart 1:

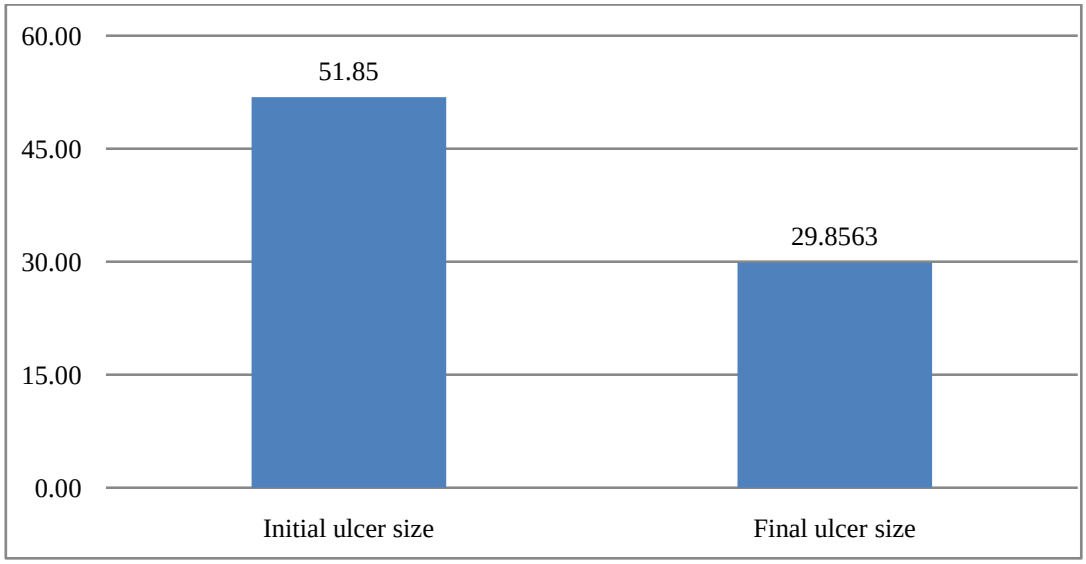


In our study, overall, the chronic leg ulcer was found most commonly in elder age group above 50yrs, with 65% in the age group between 51 to 70yrs, 8% in >71 yrs and 27% in <50 yrs.

Table : 7

	N	Mean	Std. Deviation	P value
Initial ulcer size	80	51.85	31.140	<0.0001
Final ulcer size	80	29.86	23.380	

Chart: 2



On comparing the ulcer size before and after collagen dressing there was a significant reduction in ulcer size after collagen dressing, with a p value of <0.0001.

Table: 8 Gender vs percentage reduction

Gender	N	Mean	SD	P value
Male	54	47.00	18.62	0.326
Female	26	51.10	16.63	

Chart: 3

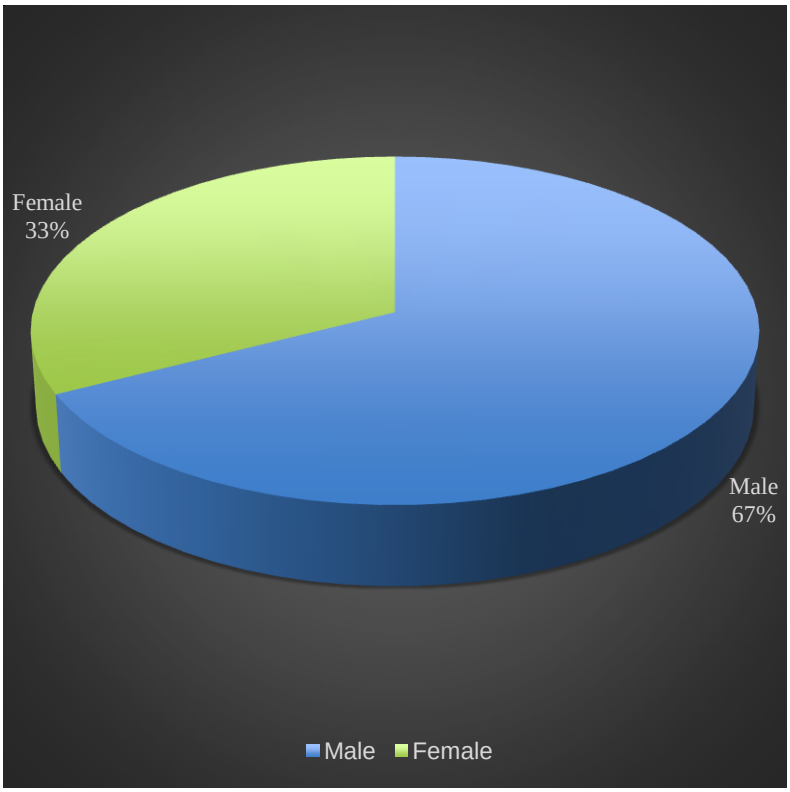
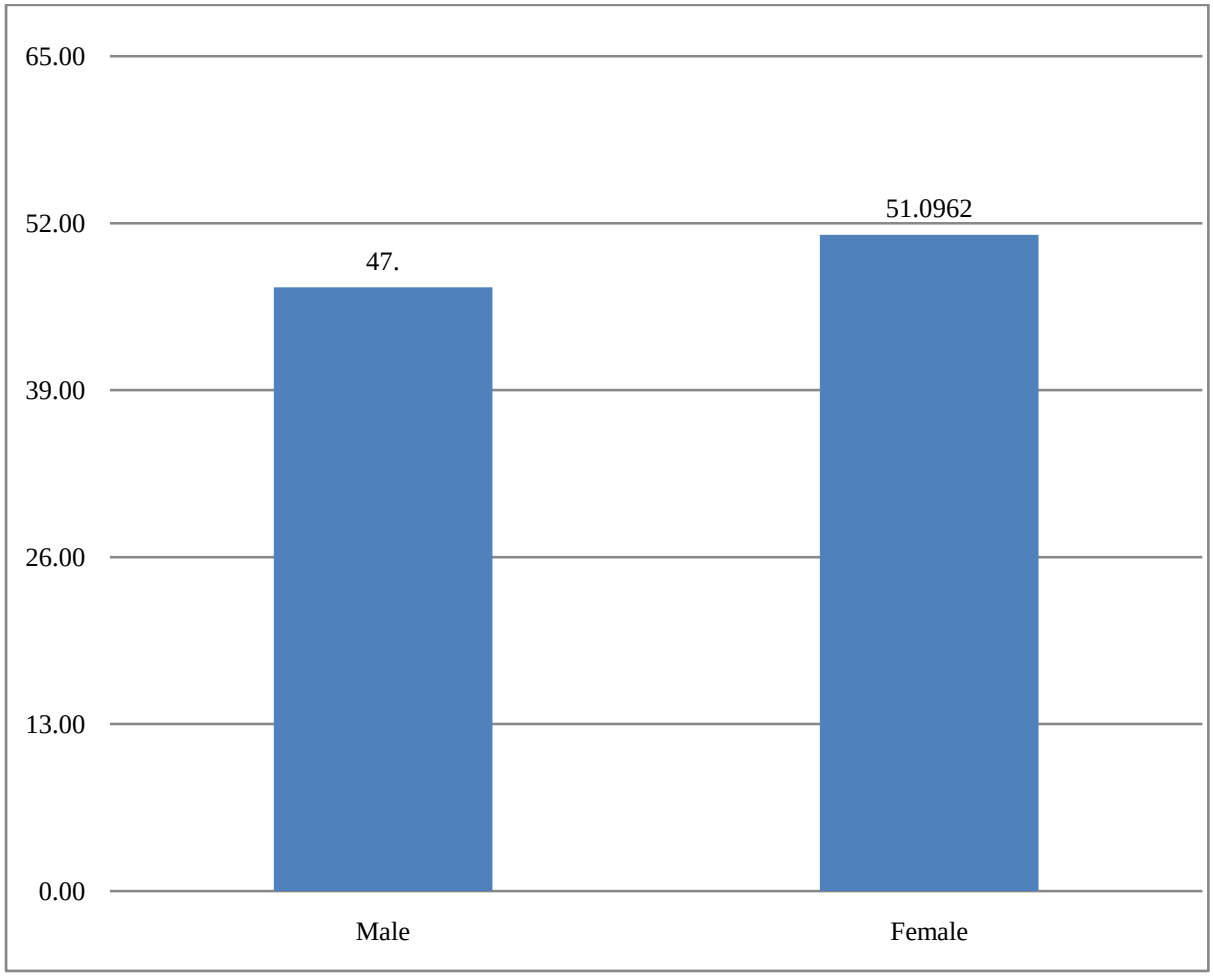


Chart: 4



High incidence of diabetic ulcers were found in males when compared to females, with comparable reduction in ulcer size in both the sexes.

Table: 9 Hypertension vs percentage reduction

Hypertension	N	Mean	SD	P value
No	25	59.12	15.2	<0.0001
Yes	55	43.43	17.11	

Chart: 5

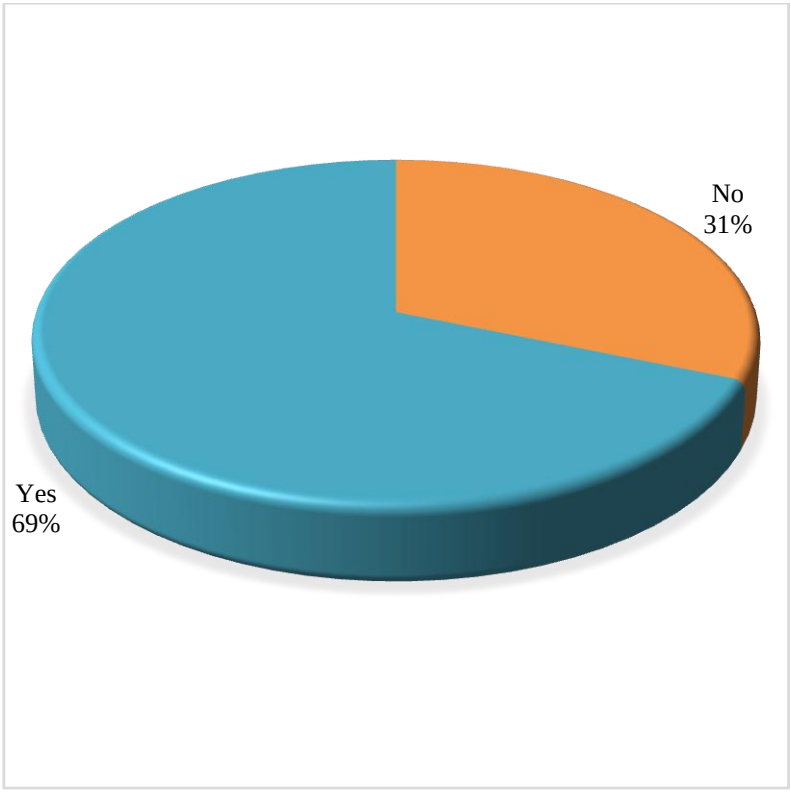
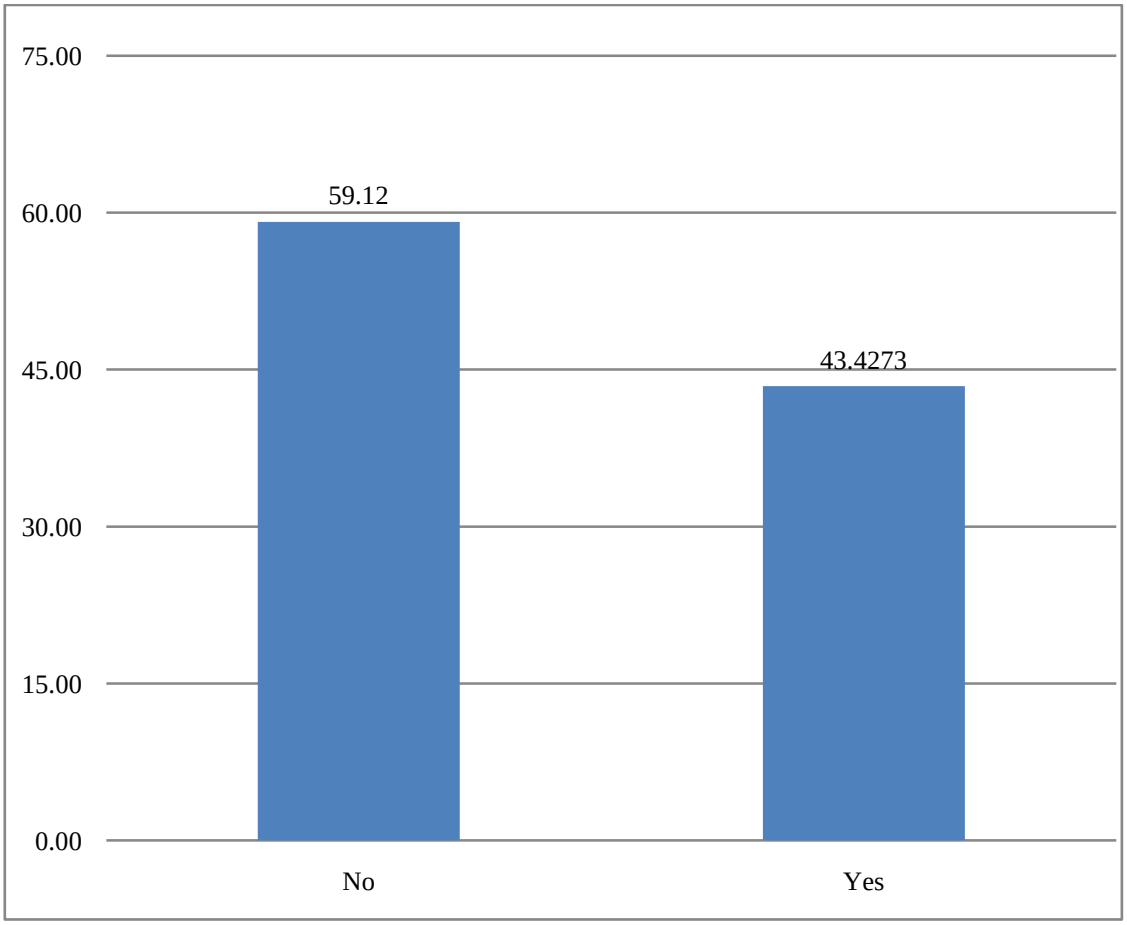


Chart: 6



In our study, out of 80 patient 55(69%) had hypertension, and showed a statistically significant lesser percentage reduction in ulcer size (43.4 ± 17.1) as compared to (59.1 ± 15.2) in patients without hypertension, with a p-value of <0.0001.

Table: 10 Smoking vs percentage reduction

Smoking	N	Mean	SD	P value
No	39	53.72	18.83	0.009
Yes	41	43.21	15.73	

Chart: 7

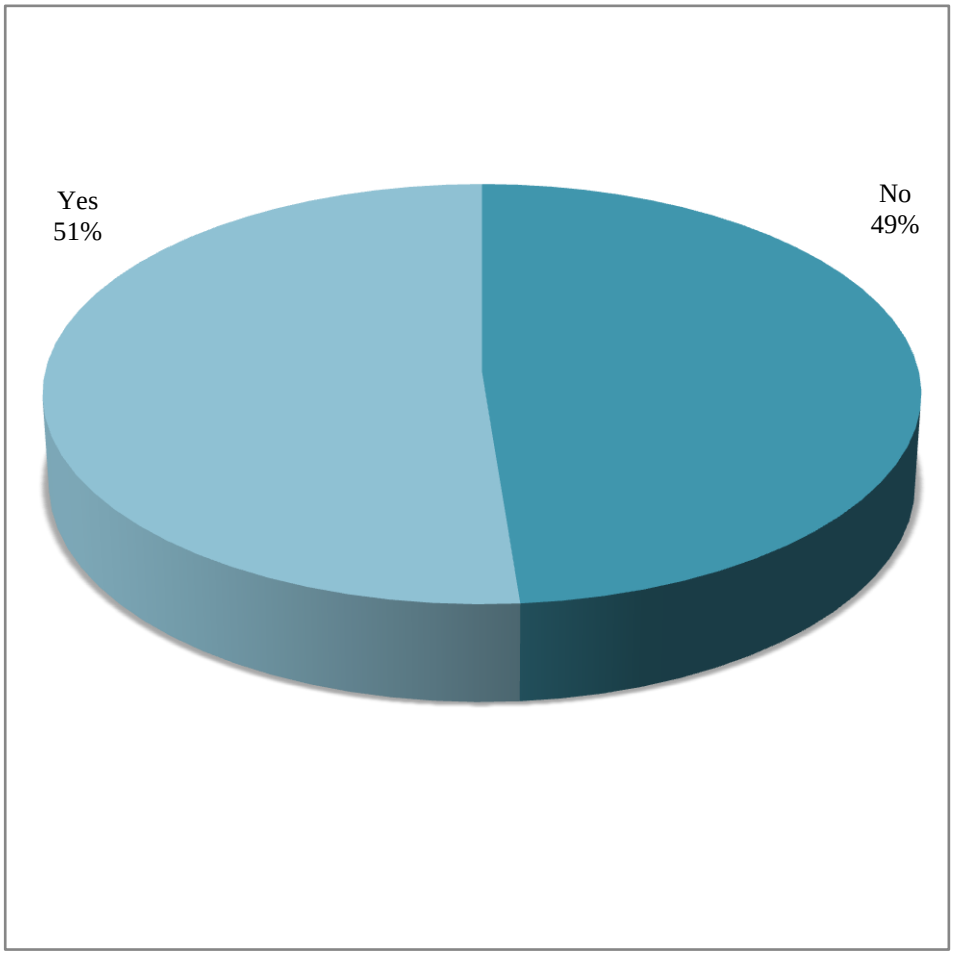
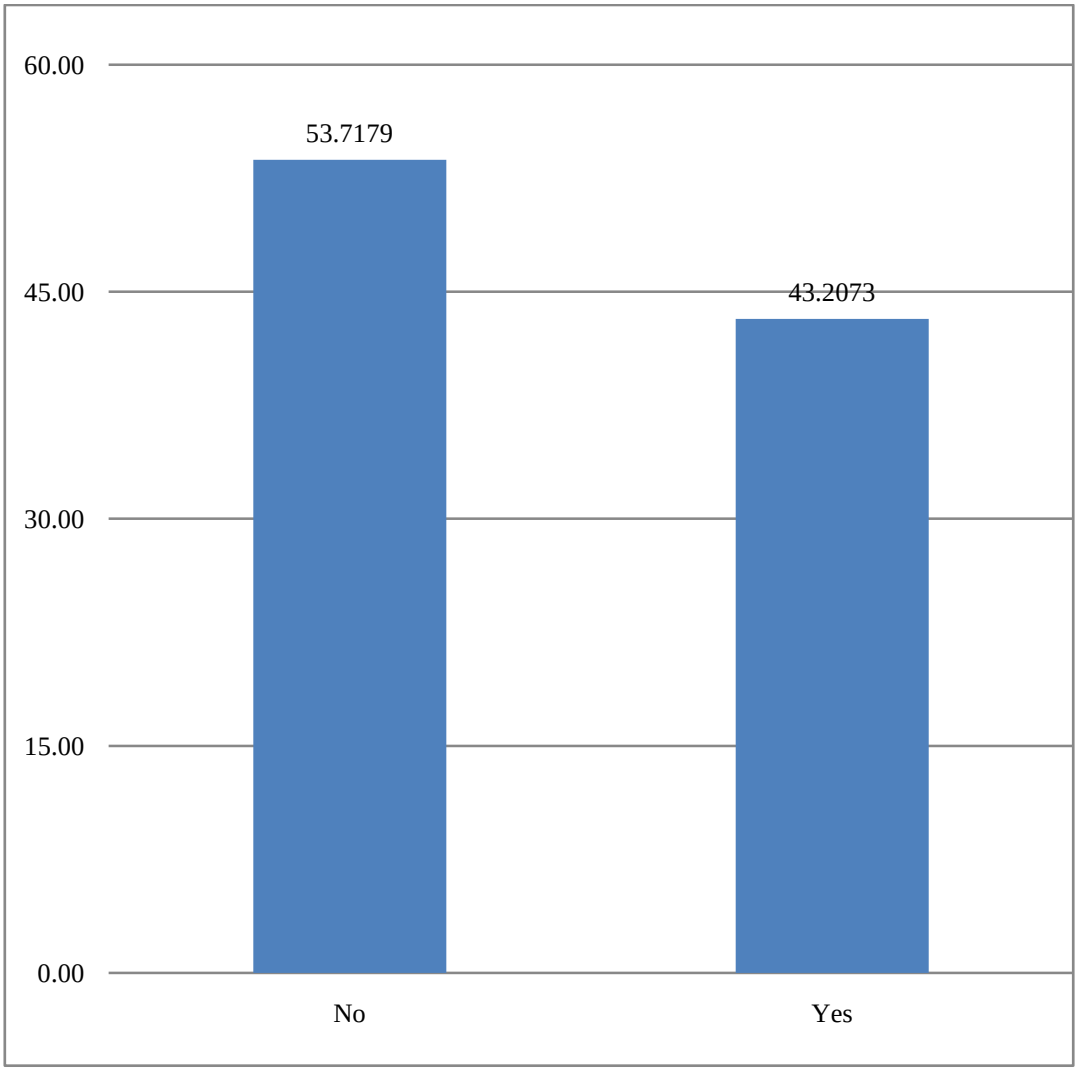


Chart 8



In our study, 41(51%) out of 80 patient were found to be smokers. Smokers had (43.2 ± 15.7) percentage reduction in ulcer size, compared to (53.7 ± 18.8) in non smokers, with a p-value of 0.009 which is statistically significant.

Table:11 Infection vs percentage reduction

Infection	N	Mean	SD	P value
No	11	69.55	13.88	<0.0001
Yes	69	44.95	16.23	

Chart: 9

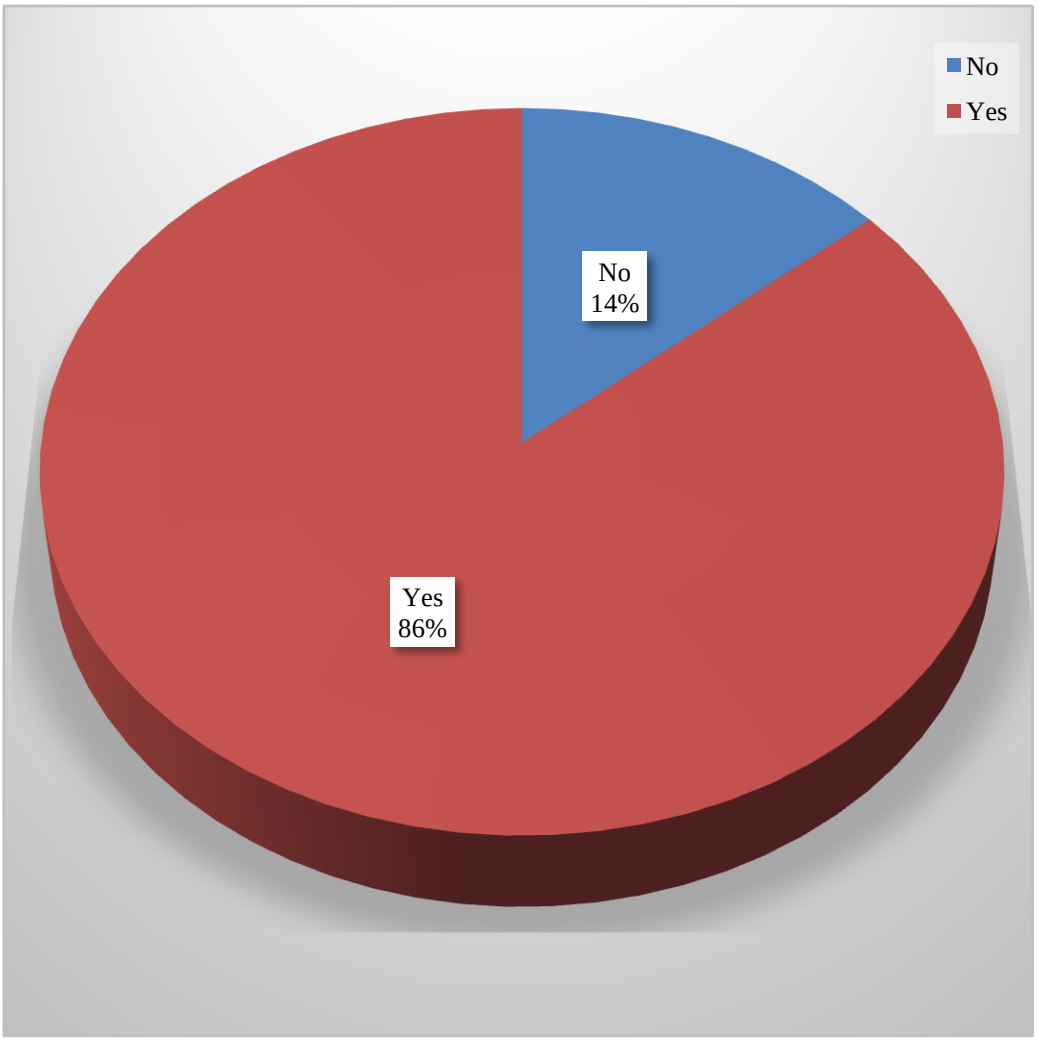
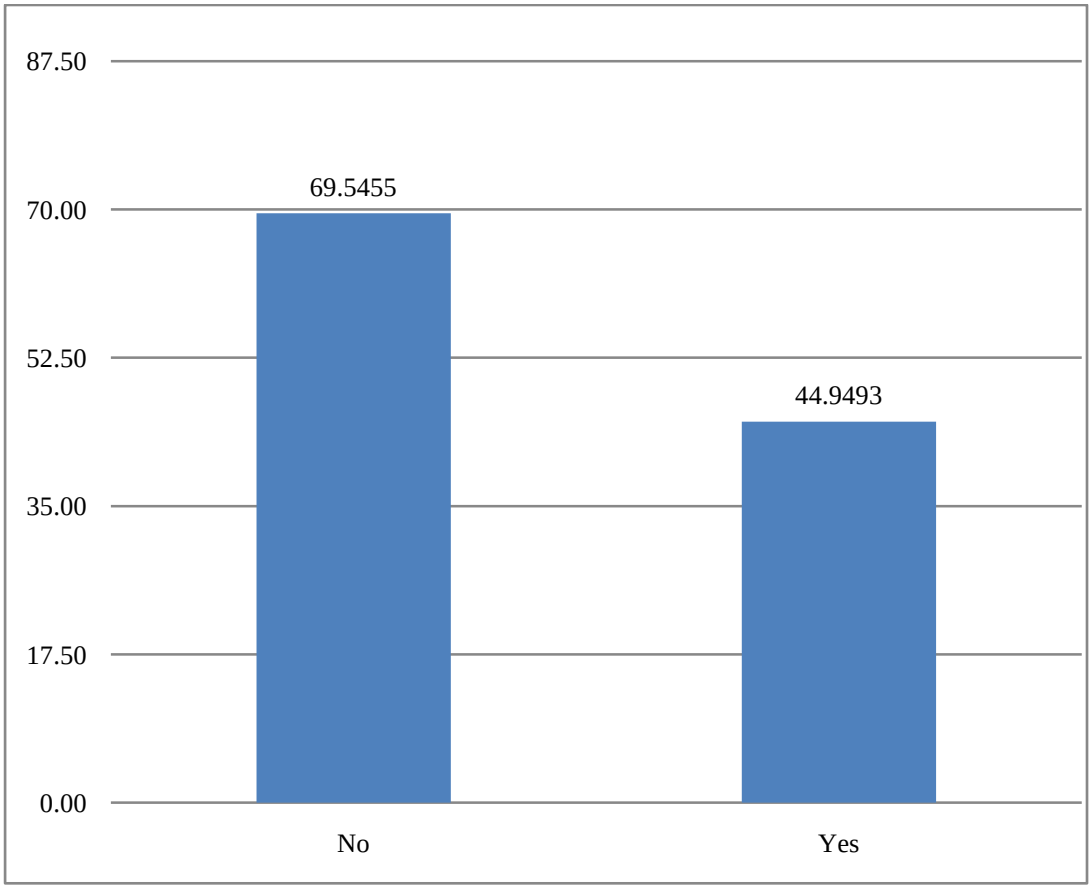


Chart:10



In our study infection rate was 86%. A significant reduction in healing was seen in patient presented with infection, with a mean percentage reduction in ulcer size of (45 ± 16), when compared to (70 ± 14) in patient who had no infection. P-value was <0.0001 which is statistically significant.

Table: 12 SSG requirement vs percentage reduction

SSG requirement	N	Mean	SD	P value
No	16	74.25	6.1	<0.0001
Yes	64	41.85	13.57	

Chart: 11

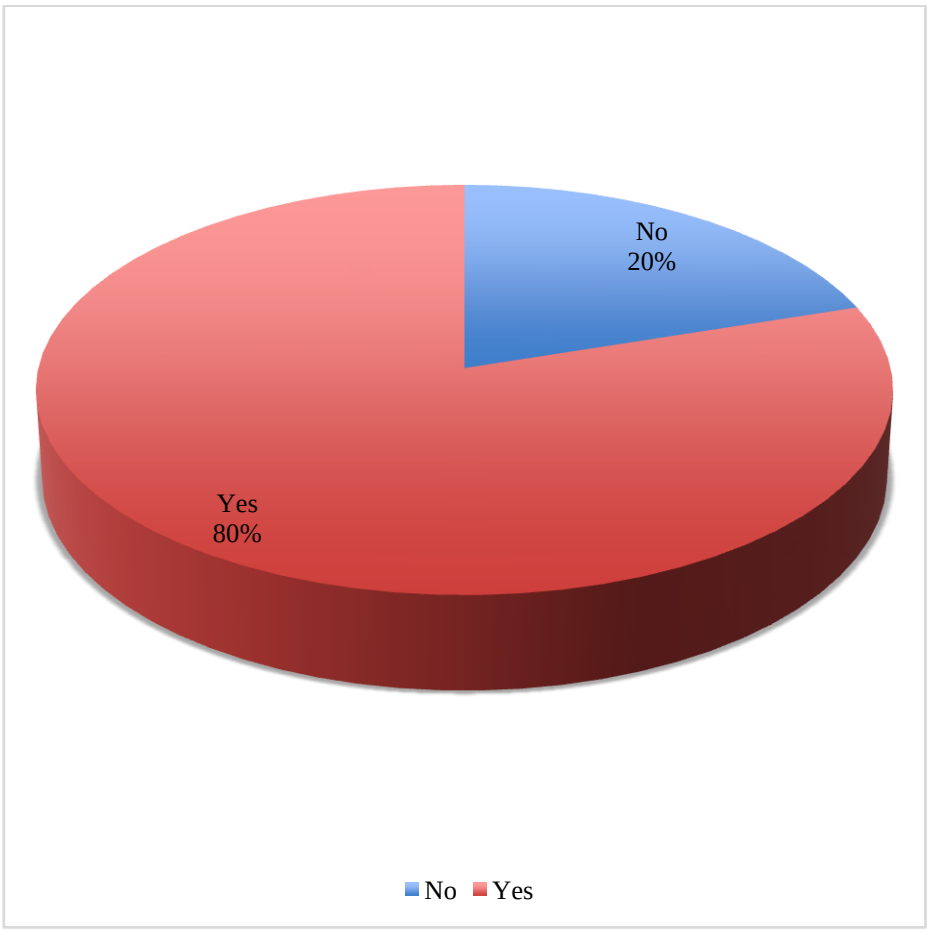
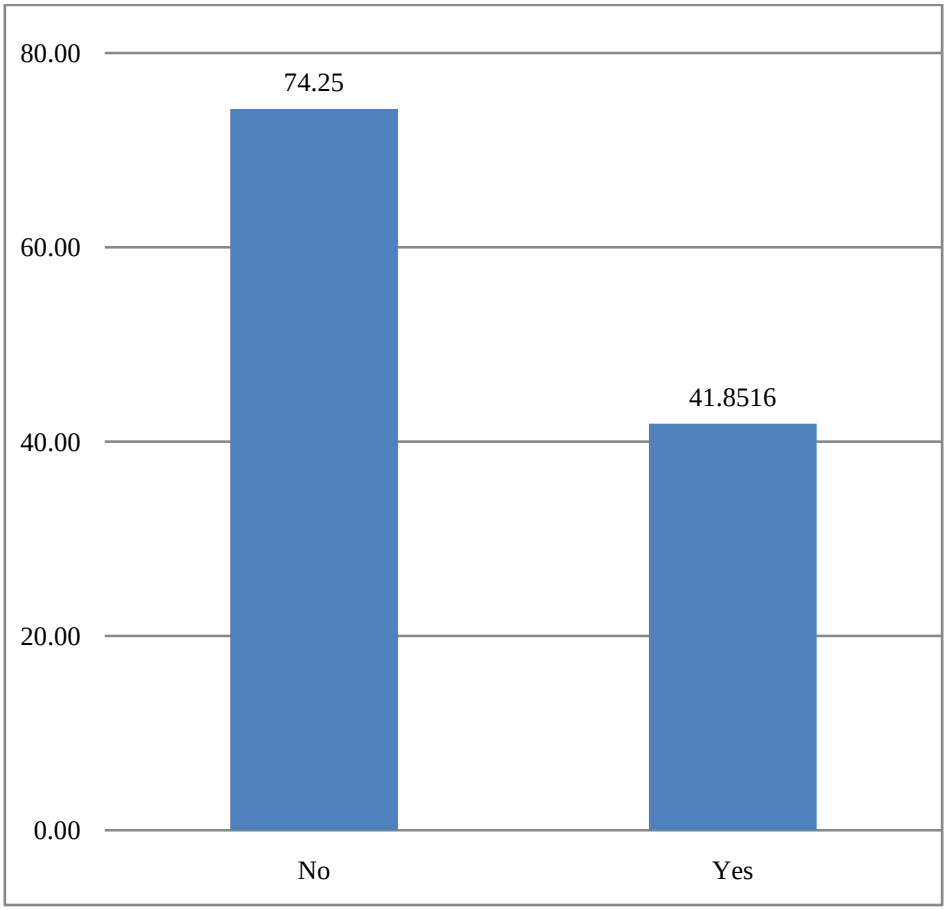


Chart:12



In our study 80% of the patients required SSG after collagen dressing. Patient who were not in a need for SSG, had a mean percentage reduction in ulcer size of about 74.25 ± 6 and those who needed SSG had 41.85 ± 13.57 percent reduction in ulcer size.

Table : 13 Glycemic control vs percentage reduction

Glycemic control	N	Mean	SD	P value
No	25	38.86	13.3	0.001
Yes	55	52.64	18.3	

Chart: 13

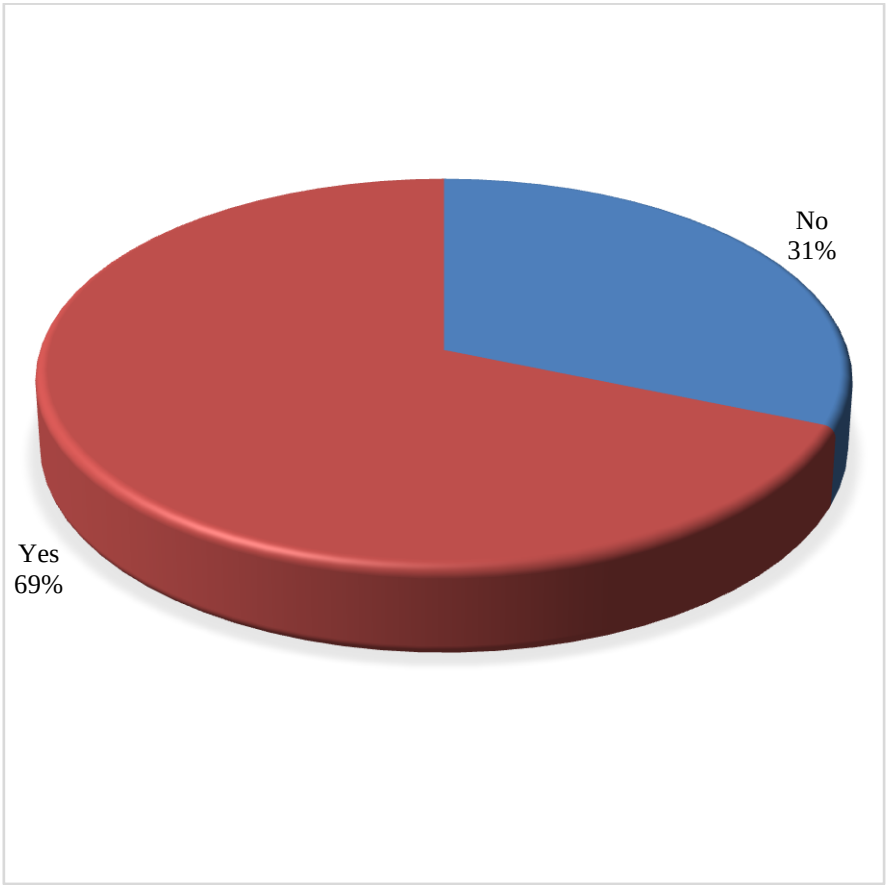
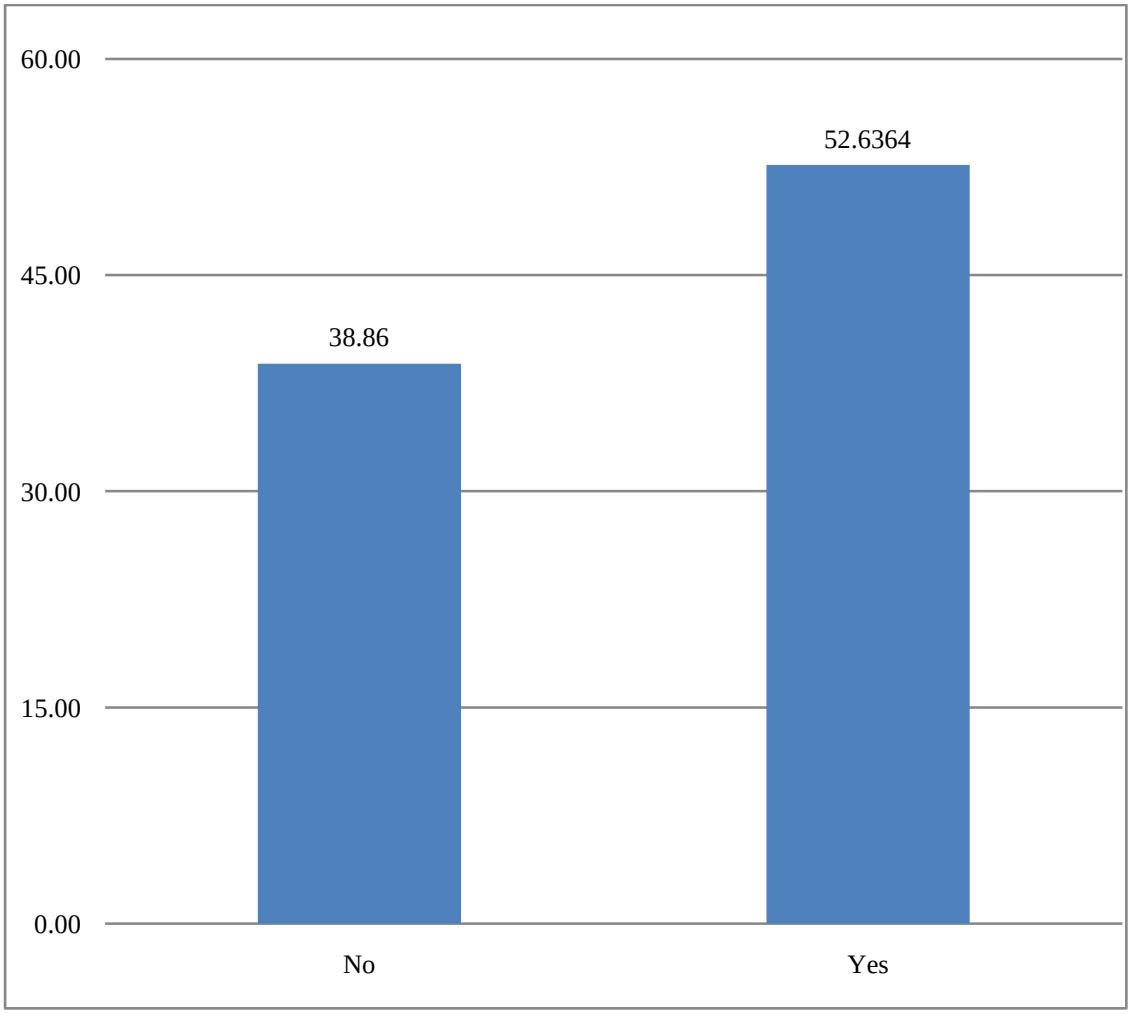


Chart: 14

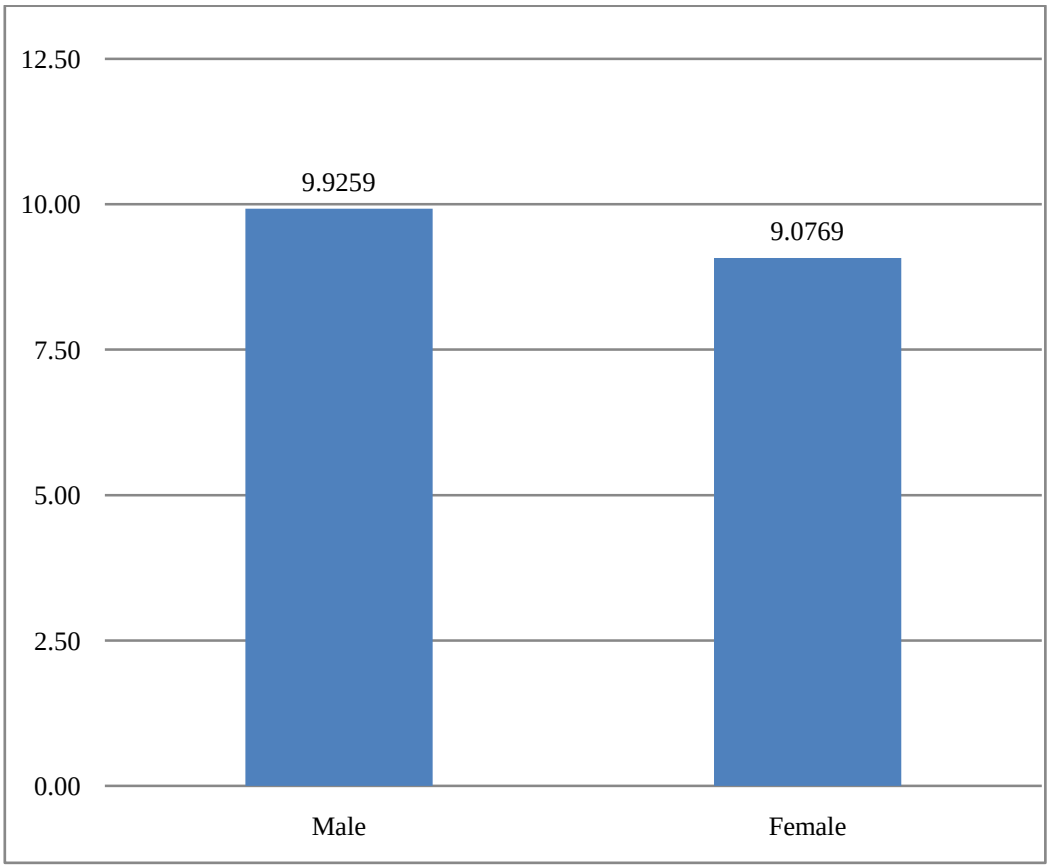


Similarly out of 80 patient, adequate glycemic control was seen in 55 patient (69%). Patient with adequate glycemic control had statistically significant more percentage reduction in ulcer size (52.6 ± 18.3) than patient without adequate glycemic control (38.8 ± 13.3), with a p-value of 0.001.

Table 14 GENDER VS DURATION OF HEALING

GENDER	N	Mean	Std. Deviation	P value
Male	54	9.93	3.408	0.318
Female	26	9.08	3.794	

Chart: 15



In our study no difference was observed in the duration of healing in both the genders, which is comparable with a p value of 0.318.

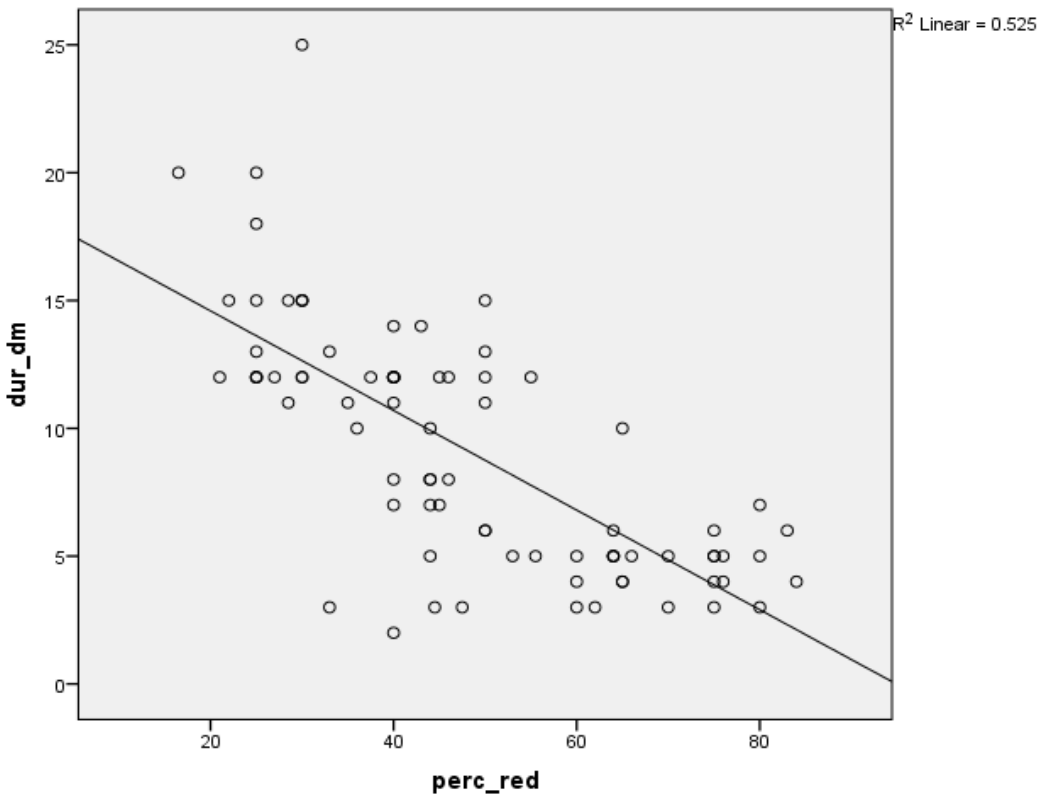
Table: 15 PEARSON CORRELATION TEST

	Percentage reduction of ulcer size		
	Pearson Correlation	Sig. (2-tailed)	N
Duration of DM	-0.724	<0.0001	80
Duration of Ulcer	-0.276	.013	80
Duration of Anitbiotics	-0.534	<0.0001	80
Duration of Hospital stay	-0.34	.002	80
Duration of Healing	-0.859	<0.0001	80
Age group	-0.553	<0.0001	80
	all having negative correlation.		

Pearson correlation test was used to test the correlation between percentage reduction in ulcer size with duration of diabetes, ulcer, antibiotics, hospital stay and duration of healing, all showing negative correlation.

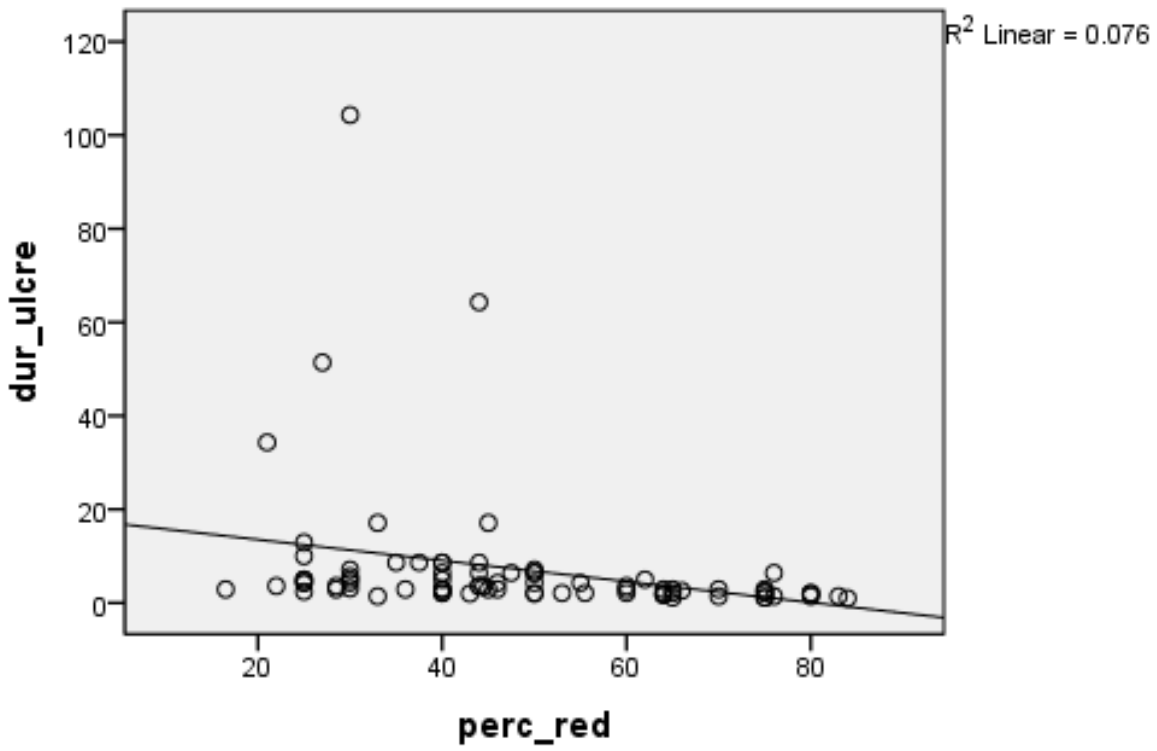
Pearson correlation curve showing the relationship between percentage reduction in ulcer size and the duration of diabetes. If the duration of diabetes increases percentage reduction in ulcer size decreases.

Chart: 16



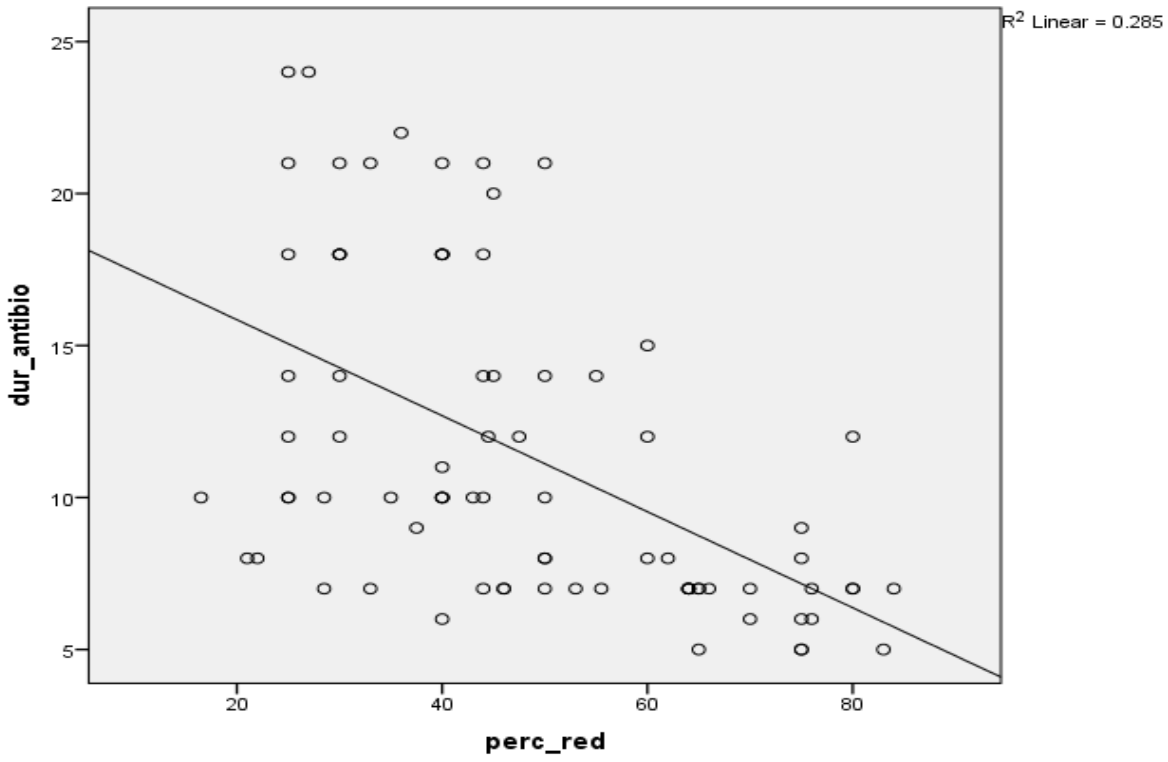
Pearson correlation curve showing the relationship between percentage reduction in ulcer size and the duration of ulcer. If the duration of ulcer increases percentage reduction in ulcer size decreases.

Chart:17



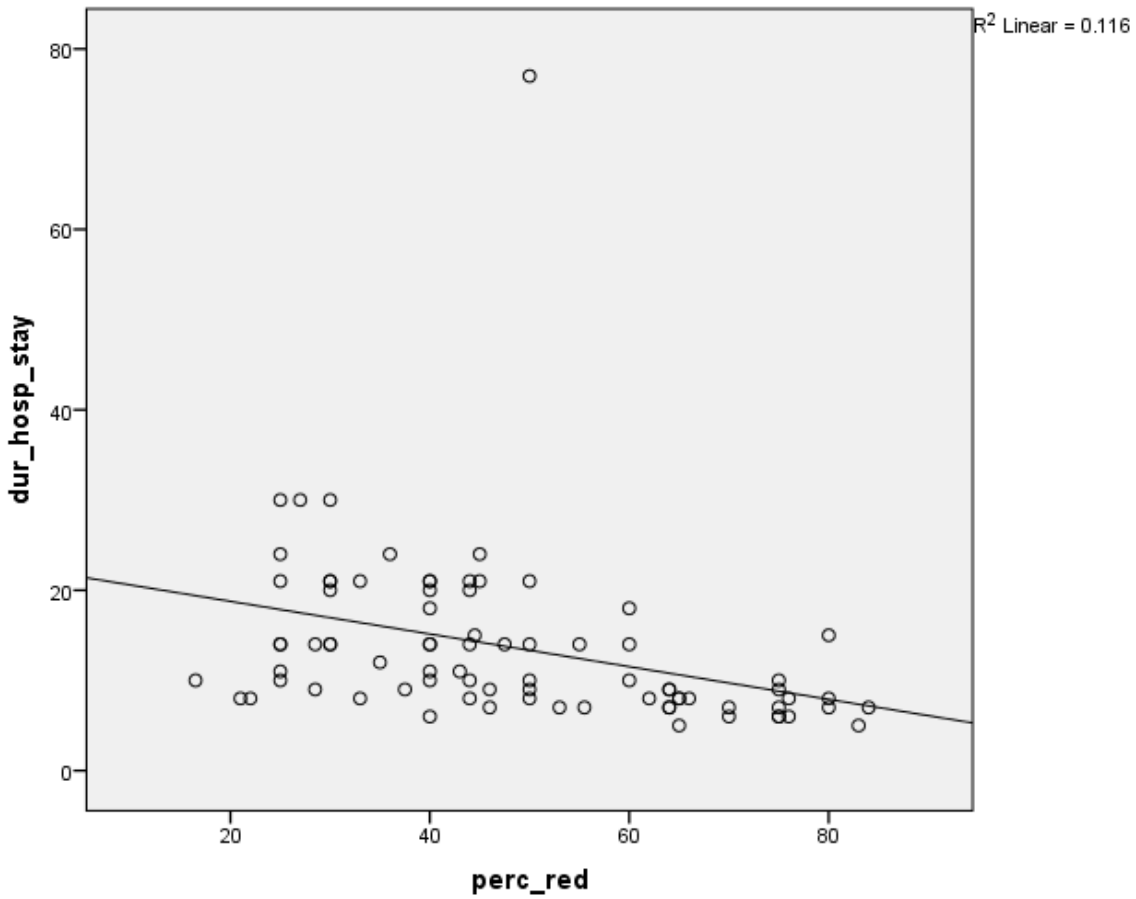
Pearson correlation curve showing the relationship between percentage reduction in ulcer size and the duration of antibiotic therapy. If the duration of antibiotic therapy increases percentage reduction in ulcer size decreases, signifying if there is infection, percentage reduction in ulcer size will be affected.

Chart: 18



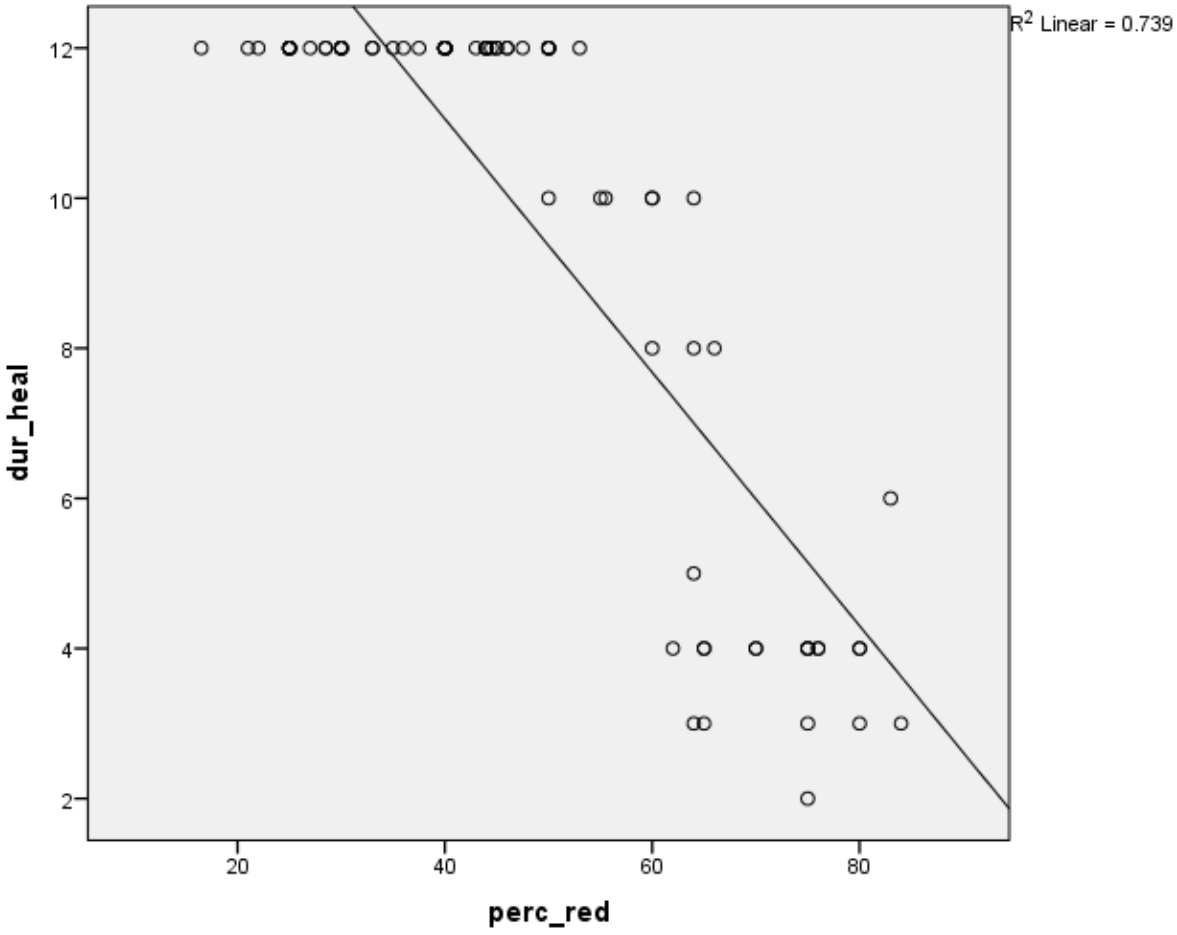
Pearson correlation curve showing the relationship between percentage reduction in ulcer size and the duration of hospital stay. If the duration of hospital stay increases percentage reduction in ulcer size decreases.

Chart:19



Pearson correlation curve showing the relationship between percentage reduction in ulcer size and the duration of healing . If the duration of healing increases percentage reduction in ulcer size decreases.

Chart:20



Pearson correlation curve showing the relationship between duration of healing and the age. With increasing age, duration of healing also increases.

DISCUSSION

Wound healing is a complex process that involves the timely expression of numerous growth factors that promote cellular migration and proliferation, production of new connective tissue matrix, and collagen deposition [26,27]. In addition, diabetic foot ulcers are chronic wounds that are stuck in the inflammation phase and show a cessation of epidermal growth or migration over the wound surface [28,29]. A common characteristic of all chronic wounds is the elevation of the levels of matrix metalloproteinases, which results in increased proteolytic activity and inactivation of the growth factors involved in the wound-healing process. The use of collagen has been shown to specifically inhibit the action of these proteases without affecting the activity of the growth factors.

This prospective study was undertaken with a main objective to evaluate the efficacy of collagen dressing as a topical wound dressing in 80 patients with chronic leg ulcer. In this study, a chronic leg ulcer was defined as any break in the skin on the lower leg (below the knee) or on the foot, which had been present for more than 4 weeks. All the patients were prospectively available for evaluation. Patients underwent dressing change every 3 to 4 days until wound healing(was taken as a reduction in ulcer size of about 60% of the initial ulcer size before collagen dressing) or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.

We found high number of male (67%) had chronic leg ulcer as compared to female (33%). There is no significant difference in healing in both the gender with a mean percentage reduction in ulcer size after collagen dressing of 47 ± 18 and 51 ± 16, in male and female respectively with a p-value of 0.326.

There is a clear association between age and chronic leg ulceration. Data suggest that the prevalence of leg ulceration progressively increases with increasing age. In our study, overall, the chronic leg ulcer was found more in older age, with 65% in the age group between 51 to 70yrs, and 27% in <50 yrs and 8% in >71 yrs. The finding is in the line with published literature. Studies by Cornwall et al [42]; Callam et al [41]; Baker et al [40]; Baker and Stacey [30]; O'Brien et al [31] reported prevalence estimates in age bands and all show an increase in prevalence with each decade of life.

It is observed that the site and duration of ulcer is not consistent across the studies. In our study, all the patients were of leg ulcer with variable duration of ulcer.

In our study the mean wound surface area was 51.85 ± 31.14 cm. Extensive debridement, control of infection, adequate off-loading of the ulcerated foot, and lower extremity revascularization when required are the cornerstones of treatment for the ulcer[32 - 34]. Collagen plays a relevant role in cutaneous tissue repair and represents a valid therapeutic option when used as a bioactive advanced dressing in chronic wound management. It improves fibroblast deposition in the dermal matrix and stimulates angiogenesis,

granulation tissue formation, and reepithelization[35]. Fibroblasts mainly participate in the biosynthesis of collagen, which acts as a mold, precursor, plastic material, and cementing substance in the wound healing process.

In the present study, the mean healing time noted in male and female was (9.93 ± 3.4 weeks) and (9.08 ± 3.7 weeks) respectively with a p-value of 0.318, which is non-significant.

In our study 64 out of 80 patient required SSG after collagen dressing. 16 patient were healed without the need for SSG, with a mean percentage reduction in ulcer size of about 74.25 ± 6(%).

In a study by Veves in 276 patients with diabetic foot ulcer, after 12 weeks of treatment, 51 (37.0%) Promogran'-a collagen/oxidized regenerated cellulose dressing-treated patients had complete wound closure as compared to 39 (28.3%) patients of control group (moistened gauze), but this difference was not statistically significant (P=0.12). In this study, author found an overall benefit of collagen on the rate of wound healing compared with moistened gauze. Donaghue compared the efficacy of a collagen-alginate topical wound dressing with that of regular gauze moistened with normal saline in 75 patients diabetic foot ulcers. The mean percent reduction of the wound area was 80.6% in the collagen-alginate dressing group and 61.1% in the gauze-dressing group. Complete healing was achieved in 48% of the collagen-alginate dressing group and 36% of the gauze-dressing group[36]. Di Mauro found that lyophilized type I collagen significantly improves wound healing in the treatment of diabetic

ulcers. The mean time for wound healing in the group treated with lyophilized collagen was 32.4 +/- 8.6 days, and in the group treated with hyaluronic acid medicated gauze was 49.0 +/- 11.0 days ($p < 0.001$). In addition, collagen dressing, unlike conventional dressing, is absorbed and does not have to be re-applied frequently. However, the ulcer should be debrided and cleaned before application. If there is evidence of infection, appropriate antibiotics should be administered.

In our study 69 out of 80 patient had infection . The presence of infection affected the healing time and the percentage reduction in ulcer size. Patient who presented with infection, had prolonged hospital stay and duration of antibiotic therapy.

In our study, patient who presented with hypertension, had lesser percentage reduction in ulcer size as compared to patients without hypertension.

55 patient in our study had adequate glycemic control, and showed a better healing and better reduction in ulcer size when compared with patient who had poor glycemic control. [Glycemic control is taken as having a HbA1c level of <7.]

Patient who found to be smokers had lesser reduction in ulcer size compared to those who do not smoke. Signifying that smoking affects collagen deposition and ultimate healing of ulcer.

This study shows that there is significant reduction in ulcer size after collagen treatment (p value <0.0001).

CONCLUSION

There is no evidence to support that collagen products should replace the gold standard of diabetic wound management, which includes etiology identification, infection management, securement of an adequate vascular supply, regular debridement of nonviable tissue, and offloading. Recently, variety of treatments methods are under clinical investigation or are available for the management of foot ulcers, including growth factors and living-skin equivalents[36, 37 - 39]. None of these treatments replace the role of wound dressing, but are used in combination with dressings.

The use of newer dressings with collagen dressing may increase the wound-healing potentials of these new treatments, and further studies will be required to evaluate the effects of the combined treatments.

However, despite the limited studies, and the need for improved study designs and increased number of randomized controlled trials, wound dressings containing collagen do appear to have some benefit in the treatment of diabetic foot ulcers and should be carefully considered by clinicians that manage wounds. There has not been sufficient evidence to prove the superiority of a particular collagen biological source or combination. Future work should further consider the inclusion of biofilm activity and the potential enhancement of extracellular targets. Finally, in order for wound care to advance beyond the current state, the most vulnerable patient populations must also be targeted to better reflect current practice.

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PROFORMA

CASE ID NO:

NAME: IP NO:

AGE/SEX: DOA:

WARD: DOD:

ADDRESS:

OCCUPATION:

Duration of DM(years):

Adequate glycemic control:

Hypertension:

Smoking:

Y	N
Y	N
Y	N

Duration of ulcer(days):

Infection:

Y	N

Ulcer size on admission(cm):

Ulcer surface area on admission(sq.cm):

Ulcer size (cm):

4th week	12th week

Duration of antibiotic therapy (days):

Duration of hospital stay (days):

Rate of healing/ Maximum duration of dressing(weeks):

Final ulcer size(cm):

Final ulcer surface area(sq.cm):

Percentage reduction in ulcer size(%):

SSG requirement:

Y	N

Pain score:

General physical examination:

Pallor

Icterus

Clubbing

Lymphadenopathy

Edema

Pulse: BP:

Local examination:

Ulcer:

Site

Size

Shape

Floor

Edge

Base

Surrounding area

Regional lymph nodes

Investigations:

FBS	
PPBS	
HbA1c	
UREA	
CREATININE	
PUS CULTURE AND SENSITIVITY	

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
(மருத்துவ ஆய்வில் பங்கேற்பதற்கு)

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

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

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

S.NO	NAME	AGE	SEX	DURATION OF DM	HT	SMOKING	INITIAL ULCER SIZE(cm)	INITIAL ULCER SURFACE AREA(sq.cm)	DURATION OF ULCER (days)	INFECTION	DURATION OF ANTIBIOTIC THERAPY (days)	DURATION OF HOSPITAL STAY (DAYS)	RATE OF HEALING (weeks)	SSG REQUIREMENT	PAIN SCORE	ADEQUATE GLYCEMIC CONTROL	FINAL ULCER SIZE(cm)	FINAL ULCER SURFACE AREA(sq.cm)	Percentage reduction in size of ulcer (%)
1	Sabur Mydeen	58	M	12	Y	Y	8*5	40	30	Y	14	14	10	Y	6	Y	6*3	18	55
2	Pattathi	52	F	8	Y	N	11*10	110	60	Y	21	21	12	Y	6	Y	8*8	64	40
3	Guruvoo	50	M	5	N	N	5*5	25	10	N	6	6	4	N	8	Y	3*2	6	76
4	Poovaiah	70	M	15	Y	Y	6*5	30	15	Y	8	8	12	Y	4	Y	5*3	15	50
5	Subramaniyan	70	M	12	Y	Y	10*7	70	20	Y	10	10	12	Y	4	Y	7*6	42	40
6	Varchala	59	F	15	Y	N	10*8	80	22	Y	18	21	12	Y	4	N	8*7	56	30
7	Sivan Raju	48	M	3	N	Y	6*6	36	14	Y	7	7	4	Y	6	Y	3.5*2	7	80
8	Palaniguru	60	M	12	Y	Y	8*5	40	35	Y	11	11	12	Y	4	N	6*4	24	40
9	Samuel Agustin	54	M	8	Y	Y	11*8	88	25	Y	21	21	12	Y	8	N	7*7	49	44
10	Muthubama	48	F	5	N	N	7*4	28	12	Y	7	7	8	Y	8	Y	5*2	10	64
11	Thenatchithai	58	F	3	Y	N	5*4	20	10	N	6	6	4	N	10	Y	3*2	6	70
12	Thangaraj	50	M	5	N	Y	6*6	36	15	Y	7	7	10	Y	8	Y	4*4	16	55.5
13	Natarajan	59	M	12	Y	Y	10*6	60	90	Y	10	11	12	Y	6	Y	9*5	45	25
14	Murugan	45	M	3	N	N	12*10	120	120	Y	21	21	12	Y	6	N	10*8	80	33
15	Subbaiah Pandian	53	M	6	Y	Y	8*5	40	45	Y	21	77	10	Y	8	Y	5*4	20	50
16	Murugan	58	M	15	Y	Y	10*6	60	40	Y	12	14	12	Y	6	N	7*6	42	30
17	Sukumar	45	M	5	N	Y	6*10	60	18	Y	7	8	8	Y	8	Y	5*4	20	66
18	Vaithiyalingam	47	M	4	N	N	4*4	16	8	N	5	7	4	N	10	Y	2*2	4	75
19	Samuthirakani	70	F	3	Y	N	5*4	20	20	Y	8	10	3	N	10	Y	2.5*2	5	75
20	Manohari	52	F	8	N	N	8*7	56	20	Y	7	9	12	Y	8	Y	6*5	30	46
21	Pappathy	57	F	12	Y	N	12*6	72	120	Y	14	21	12	Y	6	N	8*5	40	45
22	Mariappan	67	M	11	Y	Y	8*5	40	45	Y	10	14	12	Y	6	Y	6*4	24	40
23	Revathi	51	F	10	N	N	10*10	100	450	Y	14	14	12	Y	8	Y	8*7	56	44
24	Vasantha	46	F	4	N	N	6*5	30	15	Y	12	14	8	Y	6	N	4*3	12	60
25	Balan	55	M	11	Y	Y	10*8	80	60	Y	10	12	12	Y	6	Y	8*6.5	52	35
26	Mariammal	48	F	3	N	N	7*6	42	35	Y	8	8	4	Y	8	N	4*4	16	62
27	Lakshmi Narayanan	61	M	15	Y	Y	12*12	144	50	Y	21	30	12	Y	6	N	10*10	100	30
28	Muthulingam	58	M	5	Y	Y	5*5	25	12	N	7	7	3	Y	6	Y	3*3	9	64
29	Kadarkarai	56	M	12	Y	Y	8*5	40	30	Y	7	9	12	Y	8	Y	5*4	20	50
30	Valarmathi	45	F	4	N	N	7*5	35	20	Y	7	8	4	Y	8	Y	4*3	12	65
31	Lakshmanan	40	M	5	N	N	4*3	12	15	N	5	6	2	N	10	Y	2*1.5	3	75
32	Packiyam	64	F	7	Y	N	5*4	20	15	Y	7	8	3	N	8	Y	2*2	4	80
33	Pushpam	51	F	5	N	N	6*6	36	17	Y	9	9	4	N	8	Y	3*3	9	75
34	Avudaiammal	40	F	3	N	N	10*8	80	45	Y	12	14	12	Y	10	N	7*6	42	47.5
35	Kandasamy	48	M	5	Y	Y	10*10	100	60	Y	18	20	12	Y	10	N	8*7	56	44
36	Sabur	58	M	12	Y	Y	6*5	30	30	Y	7	7	12	Y	6	Y	4*4	16	46
37	Pappa	70	F	15	Y	N	11*6	66	35	Y	12	14	12	Y	10	Y	10*5	50	25
38	Alphonse	57	M	8	Y	Y	9*5	45	45	Y	10	10	12	Y	8	Y	5*5	25	44
39	Natchiyar	43	F	5	Y	N	5*4	20	20	Y	7	7	4	N	6	Y	3*2	6	70
40	Michael	55	M	10	Y	Y	4*3	12	15	N	7	8	3	N	8	Y	2*2	4	65

41	Kamaraj	54	M	7	N	Y	6*6	36	25	Y	7	8	12	Y	6	Y	5*4	20	44
42	Pasupathy	56	M	11	Y	Y	10*5	50	50	Y	10	14	12	Y	10	Y	5*5	25	50
43	Susaiyar	67	M	14	Y	N	7*5	35	14	Y	10	11	12	Y	8	Y	5*4	20	43
44	Shanmugam	72	M	20	Y	Y	12*10	120	70	Y	18	21	12	Y	18	Y	10*9	90	25
45	Shahul Hameed	65	M	12	Y	Y	8*4	32	240	Y	8	8	12	Y	8	Y	5*5	25	21
46	Rajammal	57	F	12	Y	N	8*5	40	20	Y	10	14	12	Y	6	N	6*4	24	40
47	Sundaram	48	F	3	N	N	9*9	81	25	Y	12	15	12	Y	8	N	6*6	36	44.5
48	Chandra	54	F	13	Y	N	6*4	24	10	N	7	8	12	Y	8	Y	4*4	16	33
49	Jinethbeevi	74	F	11	Y	N	7*5	35	20	Y	7	9	12	Y	8	Y	5*5	25	28.5
50	Mangayarkarasi	52	F	6	N	N	7*4	28	15	Y	7	9	10	Y	8	Y	4*2.5	10	64
51	Sundararaj	67	M	15	Y	Y	9*6	54	25	Y	8	8	12	Y	6	Y	7*6	42	22
52	Palaiah	55	M	12	Y	Y	11*9	99	360	Y	24	30	12	Y	8	N	9*8	72	27
53	Shanmugavel	61	M	12	N	Y	8*6	48	60	Y	9	9	12	Y	8	Y	6*5	30	37.5
54	Karuvelraja	55	M	4	Y	N	5*5	25	45	Y	7	8	4	N	10	Y	3*2	6	76
55	Rajakani	59	F	2	N	N	10*8	80	60	Y	18	21	12	Y	10	N	8*6	48	40
56	Iyappan	52	M	6	Y	N	4*3	12	10	N	5	5	6	N	6	Y	2*1	2	83
57	Ganesan	48	M	5	N	N	9*5	45	25	Y	15	18	10	Y	10	Y	6*3	18	60
58	Krishnamoorthy	83	M	12	Y	Y	12*8	96	30	Y	21	24	12	Y	6	N	9*8	72	25
59	Leelavathy	86	F	18	Y	N	8*5	40	35	Y	14	14	12	Y	8	N	6*5	30	25
60	Esakki	45	M	5	Y	N	5*5	25	20	Y	7	9	5	N	6	Y	3*3	9	64
61	Thangam	56	F	13	Y	N	6*4	24	14	Y	8	10	12	Y	6	Y	4*3	12	50
62	Ganesan	50	M	6	Y	Y	10*6	60	45	Y	14	21	12	Y	10	Y	6*5	30	50
63	Kamatchi	70	M	14	Y	Y	10*10	100	20	Y	18	20	12	Y	8	Y	10*6	60	40
64	Shanmugam	54	F	7	N	N	9*9	81	15	Y	18	18	12	Y	8	Y	7*7	49	40
65	Kannaiah Pandian	60	M	12	Y	Y	8*5	40	730	Y	14	14	12	Y	8	N	7*4	28	30
66	Samuthirakani	70	M	12	Y	Y	7*5	35	15	Y	6	6	12	Y	6	Y	7*3	21	40
67	Manikandan	39	M	3	N	N	9*5	45	20	Y	8	10	10	Y	8	Y	6*3	18	60
68	Malaitha	48	F	4	Y	N	5*4	20	8	N	5	5	4	N	10	Y	3.5*2	7	65
69	Ayalraj	55	M	7	Y	Y	11*8	88	20	Y	20	24	12	Y	10	N	8*6	48	45
70	Murugan	54	M	6	Y	Y	4*4	16	8	N	6	6	4	N	8	Y	2*2	4	75
71	Beer Mohammed	65	M	15	Y	Y	7*5	35	25	Y	10	14	12	Y	6	N	5*5	25	28.5
72	Narayanan	60	M	12	Y	Y	9*8	72	30	Y	10	10	12	Y	8	N	9*6	54	25
73	Poolpandi	80	M	12	Y	Y	10*6	60	35	Y	18	20	12	Y	8	N	7*6	42	30
74	Vairamuthu	50	M	5	Y	Y	6*5	30	15	Y	7	7	12	Y	8	Y	4*3.5	14	53
75	Vaithiyalingam	68	M	5	N	N	5*5	25	10	Y	12	15	4	N	8	N	2.5*2	5	80
76	Esakki Doss	70	M	20	Y	N	6*4	24	20	Y	10	10	12	Y	6	Y	5*4	20	16.5
77	Murugesan	40	M	4	N	Y	4*4	16	7	N	7	7	3	N	8	Y	2.5*1	2.5	84
78	Natarajan	69	M	25	Y	Y	12*10	120	30	Y	18	21	12	Y	8	N	12*7	84	30
79	Poothathan	51	M	10	Y	Y	10*10	100	20	Y	22	24	12	Y	8	N	8*8	64	36
80	Loorthusamy	75	M	13	Y	N	11*8	88	17	Y	24	30	12	Y	6	Y	11*6	66	25