"Comparing The Efficacy of Topical Timolol vs Amorphous hydrogel and silver colloid dressing in Chronic Diabetic Foot Ulcers: a Randomized Controlled Trial."

By

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Dissertation

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KAHER, BELAGAVI, 590010, KARNATAKA.

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DR. S. C. METGUD, M.S.
Professor and Head
Department of General Surgery,
J. N. Medical College,
Belagavi
Date :
Place: Belagavi

DEPARTMENT OF SURGERY J.N.M.C. BELGAUM

DR. N.S. MAHANSHETTI, M.D.
Principal,
J. N. Medical College,
Belagavi

PRINCIPAL
Jawaharlal Nehru Medical College
BELAGAVI

Date:
Place: Belagavi

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Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA
0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 18-03-2025

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Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BH0122009
Postgraduate Student,
2022-23 Batch,
Department of General Surgery
J. N. Medical College, Belagavi.

ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
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JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)

Website: http://www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref No.MDC/JNMCIEC/ 116. **Date: 01/04/2023**

To,
BH0122009
PG Student in General Surgery
J. N. Medical College.
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

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(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
J.N.Medical College, Belagav

LIST OF ABBREVIATIONS

ABI – Ankle-Brachial Index

AGEs – Advanced Glycation End Products

AP – Antibiotic Prophylaxis

AR – Adrenergic Receptor

bFGF – Basic Fibroblast Growth Factor

CRP – C-Reactive Protein

DFU – Diabetic Foot Ulcer

DM – Diabetes Mellitus

ECM – Extracellular Matrix

EGF – Epidermal Growth Factor

ELISA – Enzyme-Linked Immunosorbent Assay

FGF – Fibroblast Growth Factor

HbA1c – Glycosylated Hemoglobin

HR – Heart Rate

IL-6 – Interleukin-6

MMPs – Matrix Metalloproteinases

MRSA – Methicillin-Resistant Staphylococcus Aureus

NSS – Neuropathy Symptom Score

OABP – Oral Antibiotic Bowel Preparation

PAD – Peripheral Arterial Disease

PCT – Procalcitonin

PDGF – Platelet-Derived Growth Factor

PVD – Peripheral Vascular Disease

TGF-β1 – Transforming Growth Factor Beta 1

TIMPs – Tissue Inhibitors of Matrix Metalloproteinases

TCC – Total Contact Cast

TNF-α – Tumor Necrosis Factor-alpha

VEGF – Vascular Endothelial Growth Factor

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STRUCTURED ABSTRACT

Background: Diabetic Foot Ulcers (DFUs) are a major complication of Diabetes Mellitus (DM), resulting from a combination of neuropathy, peripheral arterial disease (PAD), and poor glycemic control. DFUs are a leading cause of lower limb amputations, contributing to increased morbidity and healthcare costs. Proper wound healing requires moisture retention, infection control, and vascularization, leading to the exploration of novel treatments such as topical Timolol maleate, hydrogel dressings, and silver colloid gel.

Objectives: This study aims to compare the efficacy of topical Timolol maleate (0.5%) with Amorphous hydrogel and silver colloid dressing gel in chronic DFU management. It also evaluates the safety profile of topical Timolol and its impact on wound healing rates after two weeks of treatment.

Methods: A randomized controlled trial (RCT) was conducted at a tertiary healthcare center. 114 patients with chronic DFUs (>6 weeks, uninfected, non-ischemic) were randomized into two groups: Group A (Test Group): Received topical Timolol maleate (0.5%) along with moist saline dressings. Group B (Control Group): Received Amorphous hydrogel and silver colloid gel as the standard dressing. Wound healing progress was assessed using ulcer area reduction, granulation tissue formation, and epithelialization rates.

Results: The study found that ulcers treated with topical timolol had a higher percentage reduction in wound size than compared to ulcers treated with hydrogel and silver colloid, but this difference did not reach statistical significance. Additionally, no significant adverse effects were observed in the Timolol group, making it a safe and effective treatment option for DFUs.

Conclusion: Both topical Timolol and amorphous hydrogel with silver colloid dressing demonstrated comparable efficacy in promoting wound healing in patients with diabetic foot ulcers. Despite slight differences in the percentage reduction of wound size, the results were not statistically significant, suggesting that both treatments create a similarly conducive environment for tissue repair. Topical Timolol maleate (0.5%) is a promising adjunct in chronic DFU treatment. Given its cost-effectiveness, ease of application, and safety, it holds potential for widespread clinical use, particularly in resource-limited settings. Further longitudinal and multicenter studies are needed to validate these findings.

Keywords: ***Diabetic Foot Ulcer (DFU), Timolol maleate, Hydrogel dressings, Silver colloid gel, Wound healing, Peripheral arterial disease (PAD), Neuropathy, Inflammatory response, Tissue remodeling, Advanced wound care***

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder caused by insulin insufficiency, leading to persistent hyperglycemia and multisystem complications[1]. Over the past two decades, diabetes has emerged as a major global health concern, with its incidence expected to surpass 360 million cases by 2030[2-5]. One of the most severe complications of diabetes is the development of diabetic foot ulcers (DFUs), which result from a combination of inadequate foot care, peripheral neuropathy, peripheral vascular disease (PVD), and uncontrolled blood glucose levels[6]. DFUs primarily develop in areas of the foot subjected to prolonged pressure and stress, making them highly susceptible to chronic non-healing wounds[7]. Epidemiological studies indicate that DFUs affect 15% of diabetes patients during their lifetime, with prevalence rates ranging between 4% and 27%[7-9]. These ulcers have shown an increasing trend in recent decades, leading to a substantial burden on healthcare systems[10,11].

DFUs are among the leading causes of lower limb osteomyelitis and amputation, contributing to nearly 50%-70% of all lower limb amputations worldwide[7]. The primary goal in DFU management is to achieve rapid wound closure through optimized wound healing strategies[12,13]. The choice of treatment depends on ulcer severity and vascularization of the affected limb, requiring an integrated approach involving debridement, revascularization, infection control, pressure offloading, and appropriate wound dressings[14,15]. Traditionally, saline-moistened gauze dressings were used for DFUs, but they often failed to maintain the moist wound environment essential for healing. As a result, modern advanced wound dressings such as hydrogels, silver-based dressings, and novel pharmacological agents

like topical timolol have been explored for their superior wound healing properties[16,17].

Hydrogel dressings have been widely utilized in wound care due to their ability to maintain a moist wound environment, facilitating autolytic debridement and enhancing keratinocyte migration for re-epithelialization [Dumville[16], 2013; Zhao[17], 2024]. These dressings, composed primarily of water, are particularly effective for dry wounds that require hydration to support fibroblast function and collagen synthesis [Zhao[17], 2024]. A meta-analysis of 15 randomized controlled trials showed that hydrogel dressings significantly improve healing rates, reduce healing time, and enhance epithelialization in DFUs compared to conventional dressings [Zhao[17], 2024]. However, one limitation of hydrogels is their lack of antimicrobial properties, which may make them less effective in managing infected or biofilm-associated ulcers.

Timolol, a nonselective β1/β2-adrenergic receptor antagonist, has long been used as an ophthalmic solution for reducing intraocular pressure in glaucoma patients. However, recent research has highlighted its off-label application in dermatology and wound healing. Studies indicate that β2-adrenergic receptors (β2ARs) are present in keratinocytes, fibroblasts, and melanocytes and play a role in delaying wound healing by inhibiting keratinocyte migration[18,19]. By blocking β2ARs, timolol accelerates epithelialization, promotes angiogenesis, and enhances fibroblast proliferation, making it a promising agent for chronic DFUs. Clinical trials and observational studies have demonstrated that topical timolol significantly reduces ulcer size, promotes granulation tissue formation, and shortens healing time compared to conventional treatments [Cornwell[18], 2024; Cahn[19], 2020; Menezes[20], 2023].

Additionally, timolol is low-cost, non-invasive, and easy to apply, making it particularly beneficial in resource-limited settings.

While each of these advanced treatments offers distinct benefits, a direct comparative study evaluating their relative efficacy in DFU healing remains lacking. Timolol, with its vasodilation and keratinocyte migration properties, may offer a pharmacological advantage over passive moisture-retentive hydrogel dressings. Given the complex and multifactorial nature of DFUs, understanding the comparative effectiveness of these therapies could help optimize wound management protocols and improve clinical outcomes.

OBJECTIVE OF THE STUDY

- To assess the efficacy of topical application of Timolol maleate 0.5% drops compared to topical Amorphous hydrogel and silver colloid dressing gel in healing rate for chronic uninfected diabetic ulcers at the end of 4 weeks
- To assess the safety of topical application of Timolol maleate in diabetic foot ulcers

REVIEW OF LITERATURE

WOUND HEALING

Wound healing is a complex and dynamic biological process that involves a series of coordinated cellular events aimed at restoring damaged tissue[21].

Key Factors in Wound Healing

The repair of minor and superficial skin injuries primarily relies on epidermal migration where keratinocytes move to cover the wound site. Unlike deep tissue regeneration, this process does not necessarily require extensive keratinocyte proliferation and often results in faster healing. In partial-thickness wounds, remaining hair follicles and skin appendages within the wound bed serve as reservoirs for keratinocytes, promoting healing from both the interior and exterior of the wound. However, full-thickness wounds lack these structures and must heal from the wound margins, often requiring wound contraction to facilitate closure in deeper wounds[22,23].

Phases of Wound Healing

Wound repair occurs through four interconnected and overlapping phases, each crucial for effective healing. These include coagulation, inflammation, migration-proliferation, and remodeling, all of which play a distinct role in restoring skin integrity.

FIGURE 1: GRAPHICAL REPRESENTATION OF WOUND HEALING[24]

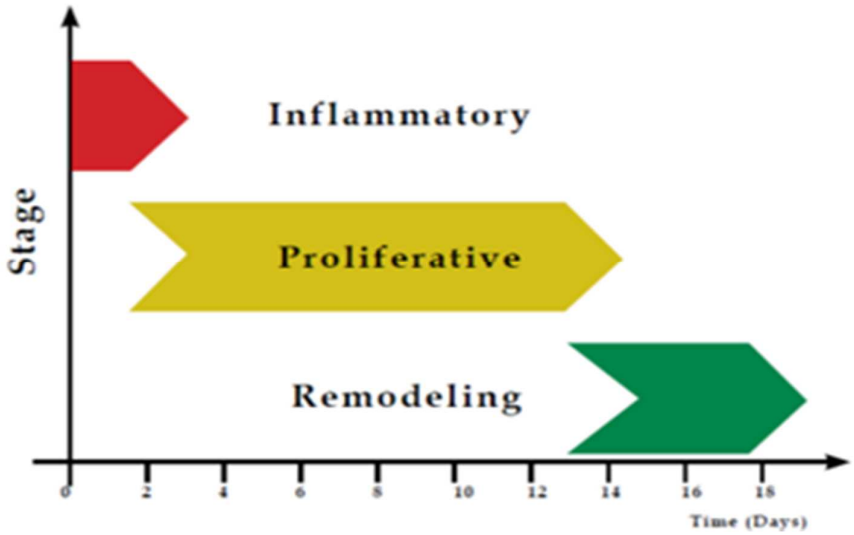
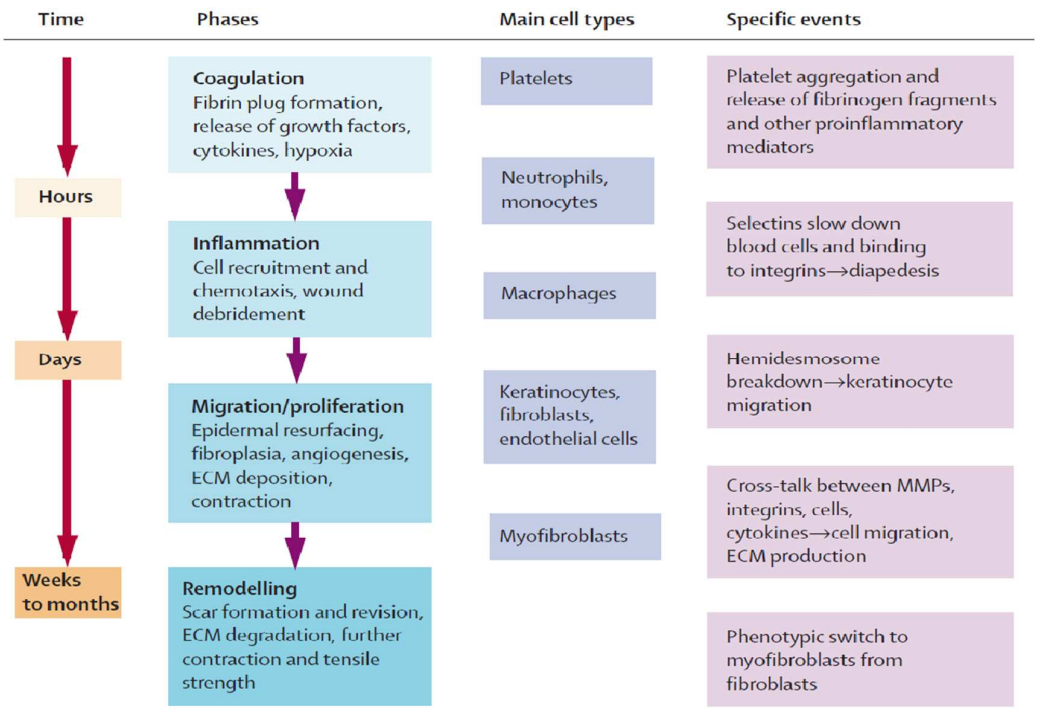


FIGURE 2: WOUND HEALING PHASES[22]



Unlike acute wounds, chronic wounds do not follow a linear progression of biological and molecular events, as illustrated in Figure 2. In non-healing wounds, different areas may simultaneously be at varying stages of the healing process, leading to asynchronous transitions between phases. This complexity extends beyond just a lack of progression, making it difficult to extrapolate findings from acute wound studies to chronic wound healing[26].

Research based on animal models has demonstrated how specific molecular anomalies can significantly impact wound healing. For example, mice deficient in P- and E-selectins, plasminogen, tissue plasminogen activator, urokinase plasminogen activator, basic fibroblast growth factor-2 (bFGF-2), fibroblast growth factor-1 (FGF-1), and inducible nitric oxide synthase (iNOS) exhibit delayed wound repair. Conversely, certain genetic modifications, such as overexpression of matrix metalloproteinase-1 (MMP-1) or antisense inhibition of CD44 (hyaluronic acid receptor), can negatively impact healing. Interestingly, some mutations have been found to accelerate wound healing, as seen in studies involving skn-1a or Smad-3 knockout mice[27]. These findings suggest that modulating growth factors, signaling pathways, and extracellular matrix interactions could provide new therapeutic avenues for enhancing human wound healing.

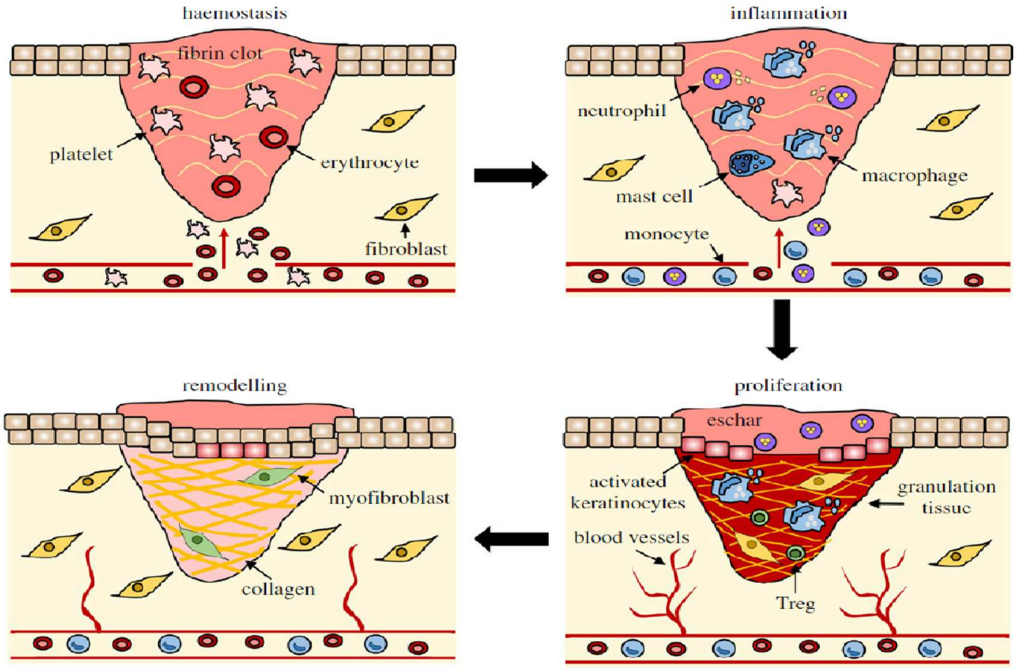
COAGULATION AND INFLAMMATION: PHASES 1, 2

The different phases of wound healing are interconnected, with overlapping effects that extend beyond their immediate biological goals. Following tissue injury, a fibrin plug rapidly forms at the site, attracting inflammatory cells and initiating the coagulation process. This plug, composed primarily of polymerized fibronectin, fibrin (from fibrinogen), thrombospondin, and vitronectin, provides hemostasis, infection protection, and a temporary wound cover[28,29]. Platelets embedded within this plug

release critical growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor-beta 1 (TGF-β1), which regulate early cell recruitment and later contribute to extracellular matrix (ECM) formation[28].

The activation of fibrinogen to fibrin by thrombin also produces fibrinopeptides A and B, which play an additional role in recruiting inflammatory cells to the wound site[29]. The endothelial synthesis of selectins slows circulating leukocytes, allowing them to bind integrins and migrate through endothelial gaps into the extracellular matrix via diapedesis[30]. These inflammatory cells perform essential roles in wound debridement, with macrophages and neutrophils being particularly important. However, in diabetic wounds, their function is often impaired, contributing to delayed healing[29].

FIGURE 3. THE STAGES OF WOUND REPAIR AND THEIR MAJOR CELLULAR COMPONENTS.[21]



Immediately following injury, tissue hypoxia results from damaged blood vessels, which may initially seem detrimental but is actually beneficial for initiating the next phase of healing. Hypoxia triggers key responses, including keratinocyte migration, fibroblast proliferation, early angiogenesis, and upregulation of cytokines and growth factors such as PDGF, VEGF, and TGF-β1[31]. Within two to three days, a wide range of cytokines and growth factors are released by inflammatory and cutaneous cells. Circulating monocytes differentiate into macrophages, while fibroblasts and endothelial cells migrate to the injury site, forming early granulation tissue that facilitates wound contraction and initiates the next stage of repair.

Wound repair begins with haemostasis, where a platelet plug prevents blood loss and a preliminary fibrin matrix is formed. Inflammation then ensues to remove debris and prevent infection, commencing with neutrophil influx, which is promoted by histamine release from mast cells. Monocytes arrive later and differentiate into tissue macrophages to clear remaining cell debris and neutrophils. During the phase of proliferation, keratinocytes migrate to close wound gap, blood vessels reform through angiogenesis, and fibroblasts replace the initially formed fibrin clot with granulation tissue. Macrophages and regulatory T cells (Tregs) are also vital for this stage of healing. Finally, the deposited matrix is remodelled further by fibroblasts, myofibroblasts generate an overall contraction of wound as blood vessels retract.

PHASES 3, 4: REMODELING AND MIGRATION-PROLIFERATION

As inflammation subsides, wound contraction initiates. These later stages depend on ECM protein production, angiogenesis, keratinocyte migration, and tissue remodeling. Structural proteins such as collagens, vitronectin, and fibronectin provide a framework to restore tissue integrity and cellular mobility. The process of angiogenesis, essential for restoring oxygen and nutrients to the wound, occurs

alongside granulation tissue development and fibroblast proliferation. Myofibroblasts, a specialized fibroblast phenotype, play a key role in contraction, which is a rapid and efficient mechanism of wound closure. However, diabetic wounds exhibit impairments in these processes, often showing excessive matrix deposition, including collagen and fibronectin accumulation, which can delay healing[31].

FUNCTIONS OF INTEGRINS

Cellular movement is fundamental for processes like angiogenesis, fibroplasia, and keratinocyte migration. Endothelial cells and fibroblasts migrate into the developing granulation tissue, while keratinocytes must traverse the fibrin-rich wound bed. This migration relies on enzymes such as urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), and matrix metalloproteinases (MMPs) to break down structural barriers[32].

Integrins, a family of transmembrane receptors, play a critical role in facilitating cell-matrix and cell-cell communication. These receptors bridge intracellular cytoskeletal components with the ECM, allowing cells to detach, migrate, and reattach during wound healing. There are at least 24 αβ heterodimers, formed from 18 α and 8 β subunits, which regulate cell movement and stability[32].

In dermal fibroblasts, integrin switching occurs 3–4 days after injury, shifting from α2 to α3 and α5 subunits, which enhances fibroblast migration through the fibrin-rich ECM. Additionally, vascular endothelial growth factor (VEGF) receptor flt-1 is upregulated during angiogenesis, though its expression is reduced in delayed-healing wounds. The interaction between αvβ5 integrin and angiogenic stimuli is necessary for endothelial cell migration and new blood vessel formation[31,32].

MIGRATION OF KERATINOCYTES

Hemidesmosomes, anchoring basal keratinocytes to the basement membrane, must break down for keratinocytes to migrate. This process requires a coordinated interaction between growth factors, integrins, MMPs, and structural proteins. The disassembly of laminin-5 from α6β4 integrin initiates keratinocyte detachment, while the clustering of α3β1 integrin facilitates lamellipodia formation, which is essential for cell movement[33]. GTPases (Rho, Rac, and Cdc42) act as molecular switches, regulating integrin phosphorylation and keratinocyte migration[34]. Keratinocytes move forward by extending lamellipodia, while basal keratinocytes exhibit a "leapfrog" movement over adjacent cell. Additionally, an actin cable forms within migrating keratinocytes, enabling wound closure via a purse-string mechanism, a process also observed in adult corneal repair[35].

Further keratinocyte proliferation is triggered by mitogen-activated protein kinases (MAPKs), interleukin-1α (IL-1α), and calcium signaling, which regulate cell motility, differentiation, and ECM interactions[36]. Proteolytic enzymes, such as MMPs and plasminogen activators, help dissolve the fibrin clot. MMP-1 (collagenase-1) is induced by interactions between keratinocytes, collagen, and α3β1 integrin, promoting ECM remodeling[37].

MMP-9 plays a crucial role by breaking down type IV and VII collagens, which are key components of anchoring fibrils and basement membranes, while MMP-10 (stromelysin-2) degrades other non-collagenous matrix proteins, further enhancing keratinocyte migration and wound remodeling[37].

PROLIFERATION OF KERATINOCYTES

Within hours of injury, keratinocytes begin migrating to cover the wound defect. However, in larger wounds, cell migration alone is insufficient, necessitating a proliferative burst to expand the keratinocyte population. This proliferation is regulated by tumor suppressor genes (TP53, CKAP4, TP73), epidermal growth factor (EGF), and transforming growth factor-alpha (TGF-α). Additionally, TGF-related activins influence fibroblast and keratinocyte proliferation, further supporting tissue regeneration[38].

REMODELLING OF ECM AND CONTRACTION OF WOUND

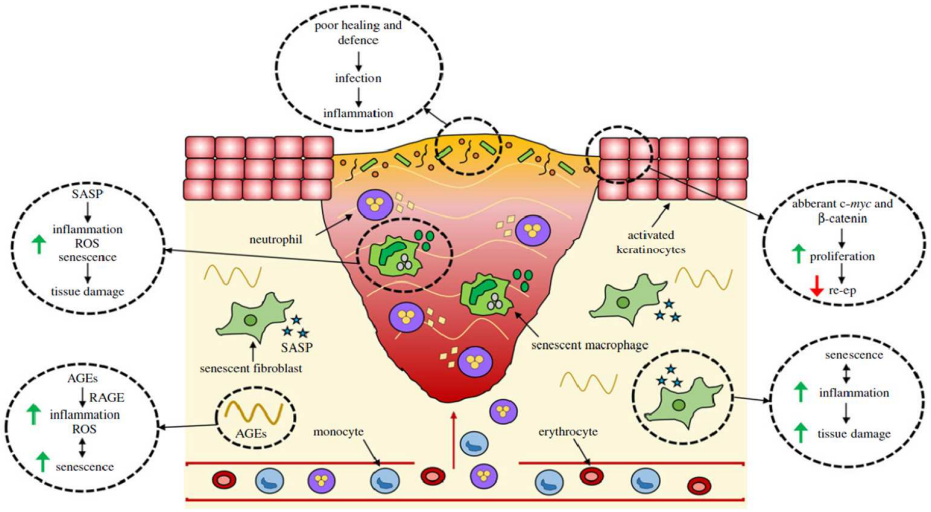
Although keratinocyte migration is vital for wound healing, angiogenesis and wound contraction also play critical roles, especially in chronic wounds. In DFUs, ineffective contraction is a significant barrier to healing.

Within a week of injury, critical processes occur, including:

- Matrix deposition, facilitated by PDGF, TGF-α, VEGF, and fibroblast growth factors (FGFs)
- Fibroblast-to-myofibroblast transition, driven by TGF-α
- Early remodeling, initiated by serine proteases and MMPs[39]

As healing progresses, MMPs degrade the ECM, which initially serves as a scaffold for cell migration. Collagen type III is deposited first, followed by collagen type I, which undergoes hydroxylation, peaking around three weeks post-injury. However, even after complete closure, healed skin achieves only 60% of the tensile strength of uninjured skin, highlighting the long-term fragility of previously wounded areas[40].

FIGURE 4. FACTORS CONTRIBUTING TO CHRONIC WOUND HEALING[21]



Chronic wounds often become colonized by bacteria, which exacerbates inflammation and disrupts the normal healing process. In these wounds, keratinocytes exhibit abnormal activation, leading to hyperproliferation but impaired migration, preventing proper re-epithelialization. A significant proportion of wound-resident cells, including macrophages and fibroblasts, enter a senescent state, characterized by the senescence-associated secretory phenotype (SASP). This phenotype amplifies inflammation, triggers the release of reactive oxygen species (ROS), and perpetuates cellular dysfunction. Additionally, advanced glycation end products (AGEs) accumulate in the wound microenvironment, further driving inflammation and cellular senescence. These combined factors contribute to excessive tissue degradation, impaired cellular activity, and the failure of chronic wounds to progress through normal healing phases.

DIABETIC FOOT ULCER

DEFINITION

The term “diabetic foot” refers to a complication of diabetes mellitus that involves infection, ulceration, or destruction of deep tissues in the lower limb, often associated with neurological impairments and varying degrees of peripheral vascular disease (PVD). A diabetic foot ulcer (DFU) is specifically defined as an open wound on the foot of a person with a current or past diagnosis of diabetes mellitus, typically accompanied by neuropathy and/or peripheral arterial disease (PAD) in the lower limbs[41].

Risk Factors for Diabetic Foot Ulcers

Several factors contribute to the development of **DFUs**, with **diabetic neuropathy, peripheral vascular disease, and foot trauma** being the primary risks.

Diabetic Neuropathy

Diabetic neuropathy is responsible for nearly **90% of DFU cases[42,43]**. It results from prolonged hyperglycemia, which **damages sensory, motor, and autonomic nerve fibers**.

- **Motor neuropathy** leads to **muscle weakness, atrophy, and deformities**, which alter foot biomechanics.
- **Sensory neuropathy** causes a **loss of pain, temperature, and pressure perception**, making patients unaware of minor injuries.
- **Autonomic dysfunction** leads to **vasodilation and decreased sweating**, resulting in **skin dryness and fissuring**, creating an entry point for bacterial infections[44,45].

Peripheral Arterial Disease (PAD)

People with diabetes are **2–8 times more likely** to develop **PAD**, which manifests earlier and progresses more aggressively than in non-diabetics. It commonly affects the **lower limb arteries**, particularly those between the **ankle and knee**[46].

- PAD is a major **risk factor for DFU** and is also independently linked to **cardiovascular disease**.
- Even minor wounds increase the **oxygen and nutrient demand** in the foot. When **PAD restricts blood supply**, tissue breakdown accelerates, increasing the risk of **non-healing ulcers and amputations**[47].
- The majority of **diabetic foot ulcers** have a **neuroischemic origin**, particularly in older adults[48].

Foot Trauma and Structural Deformities

Loss of sensation in **diabetic neuropathy** makes patients prone to **recurrent minor injuries** from both **internal factors** (e.g., **nail trauma, calluses, foot deformities**) and **external factors** (e.g., **burns, improper footwear, foreign objects inside shoes**). These unnoticed injuries **progress into chronic ulcers** over time.

Common **structural foot deformities** associated with **DFUs** include:

- **Hallux valgus**
- **Flat foot**
- **Charcot neuroarthropathy**
- **Claw toes and hammer toes**

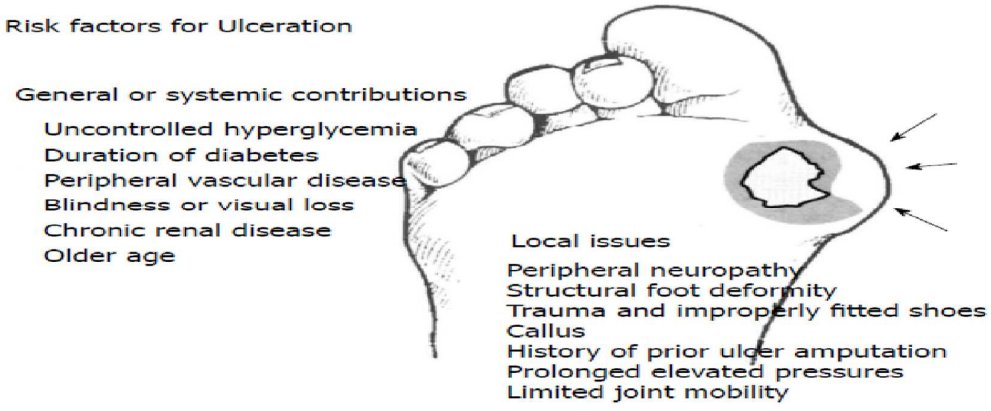
These conditions increase **abnormal plantar pressures**, which in turn elevate the risk of **ulcer formation**.

Additional Risk Factors

Other factors that further increase the likelihood of **DFU development** include:

- **History of previous foot ulcers or amputations**
- **Diabetic nephropathy and visual impairment**
- **Poor glycemic control**
- **Smoking**
- **Male sex**, as some studies suggest men with diabetes develop **DFUs more frequently than women**
- **Low socioeconomic status**, **limited healthcare access**, and **lack of education**, all of which contribute to **delayed detection and poor management of foot ulcers**[49].

FIGURE 5. DIABETIC FOOT ULCER RISK FACTORS[50]



DIABETIC FOOT ULCER PATHOPHYSIOLOGY[51,52]

Prolonged hyperglycemia in diabetes leads to nerve fiber damage through multiple pathways, including the accumulation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), increased oxidative stress (reactive oxygen species), nitric oxide (NO) inhibition, DNA damage, and chronic inflammation. Among the different types of diabetic neuropathy, the most prevalent is distal sensorimotor polyneuropathy, which progressively affects the lower limbs.

Over time, neuropathy-induced foot deformities develop, altering weight distribution and leading to areas of high-pressure loading. This results in keratosis and callus formation due to repeated mechanical stress. Since callused areas experience up to 20 times more pressure than the surrounding skin, the presence of calluses serves as an indicator of disease severity. Excessive pressure on callused areas can cause tissue breakdown, leading to ulcer formation beneath the callus and increasing the risk of skin fissuring and foot cracking.

Nearly 50% of individuals with diabetes develop foot ulcers due to peripheral vascular dysfunction, which is further aggravated by microcirculatory impairments. Early diabetes-related vascular changes include narrowed capillaries, thickened basement membranes, and arteriolar hyalinosis. Furthermore, diabetes is associated with accelerated atherosclerosis, predominantly affecting the tibial arteries, leading to restricted blood flow to the lower limbs.

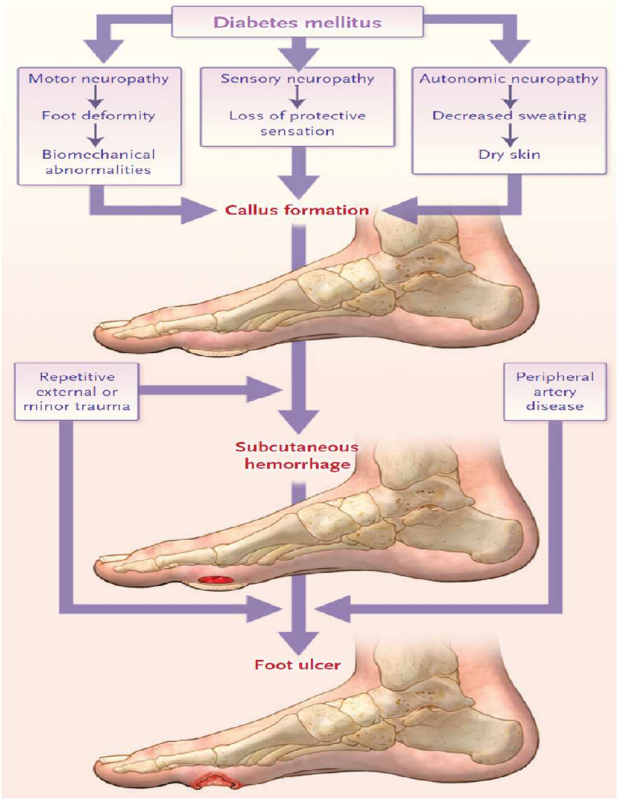
Endothelial dysfunction and vascular smooth muscle abnormalities, resulting from prolonged hyperglycemia, cause vasoconstriction due to a reduction in vasodilator production. Additionally, an increase in thromboxane A2, a vasoconstrictor and platelet aggregation agonist, promotes plasma hypercoagulability,

contributing to occlusive vascular disease. These vascular alterations result in diabetes-related ischemia, which, combined with neuropathy, leads to impaired wound healing and ulcer formation.

Disrupted Wound Healing in Diabetic Foot Ulcers

Regardless of the initial cause of diabetic foot wounds, the primary challenge lies in dysfunctional wound healing, which contributes significantly to morbidity and mortality. In normal wound healing, when the epidermal barrier is disrupted, the process is mediated by growth factors and cytokines released by immune response-activated cells, including fibroblasts, endothelial cells, keratinocytes, platelets, and phagocytes.

FIGURE 6: DIABETIC FOOT ULCER PATHOPHYSIOLOGY.[52]



This coordinated response ensures wound closure and nerve regeneration through four overlapping phases:

1. **Hemostasis Phase** – Platelets and **coagulation factors** accumulate at the injury site to prevent further bleeding and initiate clot formation.
2. **Inflammation Phase** – This phase involves the **recruitment of inflammatory cells** to clear debris and eliminate pathogens.
3. **Tissue Formation (Proliferation) Phase** – Inflammation subsides, and **fibroblasts, keratinocytes, and endothelial cells** become **proliferative**, leading to **tissue repair, angiogenesis, and granulation tissue formation**.
4. **Remodeling Phase** – The extracellular matrix (ECM) is **reorganized and strengthened**, leading to **final wound closure** and tissue maturation.

However, in **diabetic wounds**, **delays and abnormalities in these phases** prevent the transition to **efficient tissue repair**, contributing to **chronic, non-healing wounds**.

SIGNS AND SYMPTOMS OF DIABETIC FOOT WOUNDS

Diabetic foot wounds present with **a range of symptoms** that can indicate **infection, neuropathy, or vascular compromise**. Common signs include:

- **Pain** (either chronic discomfort or complete numbness)
- **Inflammation** (swelling, redness, warmth, pain, and functional impairment)
- **Infection indicators** (pus drainage, discharge, foul odor, and necrotic tissue)
- **Numbness and dull sensation** (a sign of nerve damage)

- **Fever and chills** (suggesting a **worsening infection**, which can be **limb or life threatening**)

Assessment of Diabetic Foot Ulcers (DFU)

A comprehensive evaluation of the vascular, epidermal, neurological, and musculoskeletal systems is fundamental in DFU diagnosis and management.

Visual Examination: A thorough dermatological inspection includes assessment of the plantar, dorsal, medial, lateral, and posterior foot surfaces. Particular attention is given to each toenail to identify fungal infections, deformities, or trauma. Additionally, skin fissures or maceration between toes may indicate moisture-related breakdown, increasing the risk of secondary infections. The presence of sudomotor dysfunction or autonomic neuropathy symptoms may also be evident during visual inspection[53].

Vascular Assessment: Due to the high prevalence of peripheral vascular disease (PVD) in diabetes, a thorough vascular examination is essential. This includes palpation of peripheral pulses in the superficial femoral, posterior tibial, popliteal, and dorsalis pedis arteries to assess blood flow adequacy. PVD can significantly delay wound healing, leading to persistent and infected ulcers. A simple yet effective method to evaluate arterial occlusion is by measuring systolic blood pressure in both the ankles and arms using a Doppler probe. The ankle-brachial index (ABI) is determined by dividing the higher of the two brachial pressures by the highest of the four ankle and foot pressures[53].

- **Normal ABI values** range between **1.0 and 1.3**, as ankle pressure typically exceeds arm pressure.
- **ABI > 1.3** suggests **arterial calcification** leading to non-compressible vessels.

- **ABI < 0.9** indicates **PVD**, often associated with **≥50% arterial stenosis**.
- **ABI between 0.4 and 0.9** signals **moderate arterial blockage** (claudication-related).
- **ABI < 0.4** or **ankle systolic pressure < 50 mmHg** suggests **critical limb ischemia**, indicating **advanced vascular insufficiency**[54].

Clinical correlation exists between ABI and lower extremity function, including walking speed, distance, balance, and overall physical activity. Additionally, low ABI values have been linked to coronary heart disease, renal dysfunction, transient ischemic attacks (TIA), and stroke[55]. Since arterial calcification can sometimes falsely elevate ABI values, toe blood pressure measurements and the toe-brachial index provide a more accurate assessment of vascular function[55]. If claudication symptoms persist despite a normal ABI at rest, additional segmental pressure assessments and post-exercise ABIs should be performed.

Temperature and Sudomotor Dysfunction: Foot skin temperature is measured on the dorsal surface of the hand for comparison. A normal temperature gradient exists from warm tibial regions to cooler toes[56]. A portable thermometer can provide objective foot temperature readings, with elevated temperatures being linked to sudomotor dysfunction and an increased risk of ulcer formation[57,58].

Neurological Assessment for Diabetic Neuropathy: A concise history and neurological examination can help detect diabetic neuropathy. The classic symptoms include:

- Burning sensations
- Tingling ("pins and needles")
- Sharp, stabbing pain
- Muscle spasms

Neuropathy commonly presents symmetrically in a "stocking and glove" distribution, worsening at night. The Neuropathy Symptom Score (NSS) is a validated tool used to screen for diabetic peripheral neuropathy with high predictive accuracy[59,60].

Physical Examination of Sensory Perception: To assess sensory deficits, clinicians evaluate the perception of pinprick pain, warmth, light touch, and pressure using:

- Cotton wool (for light touch sensation)
- Metal rods (for warmth perception)
- Biothesiometer or tuning fork (128-Hz) (for vibration sense assessment)

Reflex and Proprioception Testing

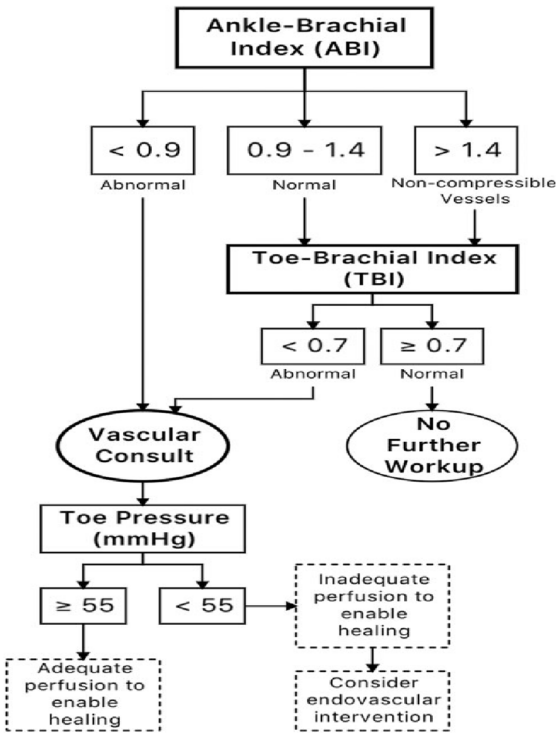
- Deep tendon reflexes (patellar and Achilles reflex)
- Position sense (proprioception testing)
- Neuropathy Disability Score (NDS) – derived from:
    - Achilles reflex loss
    - Inability to detect pinprick sensation
    - Impaired vibration sense
    - Temperature sensitivity deficits

Monofilament Testing for Protective Sensation Loss: According to the American Diabetes Association (ADA), a foot is classified as "at risk" for ulceration when it has lost protective sensation. The 5.07/10-g monofilament test, combined with at least one additional test, such as:

- Pinprick test
- Ankle reflex assessment
- Vibration test (using a 128-Hz tuning fork or biothesiometer)

is recommended for confirming neuropathy[61]. These tests demonstrate an 87% negative predictive value and a 46% positive predictive value for incident neuropathy detection[62].

FIGURE 7. ALGORITHM ASSESSING THE EVALUATION OF PERIPHERAL ARTERY DISEASE IN DIABETIC PATIENTS[55]



Grading Systems for Diabetic Foot Ulcers (DFUs)[63]

Several **classification systems** have been developed to **grade DFUs**, helping clinicians determine **severity, risk, and appropriate treatment strategies**.

University of Texas Classification System: This system grades ulcers based on depth and stages them according to the presence or absence of infection and ischemia. However, it does not account for neuropathy or the size of the ulcer.

SAD Classification: The SAD classification evaluates five ulcer characteristics:

- Size (area and depth)
- Sepsis (infection)
- Arteriopathy (vascular involvement)
- Denervation (neuropathy)

Each parameter is graded on a four-point scale (0–3) to provide a comprehensive ulcer severity assessment.

PEDIS Classification (International Working Group on the Diabetic Foot): The PEDIS system categorizes ulcers based on five critical features:

1. Perfusion – Evaluates arterial supply to the wound.
2. Extent – Measures wound area.
3. Depth – Assesses tissue involvement.
4. Infection – Identifies infectious complications.
5. Sensation – Evaluates neuropathy and loss of protective sensation.

Infectious Diseases Society of America (IDSA) Classification: The IDSA guidelines (2004) classify infected DFUs into three categories:

- Mild – Infection is limited to skin and subcutaneous tissue.
- Moderate – Infection extends deeper into tissues.
- Severe – Infection is systemic or leads to metabolic instability.

Meggitt-Wagner Classification: One of the most widely used and validated grading systems for DFUs is the Meggitt-Wagner classification (Table 1). It assesses:

- Ulcer depth
- Presence of osteomyelitis (bone infection)
- Ischemia and infection severity

Despite being one of the earliest classification systems, the Wagner system remains a standard tool for assessing DFU severity and guiding treatment decisions.

FIGURE 8. WAGNER CLASSIFICATION OF DFU

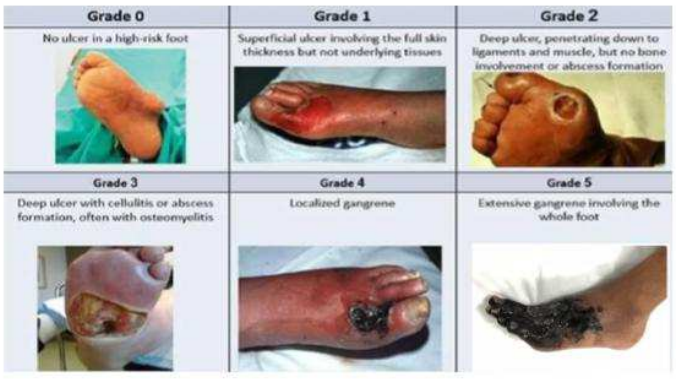


TABLE 1: WOUND CLASSIFICATION SYSTEM BY WAGNER[63]

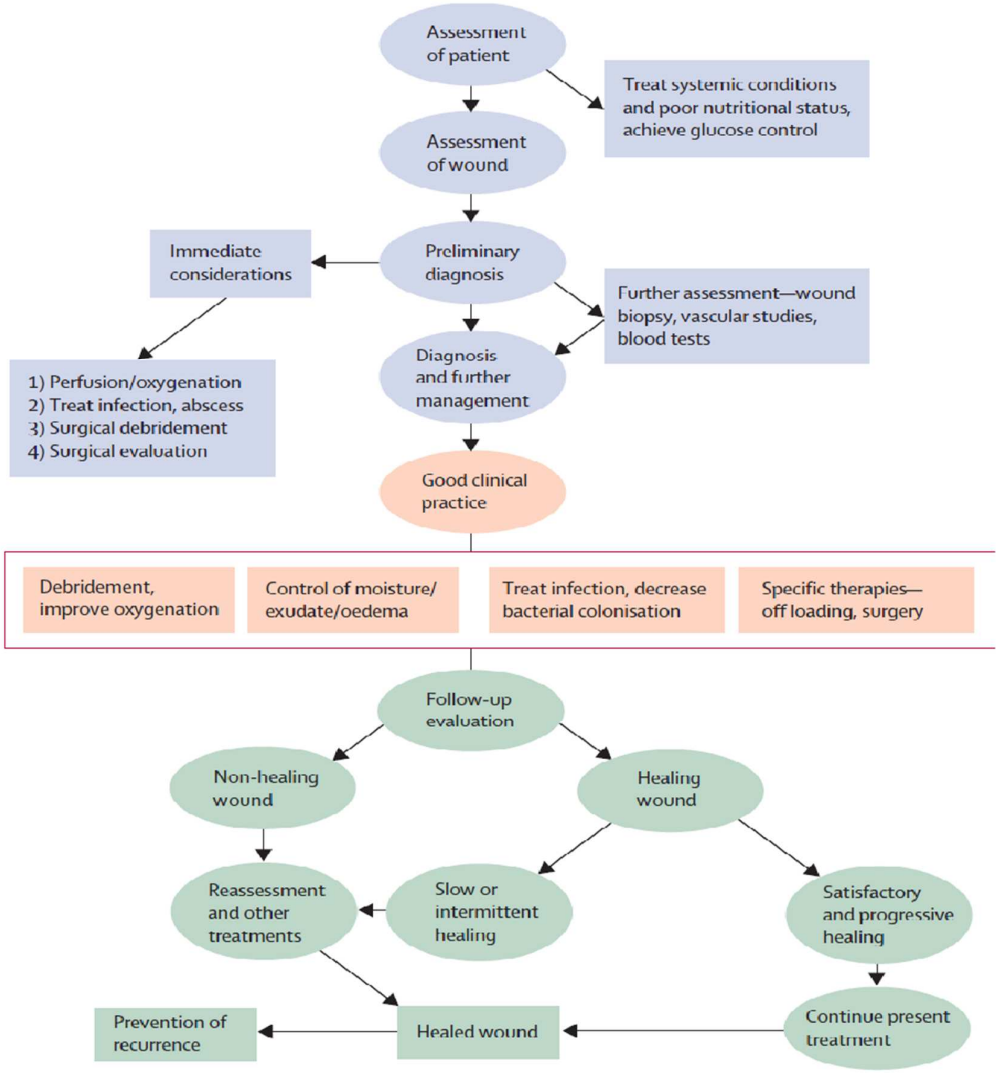
Grade 0	Pre- or post-ulcerative lesion
Grade 1	Partial/full-thickness ulcer
Grade 2	Probing to tendon or capsule
Grade 3	Deep with osteitis (bone inflammation)
Grade 4	Partial foot gangrene
Grade 5	Whole foot gangrene

Whatever method is used for the DFU evaluation, all classification systems should aim at facilitating the correct choice of treatment and reliable monitoring of the healing progress of the ulcer, while also serving as a communication tool across specialties.

Management of Diabetic Foot Ulcers (DFUs)

The primary goal in DFU management is to achieve rapid wound closure while minimizing complications. A multidisciplinary approach, as recommended by the National Institute for Health and Clinical Excellence (NICE) guidelines, is essential for optimal outcomes. This team should include a general practitioner, diabetes educator, nurse, orthotic specialist, podiatrist, and relevant specialists such as infectious disease experts, vascular surgeons, dermatologists, dieticians, endocrinologists, and orthopedic specialists. Addressing comorbidities that impact healing, such as poor glycemic control, peripheral vascular disease, and infections, is crucial. Research suggests that interdisciplinary care improves survival, enhances quality of life, and reduces complications, making it a fundamental strategy in DFU treatment[64-67].

FIGURE 9: MANAGMENT OF FOOT ULCERS IN PATIENTS WITH DIABETES[22]



EDUCATION AND MANAGEMENT STRATEGIES FOR DIABETIC FOOT ULCERS (DFUS)

Patient Education

Patient education is fundamental in preventing DFUs, emphasizing the individual's responsibility for their own foot health and overall well-being[68]. Educational programs should focus on ulcer prevention and reducing amputation risk through strategies ranging from brief education sessions to comprehensive hands-on training[69]. Patients should be informed about self-examinations, foot temperature monitoring, daily hygiene, appropriate footwear, and the importance of blood glucose control[70].

Diabetes Control

Effective glycemic control is crucial in DFU management, as poor glucose regulation is a primary risk factor for ulcer formation and progression[71]. The HbA1C level serves as the best long-term measure of glucose control, with higher levels correlating with increased glycosylation of hemoglobin in red blood cells. Patients with blood glucose levels above 220 mg/dL have 2.7 times higher infection rates than those with better-controlled glucose levels[72]. A 1% reduction in HbA1C has been associated with a 25% decrease in microvascular complications, including neuropathy[71]. Additionally, research suggests that every 1% increase in HbA1C raises the risk of peripheral arterial disease (PAD) by 25%–28%, further increasing the likelihood of DFU development[73].

Debridement

Debridement is a critical step in DFU treatment, facilitating wound closure and reducing the risk of limb amputation by removing necrotic, senescent, foreign, and contaminated tissue[74-76]. This process reduces bacterial load, enhances local growth factor production, relieves pressure on the ulcer, and improves wound drainage[77]. Debridement techniques include surgical, enzymatic, autolytic, mechanical, and biological methods, with surgical debridement demonstrating the most effective DFU healing outcomes[78-81].

TABLE 2 FOR PATIENTS WITH DIABETIC FOOT ULCER, DIFFERENT TYPES OF DEBRIDEMENT ARE[82,83]

METHOD	ADVANTAGES	DISADVANTAGES
Surgical	Cost-effective as all that is needed are sterilised scissors or a scalpel.	Need some ability to prevent the wound from getting worse
Mechanical	enables the eradication of brittle necrosis	It may eliminate granulating tissue and is not selective. Patients may have discomfort as a result.
Autolytic	It's cost-effective It is appropriate for a wound that is exceedingly painful.	It takes time, and therapy may need to be ambiguous in timing.
Enzymatic	They can be used directly on necrotic tissue.	Because streptokinase can be absorbed systemically, it should not be used in individuals who are at risk for a MI. It is also costly.
Biological	They distinguish between granulating tissue and necrotic tissue.	Patients and doctors may be reluctant to adopt this therapy since it is pricey.

DEBRIDEMENT, OFFLOADING, AND ADVANCED DRESSINGS IN DFU MANAGEMENT

Debridement

Surgical or sharp debridement involves the removal of dead and diseased tissue, followed by daily application of saline-soaked gauze to prevent infection[74]. The primary goal of debridement is to convert a chronic ulcer into an acute wound, enhancing its ability to heal. If necrotic tissue continues to form, repeat surgical debridement is necessary[84]. Studies suggest that weekly sharp debridement leads to faster ulcer healing than less frequent debridement[83-85]. In cases where surgical debridement is not required, alternative methods such as maggot debridement therapy (MDT) can be used. Also known as biological debridement, this method involves applying sterile Lucilia sericata larvae to the wound. The larvae secrete potent autolytic enzymes that break down necrotic tissue, eliminate bacterial biofilms, and promote healing[86,87]. Research indicates that MDT significantly reduces bacterial load, including Methicillin-Resistant Staphylococcus aureus (MRSA), minimizes wound odor, and can decrease the need for hospitalization and outpatient visits[88-91]. Regardless of the debridement method used, it is essential to ensure proper debridement before applying topical treatments, dressings, or advanced wound closure techniques.

Offloading

Offloading, or pressure modulation, is one of the most critical aspects of treating neuropathic DFUs. Studies confirm that effective pressure relief accelerates healing, preventing further ulcer formation. The choice of offloading technique depends on ulcer severity, location, patient mobility, and treatment adherence. Total

Contact Casts (TCCs) are considered the gold standard for offloading neuropathic ulcers, as they effectively redistribute pressure across the foot. Other methods include removable total contact casts (RTC) and instant total contact casts (iTCC), which also provide effective pressure relief[92].

Advanced Dressings

The development of innovative wound dressings has significantly advanced DFU treatment over the past few decades[93]. The ideal dressing should:

- Maintain moisture balance
- Promote protease sequestration and autolytic debridement
- Encourage granulation tissue formation and re-epithelialization
- Provide antimicrobial activity and oxygen permeability
- Ensure prolonged drug release for sustained therapeutic action

No single dressing can meet all these requirements, so the choice of dressing depends on ulcer etiology, location, depth, presence of slough or scar tissue, exudate levels, wound edge condition, infection status, pain level, and dressing adhesiveness[93].

Wound dressings are categorized into three main types:

- Passive dressings – Absorb exudate and provide basic wound protection, mainly used for acute wounds.
- Active dressings – Stimulate cellular activity and growth factor production.
- Interactive dressings – Alter wound physiology, promote moist healing, and enhance tissue regeneration, making them more effective for chronic wounds[94].

The primary types of dressings used in DFU management include hydrogels, films, hydrocolloids, foams, alginates, and silver-impregnated dressings (**FIGURE 10**).

FIGURE 10: ADVANCED DRESSING TYPES USED IN DFU CLASSIFICATION[95]

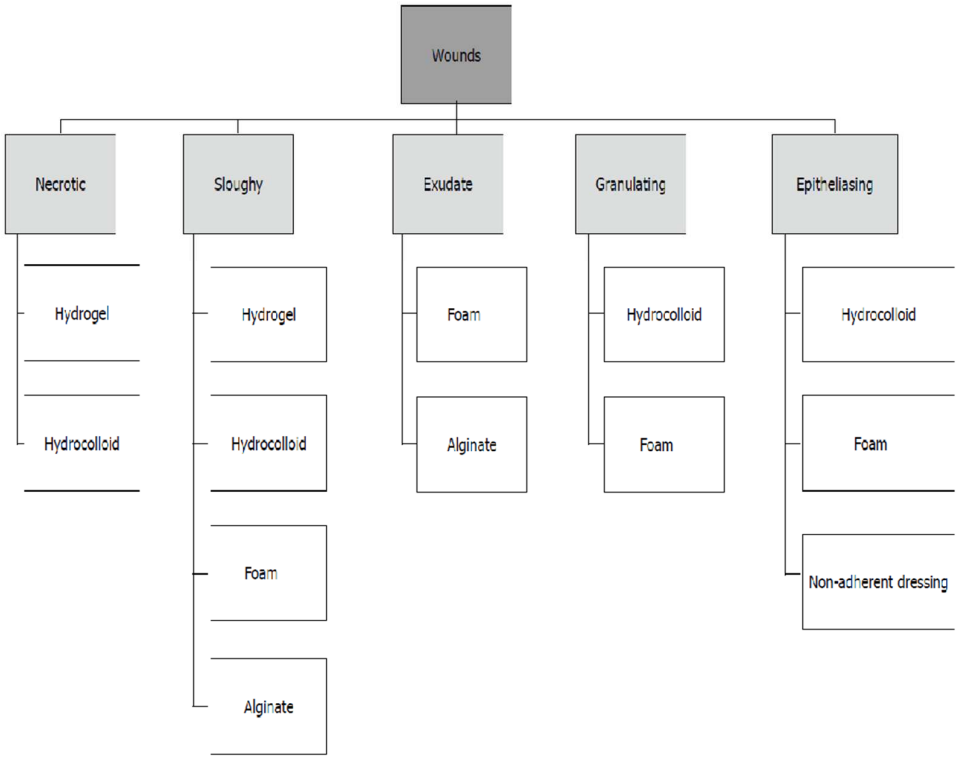


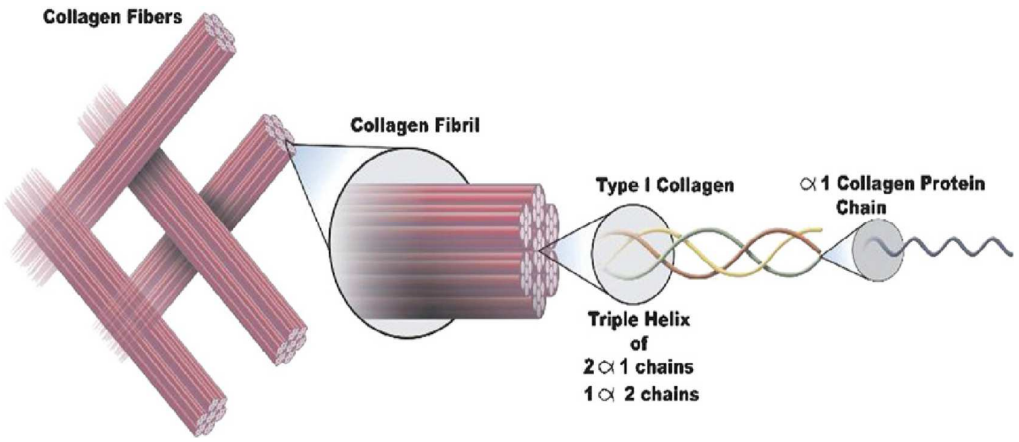
TABLE 3: WOUND DRESSING CLASSIFICATION USED IN DFU[96,97]

TYPE	ADVANTAGES	DISADVANTAGES
HYDROCOLLOIDS	Absorbent, durable over a number of days, promotes autolysis	Concerns about use for infected wounds, May cause maceration, Unpleasant odour
HYDROGELS	Absorbent, Donate liquid, Aids autolysis	putting it on wounds that are infected and very exudative raises concerns that it could lead to maceration.
FOAMS	Highly protective and absorbent, highly manipulable, and may be kept on for up to seven days, Thermal defence	Occasional dermatitis with bulky, adhesive lesions that might macerate the skin around them
FILMS	Cheap, easy manipulation, breathable to oxygen and water vapour but impermeable to water microbes	removing items can need soaking; are inappropriate for use on infected wounds. Since the film is non-absorbent, any moisture that gathers underneath it needs to be drained or replaced.
ALGINATES	Highly absorbent, Bacteriostatic, Haemostatic, Useful in cavities	Can dry out the wound bed, distinctive odor, need a secondary dressing
SILVER IMPREGNATED	Antiseptic, Absorbent Reduce odour, Reduce exudates from wounds.	High cost

Efficacy and Selection of Wound Dressings in DFU Management

The effectiveness of wound dressings remains a subject of debate among researchers and clinicians, with conflicting results regarding their overall impact on DFU healing. Despite this, dressings are an integral part of clinical practice and are selected based on DFU type and wound characteristics. Among the various dressing options, hydrogels are the most commonly used for all DFU types . They offer superior absorbency, longer wear time, reduced pain, and less traumatic removal compared to other dressing types. Additionally, hydrogels are cost-effective as they require fewer dressing changes and minimal nursing time in some cases[98-102].

FIGURE 11: ORGANIZED FIBER BUNDLES MAKING UP COLLAGEN[102]



Collagen-Based Wound Dressings

Collagen, the most abundant structural protein in the human body, plays a crucial role in all three phases of wound healing. Produced by fibroblasts, collagen promotes cellular migration and tissue regeneration, making it an effective biomaterial for wound healing[103].

Collagen dressings facilitate wound healing by:

- Stimulating fibroblast activity
- Encouraging the deposition of new collagen fibers
- Enhancing cellular migration and extracellular matrix organization

Collagen-based biomaterials also attract macrophages and fibroblasts, promoting a healing-friendly environment. These dressings can either absorb excess moisture or provide hydration, depending on the wound's needs. Typically, avian, bovine, or porcine-derived collagen is used in collagen dressings. To enhance their efficacy, collagen has been combined with oxidized regenerated cellulose (ORC), a plant-based compound that protects growth factors while binding and inactivating matrix metalloproteinases (MMPs), which are known to impair wound healing. This combination fosters optimal conditions for DFU repair by preserving essential growth factors and promoting a balanced wound environment.

Role of Collagen in Chronic Wounds and Its Impact on Healing

Chronic wounds exhibit delayed or impaired collagen deposition, hindering tissue regeneration. One of the key factors contributing to this is the reduced recruitment of fibroblasts, the predominant cells responsible for collagen production during the proliferative phase of wound healing. Additionally, in chronic wounds, fibroblasts exhibit inhibited collagen gene expression, further limiting collagen synthesis.

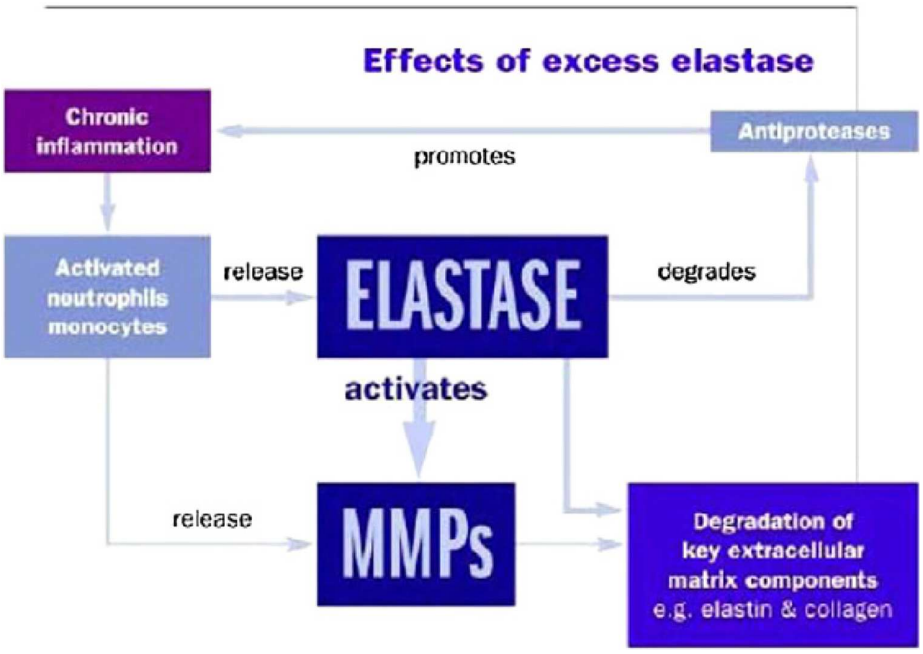
Environmental factors also play a significant role in collagen degradation within chronic wounds. Elevated levels of matrix metalloproteinases (MMPs) and elastase enzymes—which are significantly increased in chronic wound

environments—contribute to excessive extracellular matrix (ECM) breakdown. MMPs, essential for normal skin metabolism, regulate collagen synthesis and degradation, but their excessive activity in chronic wounds disrupts the normal healing balance. Normally, tissue inhibitors of MMPs (TIMPs) regulate MMP activity, but in chronic wounds, TIMP levels are abnormally low, leading to an increased MMP-to-TIMP ratio that further accelerates ECM degradation.

Elastase, another key enzyme in chronic wounds, degrades elastin, a structural protein responsible for dermal tissue elasticity. Its overactivity in chronic wounds activates pro-MMPs, increasing the MMP burden and exacerbating collagen degradation. Since elastase has a high affinity for native collagen, laboratory studies suggest that dressings containing collagen can act as a substrate magnet for elastase and MMPs, effectively diverting them from attacking endogenous collagen within the wound bed.

In conclusion, chronic wounds are characterized by impaired collagen deposition and excessive collagen degradation, driven by high elastase and MMP activity. Elastase, in particular, plays a crucial role in maintaining the destructive cycle of chronic wound pathology, emphasizing the importance of collagen-based therapies that help counteract enzymatic degradation and promote wound healing[102].

FIGURE 12: ELASTASE'S IMPACT ON WOUND MATRIX. METALLOPROTEINASES, or MMPS.[102]



COLLAGEN SILVER DRESSINGS

Silver ions, known for their broad-spectrum antimicrobial activity, attach to bacterial cell membranes, disrupt cell walls, and induce cell leakage, ultimately leading to bacterial death. Antibiotic-resistant bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE), are particularly susceptible to silver-based dressings. Studies on experimental biofilm models indicate that silver dressings reduce bacterial adhesion, disrupt biofilm structures, kill bacteria within the matrix, and enhance bacterial susceptibility to antibiotics.

Several collagen dressings incorporate silver to enhance antimicrobial protection. A randomized clinical trial by Gottrup et al. evaluated the effectiveness of

collagen, oxidized regenerated cellulose (ORC), and silver dressings in treating DFUs. In this study, 39 patients were randomly assigned to the ORC group or control group and observed for 14 weeks. At 4 weeks, 52% of ORC-treated patients achieved complete epithelialization, while 79% exhibited at least 50% wound closure. In contrast, only 43% of control group patients showed 50% healing, and 31% achieved full epithelialization by week 14. Additionally, none of the ORC-treated patients developed infections, compared to 31% of control group patients ($P = 0.012$).

A separate study by Ulrich et al.[104] investigated the mechanism of ORC dressings without silver in 32 DFU patients. Participants received either ORC dressings ($n = 22$) or hydrocolloid dressings ($n = 10$), with wound fluid samples collected on days 0, 5, and every two weeks. The study reported significant reductions in gelatinase, elastase, plasmin, and matrix metalloproteinase-2 (MMP-2) levels in ORC-treated DFUs at weeks 2, 4, 6, and 8, correlating with greater wound size reduction at weeks 2 and 4.

TABLE 4: CELLULOSE/COLLAGEN DRESSING BENEFIT[105]

Cellulose/Collagen Dressing	Conventional Dressing
● Ability to absorb wound exudates and decreases reactive oxygen species in the wound. ● Promotes quick healing and accelerates wound healing. ● Decreased hospital stay time. ● Shorter treatment duration ● Improvement in the area of wound healing ● Rapid development of granulation tissues ● GF concentration and re-epithelization improved. ● prevents bacterial invasion at wound site ● Easy application and excellent wound bed adhesion	● Deposition of slow granulation tissue ● High likelihood of harbouring pathogenic organisms ● Efficiency loss due to the weight of absorbed wound exudates ● Frequently calls for particular caution and regular dressing change

TIMOLOL

Timolol (TM), a β-adrenergic receptor (βAR) antagonist, was first approved in 1978 for the treatment of increased intraocular pressure in glaucoma[106,107]. In recent years, its potential role in wound healing has gained significant attention due to its modulatory effects on inflammation, proliferation, angiogenesis, and bacterial activity.

Timolol's Role in Wound Healing

Wound healing is a complex process divided into four distinct phases:

1. Hemostasis – Initiates clot formation.
2. Inflammation – Involves immune response activation.
3. Proliferation – Tissue regeneration and re-epithelialization occur.
4. Maturation – ECM remodeling and scar formation take place[108].

Timolol interacts at multiple phases of wound healing, particularly through β1- and β2-AR inhibition on keratinocytes, fibroblasts, and macrophages. Notably, keratinocytes not only respond to adrenergic signaling but also synthesize their own epinephrine (EPI), making the skin a self-regulated catecholaminergic system. EPI has a biphasic effect on wound healing—while physiological levels promote healing, elevated levels delay the process. Thus, targeting βAR signaling through adrenergic modulators like TM presents a novel therapeutic strategy[109].

TIMOLOL'S IMPACT ON WOUND HEALING PHASES

1. Inflammatory Phase

Upon injury, platelet degranulation triggers cytokine release (IL-8, TGF-β1, PDGFs) that amplifies inflammation. Neutrophils dominate the first 24 hours, releasing TNF-α, IL-1β, and recruiting more immune cells. Monocytes then replace neutrophils, differentiating into M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages, balancing inflammation and repair. β2-AR activation prolongs inflammation, impairing neutrophil and macrophage function, delaying healing. Timolol counteracts excessive inflammation by:

- Regulating neutrophils and macrophages.
- Promoting M2 macrophages and Th1 CD4+ differentiation, reducing inflammation[110-112].

2. Proliferative Phase

Re-Epithelialization

Keratinocyte migration is essential for wound closure but is inhibited by β2-AR activation, which increases cAMP, ERK phosphorylation, and nitric oxide (NO) overproduction, impairing proliferation. Timolol enhances keratinocyte migration by:

- Blocking β2-AR activation, preventing ERK dephosphorylation.
- Suppressing catecholamine synthesis, reducing TH and PNMT activity.
- Increasing keratinocyte migration speed by 28% and ERK phosphorylation by 2.5-fold[112,113].

Granulation Tissue & Fibroblast Activity

Fibroblasts migrate to the wound bed 3-4 days post-injury, influenced by βAR activation, which promotes excessive fibroblast proliferation and scarring. Timolol regulates fibroblast activity, preventing excessive fibrosis by reducing ERK 1/2 phosphorylation[114].

ECM Deposition & Wound Contraction

Fibroblasts synthesize collagen, fibronectin, and proteoglycans to form the ECM, crucial for wound remodeling. βARs regulate ECM development, influencing scarring. Timolol enhances wound contraction and reduces fibrosis via TGF and ERK modulation[115].

3. Angiogenesis

VEGF and PDGF drive angiogenesis, essential for wound healing. Endothelial cells express β1-, β2-, and β3-ARs, influencing blood vessel formation[116].

Timolol:

- Increases vascular permeability
- Enhances VEGF secretion, promoting capillary formation

The precise role of TM in angiogenesis remains under investigation[116].

4. Maturation Phase

As ECM transitions into a collagen-rich structure, MMPs regulate collagen degradation, but imbalances impair healing. Timolol:

- Inhibits MMP-2 and MMP-9, reducing collagen breakdown.
- Modulates β-Arrestin/NF-κB pathways, optimizing collagen remodeling.
- May upregulate beneficial MMPs (MMP-1, -3, -13) in IL-1β environments, though further research is needed[117].

Bacterial Modulation & Biofilm Control

1. Quorum Sensing (QS) Disruption

Bacteria use QS to regulate motility, biofilm formation, and gene expression[118]. Timolol inhibits QS, reducing biofilm formation in Pseudomonas aeruginosa, a key pathogen in chronic wounds. By blinding bacteria to catecholamine signals, TM lowers infection risk[118].

2. Skin Microbiota Interactions

Certain skin microbiota (e.g., Staphylococcus epidermidis) produce trace amines (TAs) that inhibit βARs, counteracting catecholamine effects and improving wound healing[119].

3. Biofilm Inhibition

Biofilms, common in chronic wounds, delay healing. Catecholamines upregulate biofilm formation, worsening wound outcomes. Timolol inhibits biofilm growth, preventing epinephrine-induced bacterial colonization[120].

RELATED STUDIES:

1. In a study done by **Ghanbarzamani[121] (2021)** to assess the efficacy and safety of topical 0.25% Timolol Gel (TG) in promoting wound healing in split-thickness skin graft donor sites, they conducted a double-blind, randomized clinical trial measuring re-epithelialization time, pain levels using the Visual Analog Scale (VAS), and wound infection incidence. They found that the healing time was significantly shorter in the TG group (11.5 ± 2.3 days) compared to the placebo group (14.5 ± 3.2 days, $P < 0.001$), with no infections in either group and three cases of transplant rejection in the placebo group. The VAS scores showed significant differences in pain reduction on multiple days ($P < 0.05$), and in the third month, there was a significant improvement in scar assessment based on the Vancouver Scar Scale ($P = 0.005$). They concluded that topical TG can be effectively administered as a therapeutic agent to enhance wound healing and reduce pain in patients undergoing skin grafts.

2. In a study done by **Tajdar[122] (2024)** to investigate the impact of conventional dressings and silver colloid dressing on diabetic foot ulcers (DFU) with and without compression therapy, they conducted a prospective, double-blind experiment involving 50 patients with non-ischemic DFUs, divided into two groups of 25 patients each, over a period of six months. They found that the ulcer area significantly decreased in the colloidal silver group (67.77 ± 17.82%) compared to the conventional saline group (21.70 ± 23.52%), with the silver group requiring fewer days to achieve total healing (23.15 ± 8.15 days vs. 48.35 ± 18.07 days). By day 14, ulcer area reduction was greater in the silver group (48%) compared to the conventional group (89.69%). They concluded that hydrogel wound dressings using ionic silver colloids are more effective than regular saline dressings for DFU management, promoting faster healing and significantly reducing ulcer size over time.
3. In a study done by **Dumville[123] (2013)** to assess the effects of hydrogel wound dressings compared with alternative dressings or none on the healing of foot ulcers in people with diabetes, they conducted a systematic review and meta-analysis of five randomized controlled trials (RCTs) involving 446 participants. They found that hydrogel dressings were significantly more effective in healing diabetic foot ulcers than basic wound contact dressings, with a risk ratio (RR) of 1.80 (95% CI: 1.27 to 2.56), though follow-up times and ulcer severities varied across studies. However, comparisons between hydrogel and larval therapy or platelet-derived growth factors showed no statistically significant differences in ulcer healing, nor was there a difference between different hydrogel brands. They concluded that while hydrogel dressings may be more effective than basic wound contact dressings for lower-grade diabetic foot ulcers, the evidence remains

uncertain due to small study sizes, potential bias, and lack of comparisons with other advanced wound dressings.

In a study done by **Zhao[124] (2024)** to investigate the differences in utility between conventional dressings and hydrogel dressings for the treatment of diabetic foot ulcers (DFU), they conducted a meta-analysis of 15 randomized controlled trials involving 872 patients. They found that hydrogel dressings significantly improved the healing rate (OR 4.09, 95% CI 2.83 to 5.91), shortened healing time (MD −11.38, 95% CI −13.11 to −9.66), enhanced granulation (MD −3.60, 95% CI −4.21 to −3.00) and epithelial formation (MD −2.82, 95% CI −3.19 to −2.46), and reduced bacterial infection incidence (OR 0.10, 95% CI 0.05 to 0.18). They concluded that hydrogel dressings are more effective than conventional dressings in promoting DFU healing, accelerating tissue regeneration, and reducing infection risk.

4. In a study done by **Sharma[125] (2017)** to compare the outcome of silver colloidal-based dressing versus conventional dressing in the management of diabetic foot ulcers (DFU), they conducted a single-institution prospective randomized controlled trial on patients with Wagner grade 1 and 2 DFUs. They found that after 12 weeks, the mean wound area decreased by 85.65% in the silver colloidal dressing group compared to 68.62% in the conventional dressing group, with complete healing observed in 84.62% of patients in the silver group versus 41.67% in the conventional group. They concluded that silver colloidal-based dressings significantly improve ulcer healing and reduce wound size more effectively than conventional dressings ($p < 0.05$).
5. In a study done by **Cahn[126] (2020)** to assess timolol's effectiveness in healing wounds of varying etiologies, they conducted a multi-center series from 2016 to

2019 at the University of Miami Health System and the Veterans Affairs Northern California Healthcare. They found that among 39 patients with 55 chronic wounds treated with topical timolol maleate 0.5% for at least four weeks, 34 wounds completely healed, 15 showed improvement in wound size area (WSA), four remained unchanged, and two worsened. They concluded that topical timolol is a safe, cost-effective, and efficacious treatment for recalcitrant wounds of different etiologies.

6. In a study done by **Cornwell[127] (2024)** to assess the effectiveness and safety of the off-label use of topical timolol as an adjunct treatment for hard-to-heal wounds, they conducted a systematic review of literature published between May 1961 and May 2021. They found that out of 878 initially identified articles, 12 studies, including two randomized controlled trials (RCTs) and 10 observational studies, met the inclusion criteria. All studies demonstrated the efficacy and safety of topical timolol, though statistical analysis was limited due to small sample sizes and lack of blinding. They concluded that topical timolol may be a safe and effective adjunct treatment for refractory wounds, particularly venous leg ulcers and diabetic foot ulcers, advocating for further rigorous studies to support its off-label use.
7. In a study done by **Thomas[128] (2017)** to assess the effect of topical timolol on the healing of chronic venous and diabetic ulcers, they conducted a case-control study involving 60 patients with chronic leg ulcers. They found that ulcers treated with 0.5% timolol maleate solution, along with antibiotics and dressings, showed significantly greater healing compared to the control group, which received only antibiotics and dressings. The mean percentage change in ulcer area at 4, 8, and 12 weeks was 25.29%, 43.77%, and 61.79% in the timolol group versus 11.92%,

22.40%, and 29.62% in the control group. They concluded that topical β-blockade using timolol significantly improves the healing of chronic leg ulcers, independent of ulcer type, alcohol consumption, or smoking history.

8. In a study done by **Kaur[129] (2020)** to examine the efficacy and safety of topically applied beta-antagonist Timoptic-XE® (timolol maleate ophthalmic gel) in diabetic foot ulcers (DFUs), they conducted a phase two, randomized, double-blinded, controlled clinical trial with two treatment arms: standard of care (SOC) plus Timoptic-XE® and SOC plus a placebo hydrogel. They found that study subjects from the Veterans Affairs Northern California Health Care System (VANCHCS) applied the topical treatment daily for up to 12 weeks, with wound size and other parameters measured weekly. They concluded that this clinical translation study would provide insights into the safety and efficacy of topical beta-antagonists in DFU healing, potentially establishing new treatment paradigms.
9. In a study done by **Menezes[130] (2023)** to evaluate the efficacy of topical timolol in treating chronic non-healing foot ulcers and its feasibility in a rural/semi-urban population, they conducted an observational, cross-sectional study at a tertiary hospital near Bengaluru from January 2021 to July 2022 with a sample size of 95. They found that the mean ulcer area decreased significantly from 70.95 cm^2 on day 1 to 51.8 cm^2 on day 15 and 39.95 cm^2 on day 30 ($p = 0.001$), with a notable percentage reduction in ulcer size over time. No adverse effects were observed. They concluded that topical timolol is a safe, inexpensive, and effective treatment for chronic foot ulcers, making it a viable option for large rural populations in countries like India.

In a study done by **Baltazard[131] (2021)** to evaluate the efficacy and safety of timolol maleate gel in managing hard-to-heal venous leg ulcers (VLUs), they conducted a prospective, phase-II randomized controlled trial. They found that after 12 weeks of treatment, 67% of patients in the timolol group achieved a ≥40% reduction in ulcer area compared to 32% in the control group receiving standard care alone. No serious adverse events were reported, though local wound infections occurred in five timolol-treated patients and one control patient. They concluded that timolol maleate gel is a beneficial and safe adjunct in VLU management, though larger phase-III trials are needed to confirm these findings.

10. In a study done by **Lyle[132] (2024)** to explore the repurposing of timolol for wound healing, they reviewed preclinical and clinical studies highlighting its potential therapeutic benefits. They found that timolol enhances wound healing through mechanisms such as improved re-epithelialization, modulation of inflammation, and wound maturation, along with its effects on microbial quorum sensing and virulence. However, they noted the need for larger, more comprehensive clinical trials to establish optimal dosing, efficacy, and safety, with some such trials currently underway. They concluded that timolol offers a promising new avenue for wound healing therapies, addressing limitations in existing treatments, though further studies are required to validate its clinical use.
11. In a study done by **Gallegos[133] (2019)** to assess the safety and systemic absorption of topical timolol in chronic wound treatment, they conducted a prospective, observational, cross-sectional comparative study measuring plasma levels of timolol in wound patients versus glaucoma patients using ocular administration. They found no statistically significant difference in the average plasma levels between the two groups, with no observed cases of bradycardia or wheezing after

application. They concluded that the topical application of timolol for chronic wounds shares a similar safety profile to its well-established ocular use for glaucoma, supporting its potential as a safe off-label treatment.

12. In a study done by **Valluru[134] (2023)** to assess the effectiveness of topical timolol 0.5% in accelerating wound healing in chronic non-healing foot ulcers, they conducted a prospective observational study at Government General Hospital, Rangaya Medical College, Kakinada, from March 2021 to March 2023. They found that among 100 patients, the majority (60%) were aged 20-55 years, and the topical application of timolol led to a significant reduction in mean ulcer area by day 15 and day 30. They concluded that timolol may promote wound healing by enabling keratinocyte migration and re-epithelialization, offering a cost-effective alternative for managing chronic ulcers resistant to conventional therapy.

MATERIALS AND METHODS

- **STUDY DESIGN:** Randomized Controlled Trial
- **STUDY DURATION:** 12 months (1st September, 2023 to 31st August, 2024).
- **STUDY AREA:** KAHER's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi.
- **STUDY PARTICIPANTS:** Patients with chronic diabetic ulcers attending the department of general surgery in KAHER's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi.
- **INCLUSION CRITERIA**

  1. Patients of age >18 years of both sexes
  2. Patients with confirmed diagnosis of diabetes mellitus
  3. Patients with diabetic ulcer of >6 weeks duration with surface area >0.5 cm2
  4. Patients who give consent to participate in the study

- **EXCLUSION CRITERIA**

  1. Ulcer of non-diabetic etiology (venous, arterial, burn wounds)
  2. Ulcer present with any of the following: cellulitis, exposed bone/ tendon/ fascia, purulent exudate, gangrene, osteomyelitis,
  3. Ulcer shows evidence of infection
  4. Immunocompromised status or severe protein malnutrition
  5. Chronic renal insufficiency or failure (S. creatinine > 3mg/dl)

6. Known cardiac patients or Cardiovascular symptoms (angina/ fatigue/ palpitations/ dyspnoea)/ history of bradycardia (HR<60 bpm) or on COPD/ Asthma medication
7. Known active malignancy on the study limb
8. Patients who are pregnant/ lactating
9. Patients who don't give consent to participate in study

Sampling technique: Computer generated random numbers

METHOD OF COLLECTION OF DATA:

Patients with chronic diabetic ulcers attending the department of general surgery in KAHER's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi were included in the study. Clearance from the institutional ethical committee was taken before starting the study. Study participants were included in the study by Purposive Sampling technique.

The study participants were included in the study, till the sample size was reached. Written informed consent/assent was taken from the parents before collecting the data. A pre-tested, semi-structured questionnaire was used to collect information on socio-demographic variables and history by interview method. After carrying out a detailed clinical examination, patients will be randomized into two groups, Group A and Group B. Before enrolling the patients for study, culture and sensitivity swabs will be taken for all ulcers and the ulcers will be cleaned with normal saline, surgical debridement will be done for dirty ulcers. Once the ulcers are clean, they will be included in the study. All diabetic patients will be brought under adequate glycemic control with appropriate antidiabetic therapy.

Group A(testing group) will receive **Timolol maleate** 0.5% drops, with each ml containing 5 mg of drug, and each drop containing 0.25mg of drug, and the patients in the group will receive 1 drop per cm2 of wound area or 0.25mg/ cm2 dosage of timolol maleate, and the ulcer will then be covered with moist saline dressing.

Group B (control group) will receive conventional dressing with Amorphous hydrogel and silver colloid dressing gel to cover the ulcer area followed by moist saline dressing.

Calculation of the wound area:

The dimensions of the ulcer i.e. length and the width in the greatest dimensions will be measured by outlining the ulcer over a sterile transparent film placed over it, followed by placing the film over graph paper and counting the number of squares, with length of the smallest square being 1mm, and the same will be used to measure the ulcer area.

The measurement of ulcer dimensions on day 0(x)= initial wound area

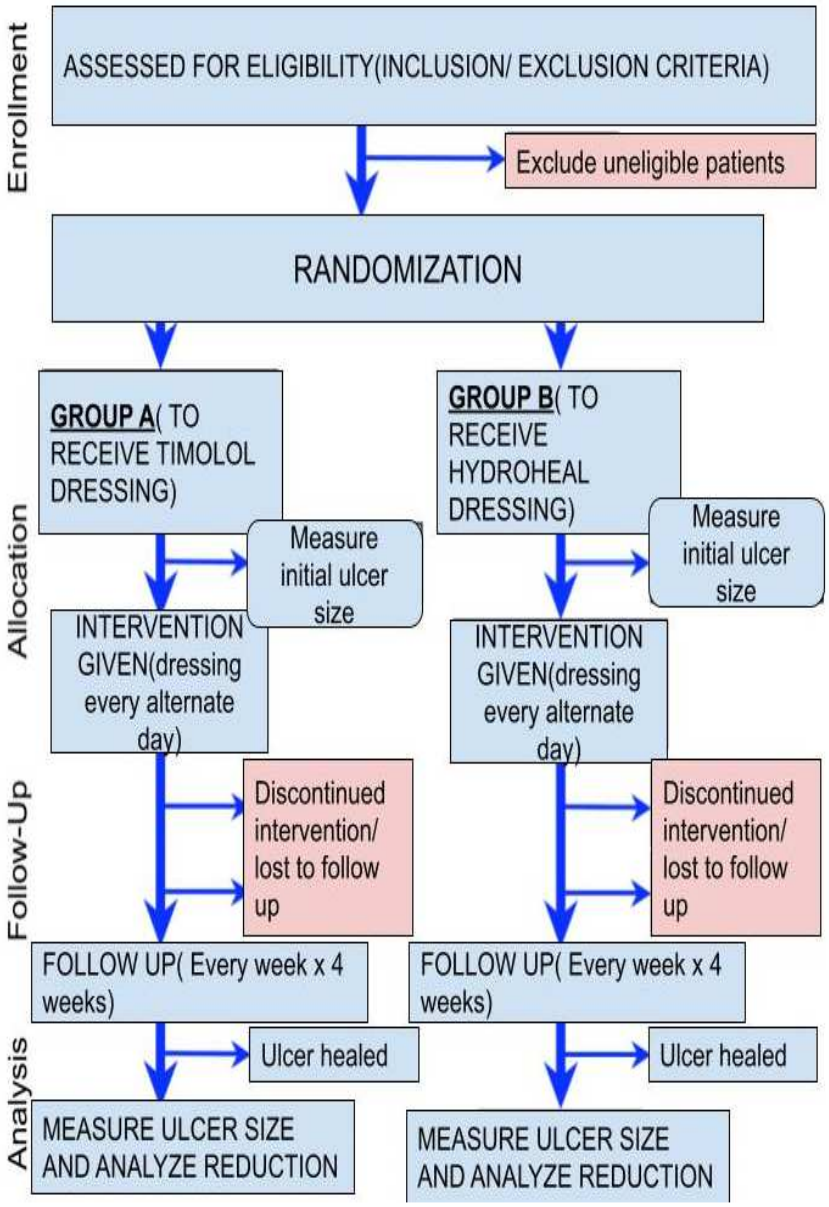
The measurement of ulcer dimensions on day 28(y)= Final ulcer area

The reduction in area and percentage reduction in area are calculated as:

wound area reduction= x-y

% wound area reduction= (x-y)/x * 100

STUDY PROTOCOL



STATISTICAL ANALYSIS:

The data was collected and compiled in MS Excel. Descriptive statistics has been used to present the data. To analyse the data SPSS (Version 26.0) was used. Significance level was fixed as 5% ($\alpha = 0.05$). Qualitative variables are expressed as frequency and percentages and Quantitative variables are expressed as Mean and Standard Deviation.

SAMPLE SIZE ESTIMATION

Sample size at 95% confidence interval and 90% power,

n= **[(Z1-a/2 + Z1 - b/2)2(**SD12 + SD22)] / (X1-X2)2

n= 56.7= 57

2xn= 114

Hence Sample Size= 114

Where X1=11.2 and X2= 9.46(duration of weeks of wound healing)

SD1= 3 and SD2= 2.41

Reference: Topical timolol promotes healing of chronic leg ulcer[128]

RESULTS

TABLE 5: AGE GROUP

AGE GROUP		G		P VALUE
		A	**B**	
30-50	**Count**	12	24	**0.046**
	%	21.1%	42.1%	
51-70	**Count**	34	23	
	%	59.6%	40.4%	
71-90	**Count**	11	10	
	%	19.3%	17.5%	
Total	**Count**	**57**	**57**	
	%	**100%**	**100%**	

The study included 114 participants, evenly distributed across both groups (57 in each group). The age distribution showed a statistically significant difference between groups (p = 0.046), with more patients in Group A (Timolol) aged between 51–70 years, whereas Group B (hydrogel and silver colloid) had a higher proportion of younger patients (30–50 years).

FIGURE 13: AGE GROUP

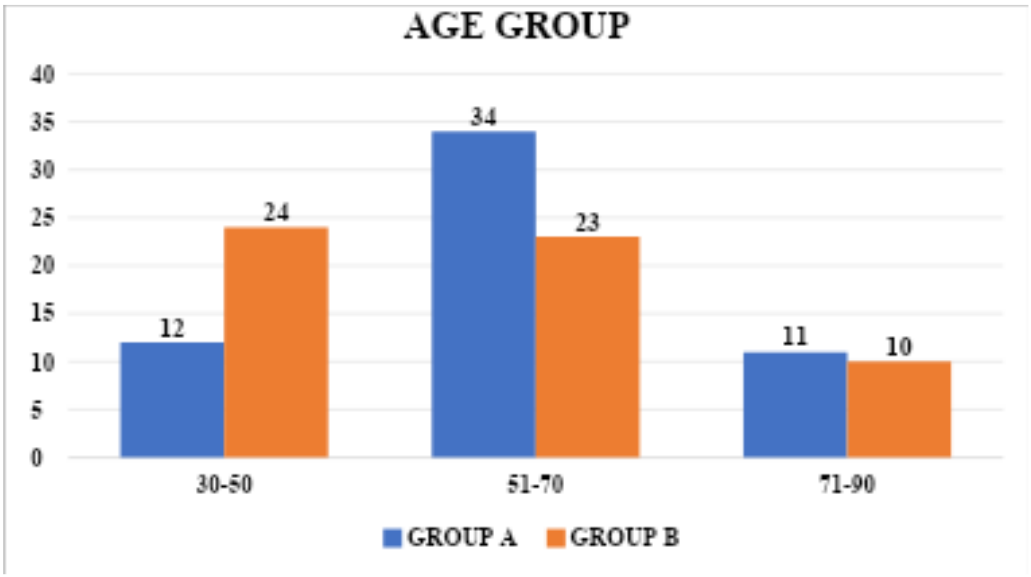


TABLE 6. SEX

Sex		G		P VALUE
		A	B	
Male	**Count**	48	48	1.00
	%	84.2%	84.2%	
Female	**Count**	9	9	
	%	15.8%	15.8%	
Total	**Count**	**57**	**57**	
	%	**100%**	**100%**	

Gender distribution, however, was identical across groups, with 84.2% of participants being males and 15.8% females (p = 1.00).

FIGURE 14. SEX

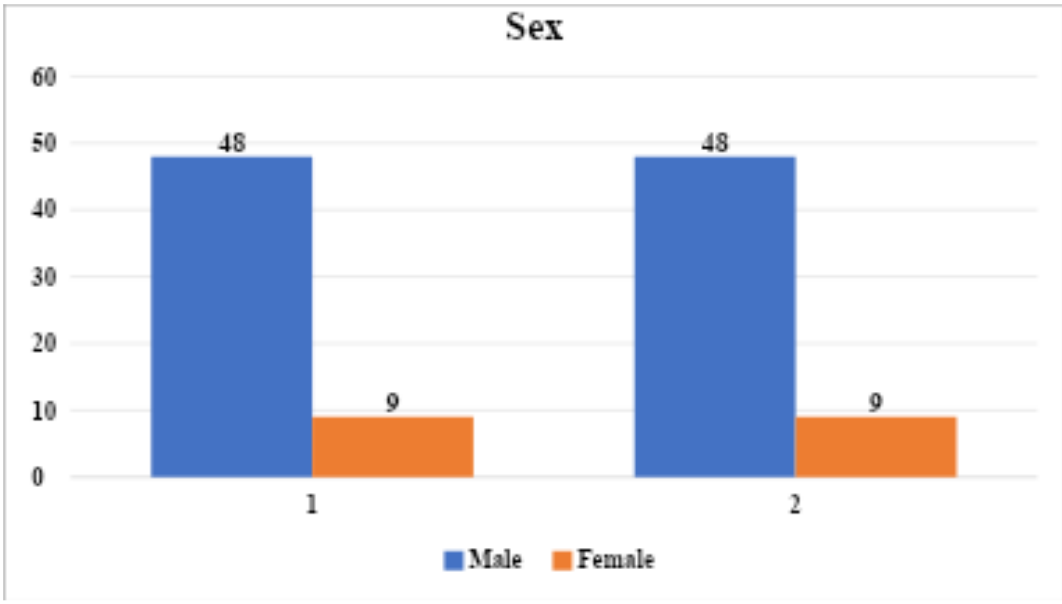


TABLE 7. ULCER DURATION

ULCER DURATION		G		P VALUE
		A	B	
6 weeks	Count	5	4	0.578
	%	8.8%	7%	
2 months	Count	13	17	
	%	22.8%	29.8%	
3 months	Count	22	18	
	%	38.6%	31.6%	
4 months	Count	6	11	
	%	10.5%	19.3%	
6 months	Count	8	6	
	%	14.0%	10.5%	
1 year	Count	3	1	
	%	5.3%	1.8%	
Total	**Count**	**57**	**57**	
	%	**100%**	**100%**	

Table 7 presents the duration of ulcers across both groups, revealing no statistically significant difference between them ($p = 0.578$). In Group A (topical Timolol), the most common ulcer duration was 3 months (38.6%), followed by 2 months (22.8%) and 6 months (14%). Group B (amorphous hydrogel and silver colloid) had a similar distribution, with 31.6% of ulcers present for 3 months and 29.8% for 2 months, suggesting that most patients in both groups had moderately chronic ulcers. Longer-standing ulcers were less frequent, with only 5.3% in Group A and 1.8% in Group B persisting for 1 year or more.

FIGURE 15. ULCER DURATION

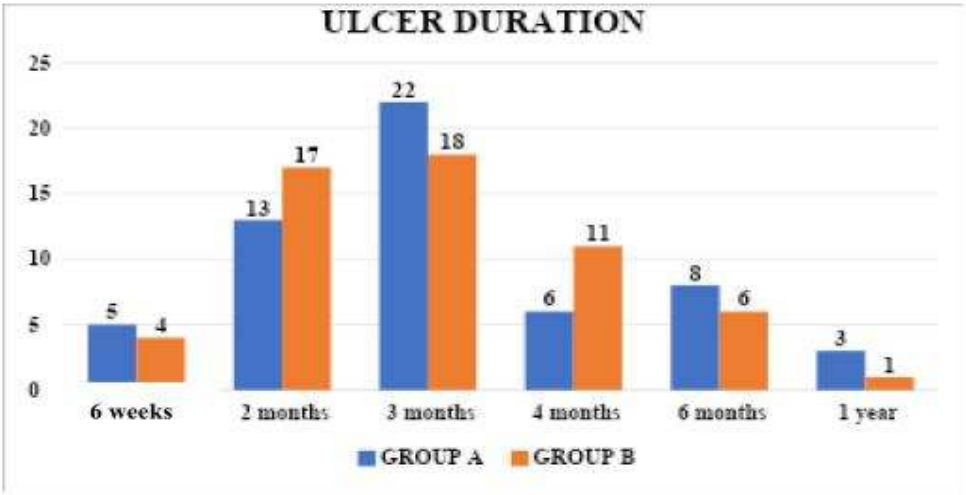


TABLE 8. DIABETES DURATION

DIABETES DURATION		G		P VALUE
		A	B	
1 MONTH- 1 YEAR	Count	3	4	0.692
	%	5.3%	7%	
1-5 YEARS	Count	11	16	
	%	19.3%	28.1%	
6-10 YEARS	Count	19	20	
	%	33.3%	35.1%	
11- 15 years	Count	14	11	
	%	24.6%	19.3%	
16-20 years	Count	9	6	
	%	15.8%	10.5%	
>20 YEARS	Count	1	0	
	%	1.8%	0%	
Total	**Count**	**57**	**57**	
	%	**100%**	**100%**	

Table 8 shows that both groups had a comparable distribution of diabetes duration, with no statistically significant difference ($p = 0.692$). In Group A, the majority of patients had diabetes for 6–10 years (33.3%), closely matched by Group B at 35.1%. A smaller proportion had diabetes for 1–5 years (19.3% in Group A, 28.1% in Group B), while 24.6% of Group A and 19.3% of Group B had diabetes for 11–15 years. Only 1.8% of patients in Group A had diabetes for over 20 years, and none in Group B.

FIGURE 16. DIABETES DURATION

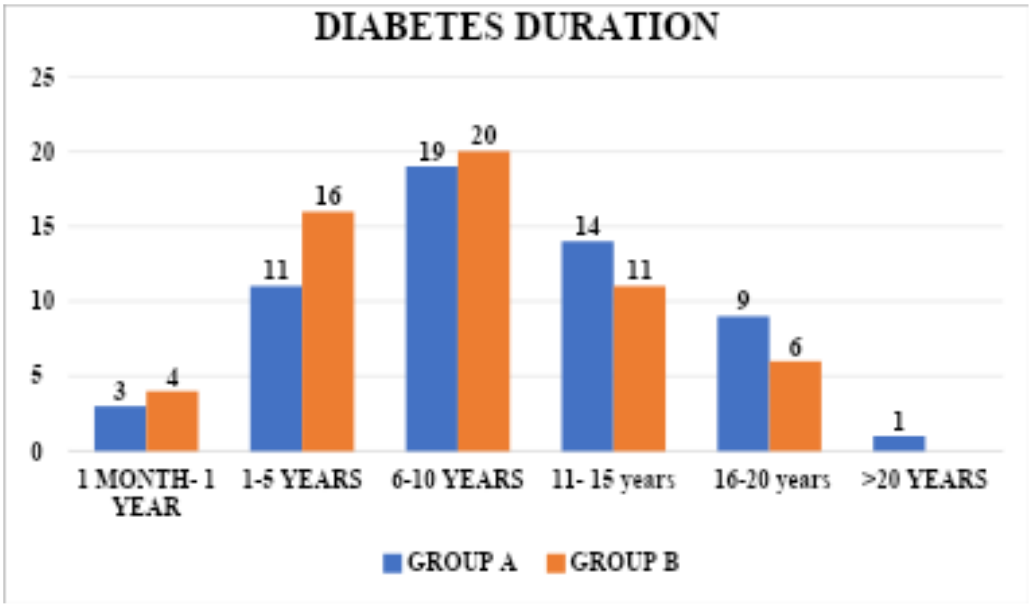


TABLE 9. DRUG HISTORY

Drug history		G		P VALUE
		A	B	
Insulin	**Count**	22	20	0.698
	%	38.6%	35.1%	
OHA	**Count**	35	37	
	%	61.4%	64.9%	
Total	**Count**	**57**	**57**	
	%	**100%**	**100%**	

Medication use was similar across groups, with 38.6% of Group A and 35.1% of Group B using insulin, while the majority relied on oral hypoglycemic agents (61.4% and 64.9%, respectively). There was a lack of significant difference (p = 0.698).

FIGURE 17. DRUG HISTORY

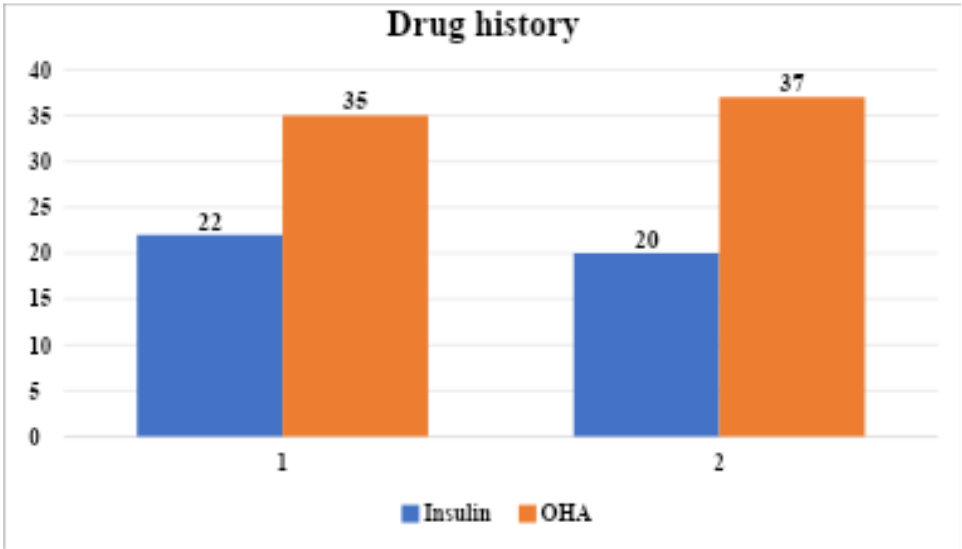


TABLE 10. LIFESTYLE FACTORS

	G		Total
	A	**B**	
Smoker/non-smoker	19 (33.3%)	24 (42.1%)	0.334
Alcohol history	23 (40.4%)	28 (49.1%)	0.346
Drug allergies	0 (0%)	0 (0%)	**<0.05**

In this study, 33.3% of Group A were smokers, compared to 42.1% in Group B (p = 0.334), while alcohol use was reported by 40.4% of Group A and 49.1% of Group B (p = 0.346). No participants in either group reported drug allergies.

FIGURE 18. LIFESTYLE FACTORS

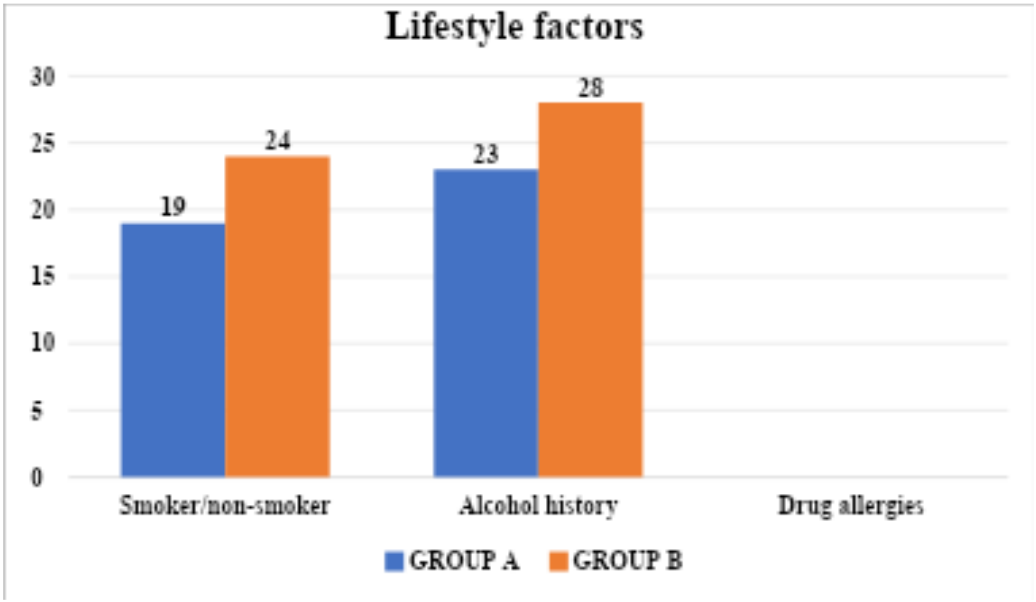


TABLE 11. HbA1c Levels

Hba1c		G		P VALUE
		A	B	
<7.5	Count	11	14	0.793
	%	19.3%	24.6%	
7.5-9	Count	28	26	
	%	49.1%	45.6%	
>9	Count	18	17	
	%	31.6%	29.8%	
Total	Count	57	57	
	%	100.00%	100.00%	

Glycemic control, as reflected by HbA1c, was similar between groups (p = 0.793). About half of the patients in both groups had moderately elevated HbA1c levels between 7.5–9% (49.1% in Group A and 45.6% in Group B), while around 30% had HbA1c >9%, indicating poorly controlled diabetes. Only about 20% of patients in each group had HbA1c levels below 7.5%.

FIGURE 19. HbA1c LEVELS

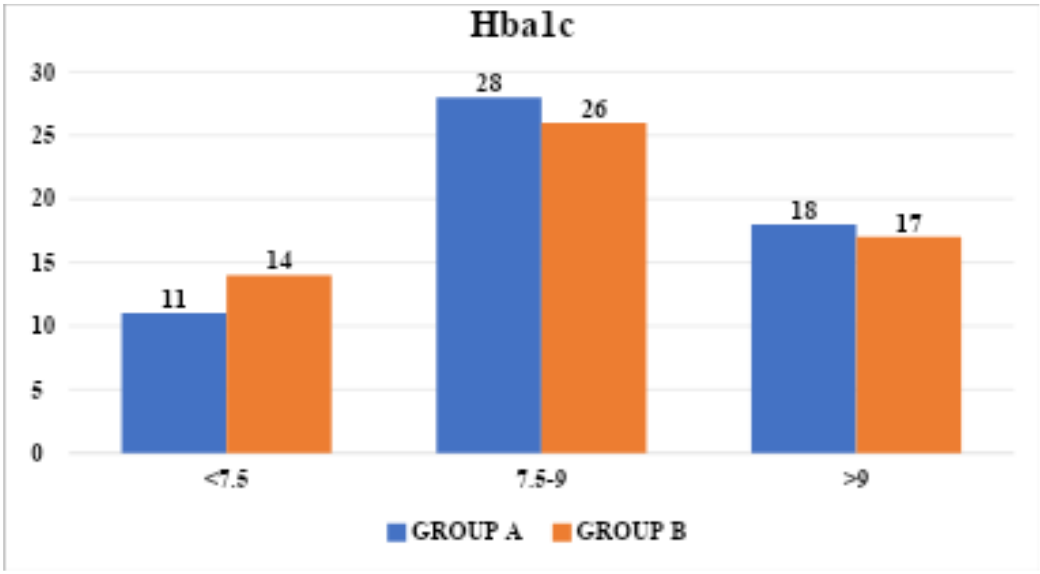


TABLE 12. PERIPHERAL PULSATIONS

Peripheral pulsations		G		P VALUE
		A	B	
Present	Count	57	57	<0.05
	%	100%	100%	
Total	Count	57	57	
	%	100%	100%	

Peripheral pulsations were present in 100% of participants in both groups, with a statistically significant p-value (<0.05).

FIGURE 20. PERIPHERAL PULSATIONS

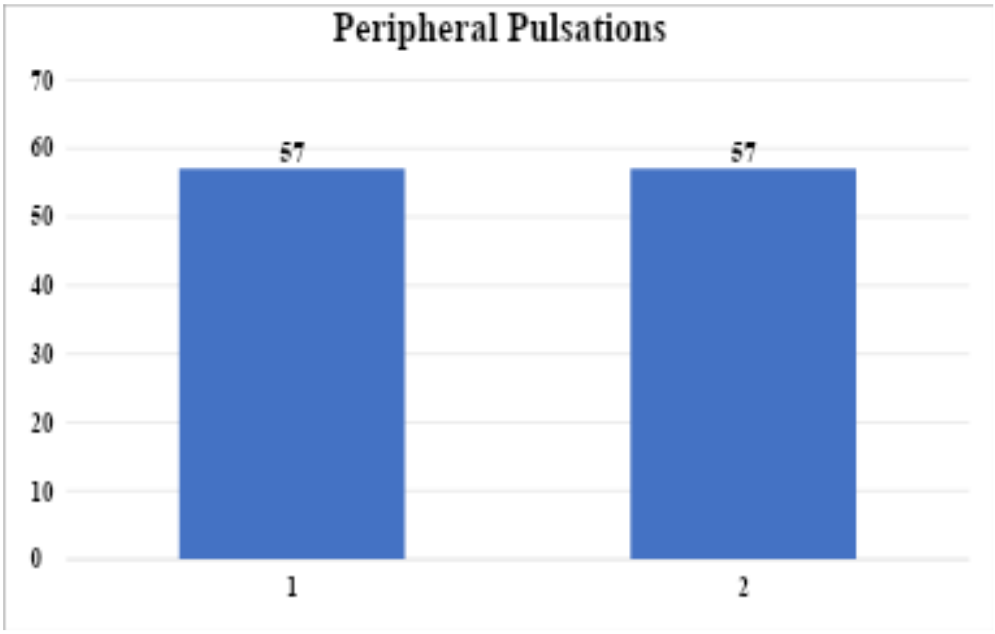


TABLE 13. Varicosities

Varicosities		G		P VALUE
		A	B	
Yes	Count	4	4	1.00
	%	7%	7%	
No	Count	53	53	
	%	93%	93%	
Total	Count	57	57	
	%	100%	100%	

Varicose veins were rare, affecting only 7% of patients in both groups (p = 1.00).

FIGURE 21. VARICOSITIES

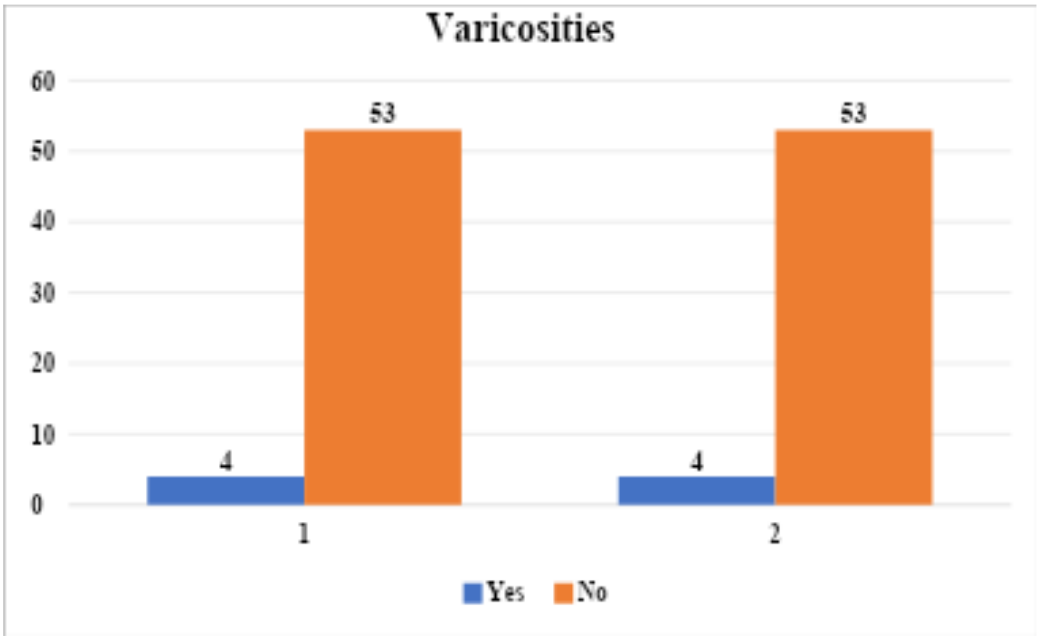


TABLE 14. Evidence of Infection

Evidence of infection		G		P VALUE
		A	B	
No	Count	57	57	<0.05
	%	100%	100%	
Total	Count	57	57	
	%	100%	100%	

None (0%) of the patients in either group showed evidence of infection, with a statistically significant p-value (<0.05).

FIGURE 22. Evidence of Infection

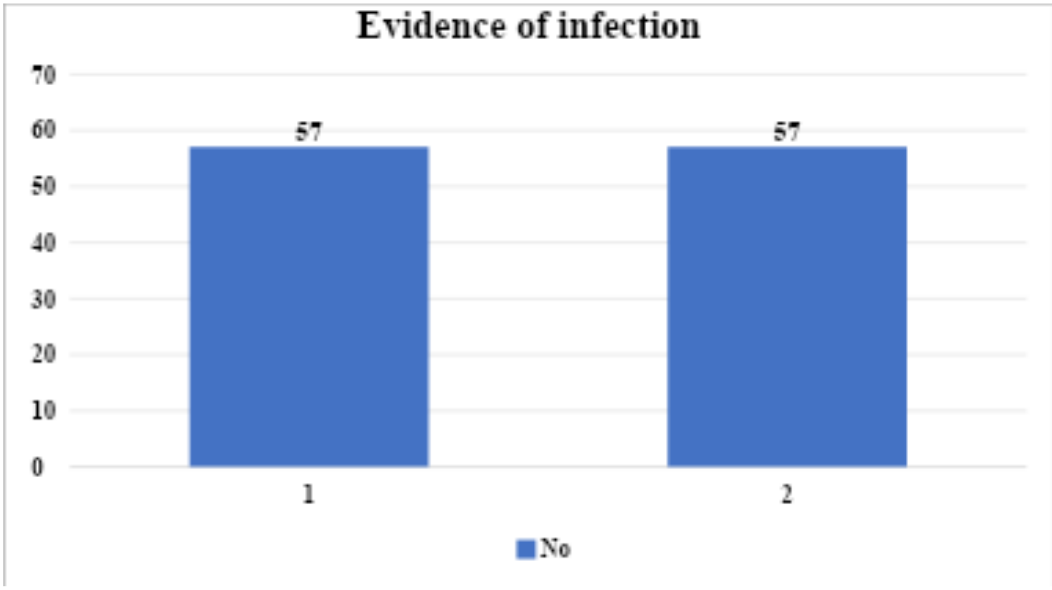


TABLE 15. Granulation Tissue

Granulation tissue		G		Total
		A	B	
Present	Count	57	57	<0.05
	%	100%	100%	
Total	Count	57	57	
	%	100%	100%	

All patients in both groups had granulation tissue present (100% in each group, $p < 0.05$).

FIGURE 23. Granulation Tissue

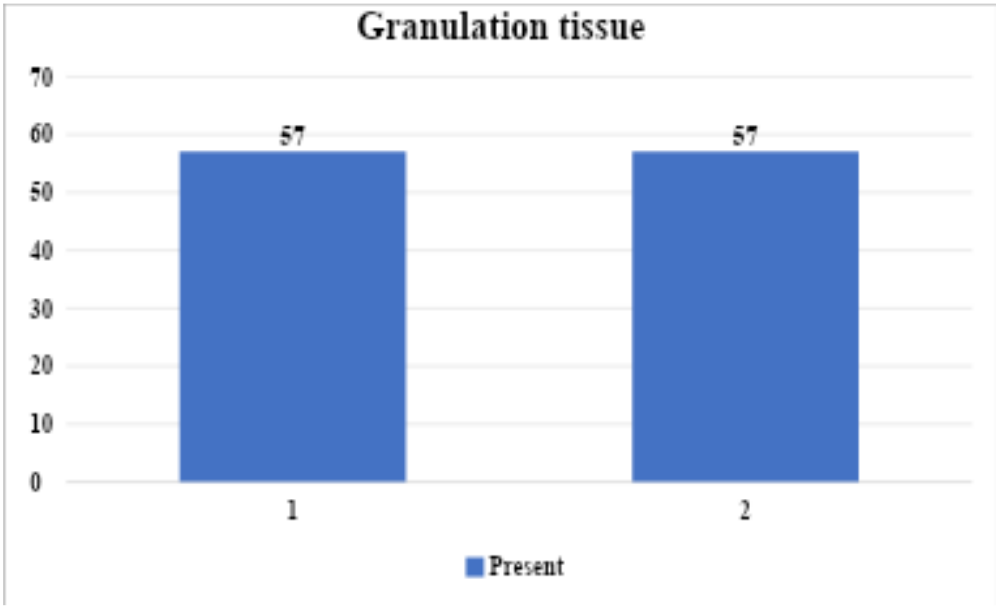


TABLE 16. Wound Length

length		G		P VALUE
		A	B	
0 day	**MEAN**	8.07	7.95	0.871
	SD	4.22	4.06	
7 days	**MEAN**	7.70	7.81	0.879
	SD	3.99	4.12	
14 days	**MEAN**	7.43	7.53	0.891
	SD	3.92	4.06	
21 days	**MEAN**	7.17	7.23	0.938
	SD	3.86	4.02	
28 days	**MEAN**	6.72	6.73	0.985
	SD	3.66	3.81	

Wound dimensions gradually decreased over 28 days in both groups, but the differences were not statistically significant. Regarding wound length, Group A reduced from 8.07 cm to 6.72 cm, and Group B from 7.95 cm to 6.73 cm (p = 0.985).

FIGURE 24. Wound Length

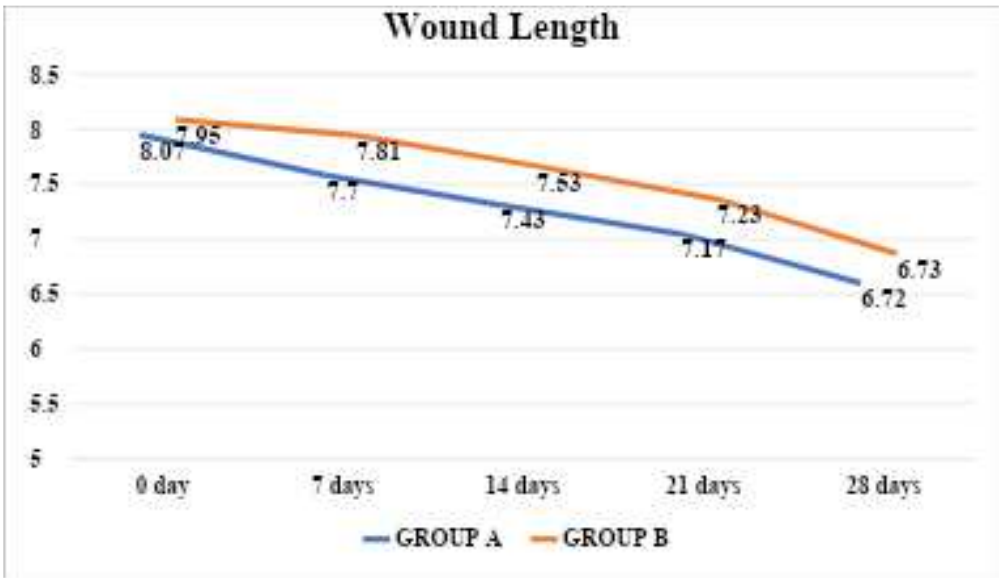


TABLE 17. Wound Width

Width		G		P VALUE
		A	B	
0 day	**MEAN**	5.01	5.24	0.541
	SD	2.11	1.89	
7 days	**MEAN**	4.84	5.08	0.53
	SD	2.07	1.86	
14 days	**MEAN**	4.65	4.91	0.476
	SD	2.04	1.83	
21 days	**MEAN**	4.46	4.73	0.459
	SD	2.01	1.81	
28 days	**MEAN**	4.25	4.54	0.412
	SD	1.97	1.79	

Regarding width, Group A reduced from 5.01 cm to 4.25 cm, and Group B from 5.24 cm to 4.54 cm (p = 0.412).

FIGURE 25. Wound Width

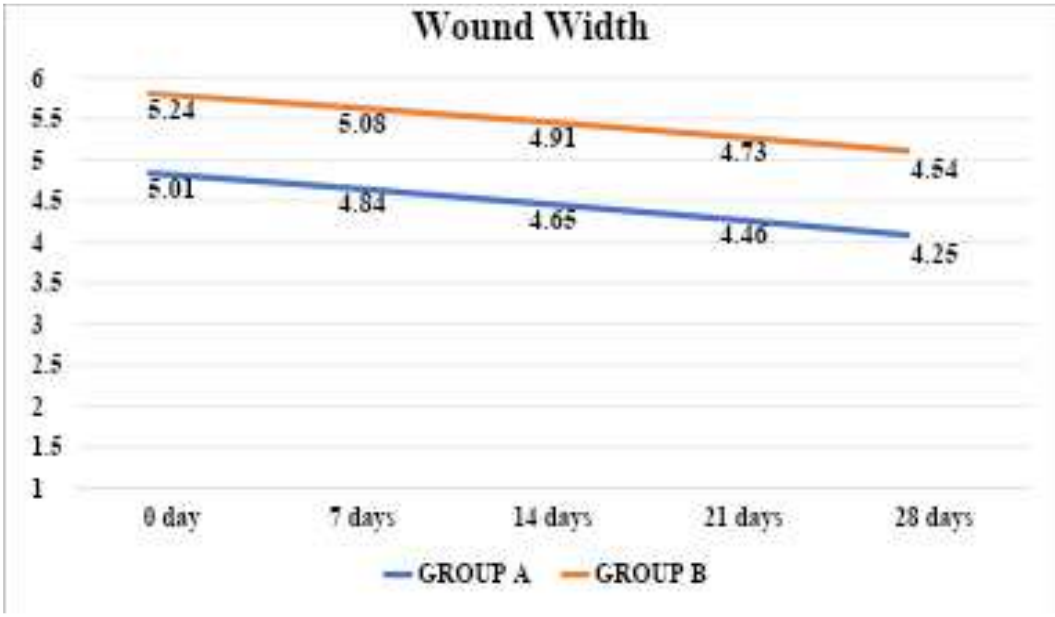


TABLE 18. Wound Area

Area		G		P VALUE
		A	B	
0 day	**MEAN**	46.32	46.20	0.986
	SD	39.79	35.56	
7 days	**MEAN**	43.50	43.46	0.996
	SD	37.64	33.55	
14 days	**MEAN**	40.60	40.73	0.983
	SD	35.88	31.62	
21 days	**MEAN**	37.65	38.03	0.95
	SD	33.95	29.91	
28 days	**MEAN**	33.77	34.55	0.89
	SD	31.53	27.93	

Regarding wound area, Group A reduced from 46.32 cm^2 to 33.77 cm^2, and Group B from 46.20 cm^2 to 34.55 cm^2, however was not statistically significant ($p = 0.89$).

FIGURE 26. Wound Area

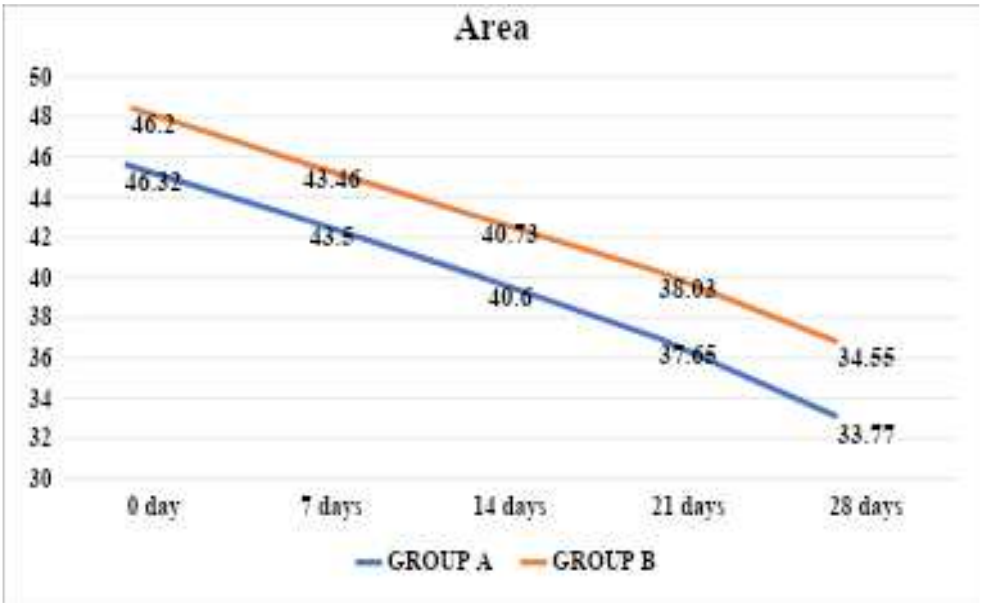
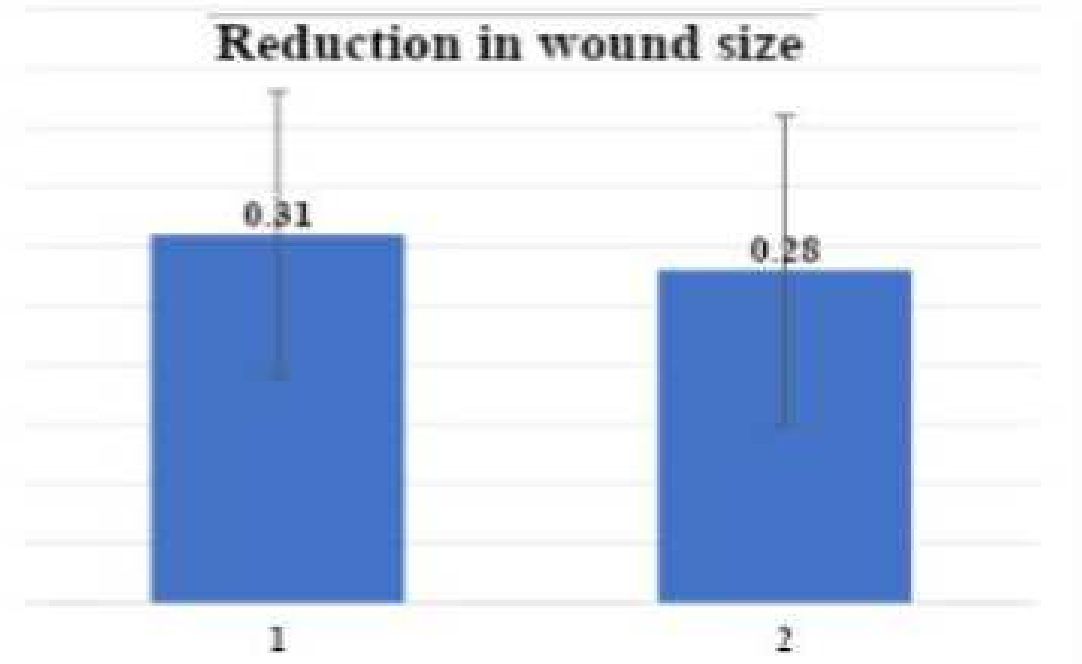


TABLE 19. Wound Size Reduction

Reduction in wound size (%)	G		P VALUE
	A	B	
MEAN	0.31	0.28	0.175
SD	0.12	0.13	

By day 28, the percentage reduction in wound size was slightly higher in Group A (31%) compared to Group B (28%), but this difference did not reach statistical significance (p = 0.175).

FIGURE 27. Wound Size Reduction



DISCUSSION

Wounds can be classified as either acute or chronic, and they may arise from various causes, including venous or arterial insufficiency, diabetes, burns, trauma, prolonged pressure, or surgical procedures. While antiseptic agents help control bacterial load and prevent infections, they can sometimes harm fibroblasts and other healthy cells. Interestingly, silver has minimal toxicity and rarely induces microbial resistance. Studies have shown that silver-based dressings are effective against pathogenic bacteria, making them a valuable option for wounds at risk of infection, especially when combined with debridement[135-138].

With advancements in nanotechnology, it is now possible to produce ultra-small silver particles with larger surface area-to-volume ratios, enhancing their antimicrobial activity while reducing toxicity to human tissues. Historically, the use of silver for infection prevention and treatment dates back to around 1000 BC, when ancient Greeks and Romans employed it as a disinfectant[138-141].

Diabetic foot ulcer (DFU) is a broad term encompassing various foot-related complications that are among the most prevalent, complex, and expensive consequences of diabetes mellitus (DM). DFUs are characterized as full-thickness wounds located below the ankle in individuals with diabetes. These patients are often at higher risk for other diabetes-associated conditions, including nephropathy, retinopathy, ischemic heart disease, and cerebrovascular disease. Surgical debridement remains the gold standard for treating DFUs, aiming to minimize the loss of healthy tissue, preserve foot functionality, and prevent deformities that could trigger ulcer recurrence. Hydrogel dressings are particularly effective for dry wounds with necrotic tissue, as they provide moisture and promote hydration in sloughy

wounds. However, while hydrogels can absorb exudates well, their use in plantar ulcers should be avoided due to the risk of macerating the surrounding skin[142-146].

Timolol is a powerful non-selective beta receptor antagonist widely recognized for its role in treating conditions such as hypertension, congestive heart failure, migraine prevention, open-angle glaucoma, and intraocular hypertension. Research has shown that β2 adrenergic receptors (β2-AR) are present in various tissues, including keratinocytes. By blocking these receptors, timolol facilitates wound healing through enhanced keratinocyte migration, which aids in the re-epithelialization process[147-150]. The effectiveness of topical timolol for chronic wound management is well-established. Rai et al.[147] demonstrated its benefits in treating chronic venous ulcers, while Kaur et al[151]. highlighted its success in managing diabetic foot ulcers. Additionally, studies by Braun et al [152]. and Vestita et al[153]. further supported timolol's efficacy in promoting healing in chronic, non-healing wounds.

In the present study, 114 participants were evenly distributed across both groups, with 57 participants in group A receiving Timolol maleate and 57 participants in group B receiving conventional dressing with amorphous hydrogel and silver colloid dressing gel. The age distribution in our study showed a significant difference ($p = 0.046$). In Group A, the majority of patients were aged 51–70 years (59.6%), while 40.4% of Group B patients fell within this range. Interestingly, a higher proportion of younger patients aged 30–50 years were observed in Group B (42.1%) compared to Group A (21.1%). Meanwhile, the 71–90 years age range was relatively balanced, with 19.3% in Group A and 17.5% in Group B. This variation in age distribution suggests that patient age could have influenced healing responses. In the present study, the gender distribution was identical across both groups, with 84.2% of

patients being male and 15.8% female (p = 1.00). This equal distribution ensures that sex-related factors did not affect treatment outcomes.

Similar to our study, the Rai et al.[147] study compared topical timolol with saline dressings for chronic venous ulcers and included patients above 18 years of age in their research. In another study by Menezes et al.[158] studied a larger cohort of 95 patients with chronic non-healing foot ulcers, with no division into control or comparison groups, focusing solely on timolol's effect over time. The mean age in the Menezes et al.[158] study was 48.74 years, with 60% of patients aged 19–50 years, which aligned with our study findings. Comparatively, in the Sharma et al.[138] study, the average age of patients in the silver colloidal dressing group was 58.23 ± 11.59 years. The risk of developing peripheral vascular disease, and consequently diabetic foot, increases with age. Studies have shown that older individuals are more prone to these complications[159,160].

In the current study, the duration of ulcers was comparable between the two groups, with no statistically significant difference (p = 0.578). In Group A, most patients had ulcers for 3 months (38.6%), followed by 2 months (22.8%). In Group B, 31.6% had ulcers for 3 months, and 29.8% had ulcers for 2 months. A smaller proportion of patients in both groups had ulcers lasting 6 months or longer. At the same time, Menezes et al.[158] focused on chronic foot ulcers, particularly on pressure points, with ulcer durations ranging from 4 to 24 weeks. This balance in ulcer chronicity ensures that any differences in healing outcomes were more likely due to the treatments themselves rather than the duration of the ulcers.

In the present study, the duration of diabetes was evenly distributed between groups (p = 0.692). The largest proportion of patients had diabetes for 6–10 years (33.3% in Group A, 35.1% in Group B), followed by 11–15 years. Only a small percentage had diabetes for over 20 years (1.8% in Group A, 0% in Group B). Given that longer diabetes duration can impair wound healing, this even distribution helps strengthen the study's validity by minimizing the impact of disease duration on the results. Similar to our study, a higher incidence of diabetic foot was observed in patients with a history of diabetes mellitus lasting between 6 to 15 years in the Sharma et al.[138] study. It is well established that the longer a person has diabetes, the greater their risk of developing diabetic foot complications. Chronic complications of diabetes, including diabetic foot, often emerge approximately 15 years after the onset of hyperglycemia[161].

In our study, the majority of patients in both groups controlled their diabetes with oral hypoglycemic agents (61.4% in Group A, 64.9% in Group B), while 38.6% in Group A and 35.1% in Group B used insulin (p = 0.698). As insulin use can indicate more severe diabetes, the similar medication patterns across groups help reduce potential biases related to glycemic control.

In the present study, lifestyle factors such as smoking and alcohol use were evenly distributed between groups. Smoking was reported by 33.3% of Group A and 42.1% of Group B, while alcohol consumption was reported by 40.4% of Group A and 49.1% of Group B, with neither factor reaching statistical significance. Notably, no patients in either group reported drug allergies. This similarity in lifestyle factors is important, as smoking and alcohol use can both delay wound healing.

In our study, glycemic control, as measured by HbA1c levels, was comparable between groups ($p = 0.793$). About half of the patients in each group had HbA1c values between 7.5–9%, while approximately 30% had values above 9%, indicating poor glycemic control. Only about 20% had HbA1c levels below 7.5%. The similar distribution of HbA1c values suggests that differences in healing outcomes were unlikely to be influenced by baseline blood sugar levels.

In the current study, peripheral pulsations were present in 100% of patients in both groups ($p < 0.05$), indicating adequate blood flow to the affected limbs. Proper circulation is essential for healing, as it ensures sufficient oxygen and nutrients reach the wound site to support tissue repair. In the present study, vascular and structural factors were rare and evenly distributed. Varicose veins were observed in only 7% of patients in both groups ($p = 1.00$).

In our study, none of the patients in either group exhibited signs of infection. The absence of infection and universal presence of granulation tissue indicate that both treatments created a favorable environment for tissue regeneration and wound closure.

In the present study, both groups experienced gradual reductions in ulcer length, width, and area over the 28-day follow-up, with no statistically significant differences between treatments. By day 28, the average wound size had decreased by 31% in Group A and 28% in Group B ($p = 0.175$). While the percentage reduction was slightly higher in the topical Timolol group, the difference was not statistically significant, suggesting that both treatments were similarly effective in promoting wound size reduction over time.

At the same time, the healing rates reported in Rai et al.[147] study highlighted the superiority of timolol over saline, the percentage reduction in ulcer size in the timolol group was 23.06% after 1 week, 36.57% after 2 weeks, 67.18% after 3 weeks, and 86.80% after 4 weeks and however, their saline group achieved only 11.01%, 17.53%, 31.78%, and 43.82%, respectively, over the same intervals as reported in their study. They also reported that observed complete ulcer closure in 50% of patients treated with timolol, while no patients in the saline group achieved full closure.

In another study by Menezes et al.[158] observed a slower initial response (mean 34.78% reduction at day 15) but a substantial 66.44% reduction by day 30, with some patients achieving complete healing in their study. The Menezes et al.[158] study also explored age-based differences, showing similar healing patterns across younger and older groups, with consistent reductions between day 1, day 15, and day 30, however we did not observe this finding in our study.

Similarly, a cohort study conducted by Chakkittakandiyil et al.[154] demonstrated the effectiveness, safety, and tolerability of using timolol maleate 0.5% solution for the treatment of infantile hemangiomas. Also, Manahan et al.[155] explored the use of topical timolol as an affordable and safe option for managing chronic ulcers. Braun et al.[152] applied 0.5% topical timolol to chronic, recalcitrant wounds in five patients, all of whom showed improvement, with complete healing observed in three patients. The average wound size reduction after 7 weeks was 78.2%. Lev-Tov et al.[156] also successfully treated chronic venous leg ulcers with topical timolol. Additionally, Thomas et al.[157] found that patients treated with topical timolol had a significantly higher healing rate — 61.79% in the study group versus 29.62% in the control group after 12 weeks. Their analysis revealed a substantial difference in ulcer

reduction between the groups, highlighting that topical timolol promotes faster healing compared to conventional treatments, however our study findings observed ulcer reduction in the Timolol group without any significance.

LIMITATIONS

Our study had some limitations. First, the sample size was relatively small, with only 114 participants, which may limit the generalizability of the results to broader populations. Larger, multi-center studies would be necessary to validate these findings across diverse demographic and clinical settings. Second, the study duration was limited to 28 days, which may not fully capture the long-term effects of the treatments or the complete wound healing process, especially for more chronic or severe ulcers. Third, while key variables like diabetes duration, glycemic control, and ulcer chronicity were well-balanced between groups, other unmeasured factors — such as nutritional status, patient adherence to treatment protocols, and individual variations in inflammatory response — could have influenced healing outcomes. Additionally, the absence of blinding in treatment administration may have introduced potential bias, even though objective wound measurements were used. Addressing these limitations in future research could strengthen the evidence base for these treatment strategies.

CONCLUSION

Our study identified that both topical Timolol and amorphous hydrogel with silver colloid dressing demonstrated comparable efficacy in promoting wound healing in patients with diabetic foot ulcers. Despite slight differences in the percentage reduction of wound size, the results were not statistically significant, suggesting that both treatments create a similarly conducive environment for tissue repair. The universal presence of granulation tissue and absence of infection in both groups further highlight the effectiveness of these interventions in supporting the early stages of healing. The study's balanced distribution of patient characteristics — including age, diabetes duration, glycemic control, and lifestyle factors — reinforces the internal validity of the findings. Ultimately, these results suggest that both treatment options are viable and safe choices for managing diabetic ulcers, allowing clinicians to tailor treatment decisions to individual patient preferences, cost considerations, and clinical judgment. Future studies with larger sample sizes and extended follow-up periods would help refine treatment protocols and determine whether one approach offers superior long-term outcomes.

SUMMARY

A randomized controlled trial was conducted at KAHER's Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belagavi, among 114 patients with chronic diabetic foot ulcers (DFUs). The study aimed to compare the efficacy and safety of topical Timolol maleate 0.5% drops versus Amorphous hydrogel and silver colloid dressing in promoting ulcer healing over two weeks.

After obtaining ethical clearance and informed consent, patients were randomized into two groups:

- Group A (Experimental): Received topical Timolol maleate 0.5% drops followed by moist saline dressing.
- Group B (Control): Received Amorphous hydrogel and silver colloid dressing followed by moist saline dressing.

Wound healing progress was assessed using ulcer area measurements at day 0 to day 28, and the percentage reduction in wound size was calculated.

The study revealed the following findings:

1. Demographics & Baseline Characteristics:
    - No significant differences in gender distribution, diabetes duration, drug history, and HbA1c levels between groups.
    - Majority of patients in both groups had diabetes for 6-10 years.
2. Ulcer Healing Outcomes:
    - Greater ulcer size reduction in Group A (Timolol) compared to Group B (hydrogel & silver colloid dressing), but not statistically significant

3. Safety & Adverse Events:
    - No significant adverse effects reported in either group.
4. Diabetes & Lifestyle Factors:
    - Similar glycemic control (HbA1c levels) in both groups.
    - Around 40% of participants were smokers or alcohol consumers, with no significant impact on ulcer healing differences.

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ANNEXURE I:

KAHERs JNMC

BELAGAVI

INFORMED CONSENT FORM

"Comparing the efficacy of Topical Timolol vs Amorphous hydrogel and silver colloid dressing in Chronic Diabetic Foot Ulcers: a Randomized Controlled Trial"

Introduction: Respected Sir/Madam, We request you to participate in our study as titled above, which is being performed to test and find out new and better methods to assist healing of chronic diabetic foot ulcers. A drug named Timolol which is already available in the market and is commonly used as eye drops, has shown promising results in previous studies in healing chronic diabetic ulcers when applied locally to the ulcer. In this study, we aim to use this drug and compare its effectiveness to the conventionally used Amorphous hydrogel and silver colloid dressing gel for dressing and treatment of chronic diabetic ulcers and to compare the healing rate of the ulcer in each to find out if this drug is actually effective in improving healing rates.

Explanation of procedure: After obtaining your consent and clinical examination, you will be placed randomly in one of two groups, one of which will receive the new drug and the other one will receive the conventional treatment, in the form of alternate day dressings of the ulcer with the drug alloted to your group. After every week or 7 days, your ulcer size will be measured and documented, and pictures taken, for a total of 4 weeks. Any side effects that occur during the period of the study will be taken care of and managed by the principal investigator. You will not be charged or have to spend any money for the study. During the period of study, your diabetic control will also be regularly monitored using daily blood sugar monitoring and you will continue your diabetic drugs during the period of study, which may be changed/ insulin added to

achieve adequate sugar control. You will be required to participate and will be followed up with for a period of 4 weeks.

Withdrawal from participation in the study: Participation in this study is voluntary. Your decision to participate in the study or otherwise will not affect the relationship with KLES Prabhakar Kore Hospital. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: By participating in this study, you have a chance of getting a potentially better drug for ulcer dressing that may help heal your ulcer faster. Also, you will receive regular sugar monitoring which will help tailor your diabetic medication dose to achieve the best control for your sugars and you will also receive dietary guidance. Even if you are placed in the control group, you will receive regular care in the form of regular dressings with the conventionally known and effective techniques. Also, the contribution you make by participating in this study will help the population at large.

Possible risks from participating in the study: There are no major risks involved in participating in this study. Minor risks which may occur include skin allergy and itching. Any side effects that may occur will be taken care of by the principal investigator at no cost to you

Privacy and confidentiality: The information collected from you will be coded, to prevent any person from identifying you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations done during the course of study will be paid by the **principal investigator.**

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Questions: If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "**Comparing the efficacy of Topical Timolol vs Amorphous hydrogel and silver colloid dressing in Chronic Diabetic Foot Ulcers: a Randomized Controlled Trial**". My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II: PROFORMA

DATE:

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

PHONE NO:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

Ulcer duration	< 6 weeks		> 6 weeks	
Ulcer Size	< 0.5cm^2		> 0.5cm^2	
Pus Discharge	Yes		No	
Pain over surrounding skin	Yes		No	

PAST HISTORY: H/o diabetes since-

On medication-

H/o Hypertension-

FAMILY HISTORY:

PERSONAL HISTORY:

SMOKER	Yes		No	
ALCOHOL/ DRUG USE HISTORY	Yes		No	
KNOWN DRUG ALLERGIES	Yes		No	

TREATMENT/ SURGICAL HISTORY:

ON GENERAL EXAMINATION:

Temperature-

BP-

PR-

Examination of Ulcer:

Location:

Ulcer Dimensions(LxB)(in cm):

Ulcer Area(in cm^2):

Ulcer Depth(in cm):

Ulcer showing evidence of infection	Yes		No	
Exposed bone/ tendon/ fascia/ Gangrene	Yes		No	
Peripheral Pulsations	Present		Absent	
Varicosities/ Skin pigmentation	Present		Absent	

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

C.N.S.:

P.A.:

Eligible for Study:

Patient willing to give consent:

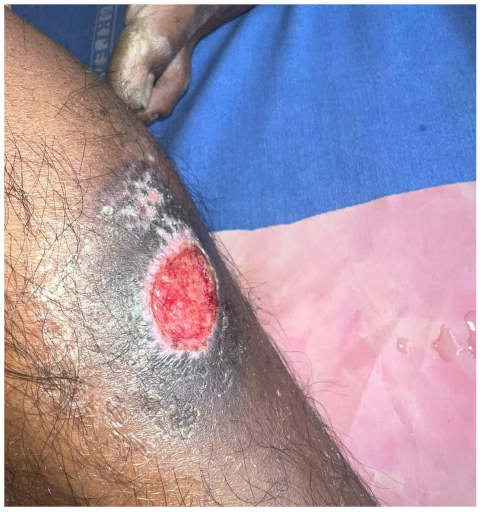
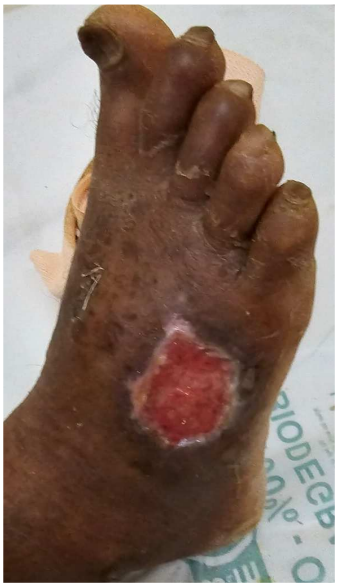
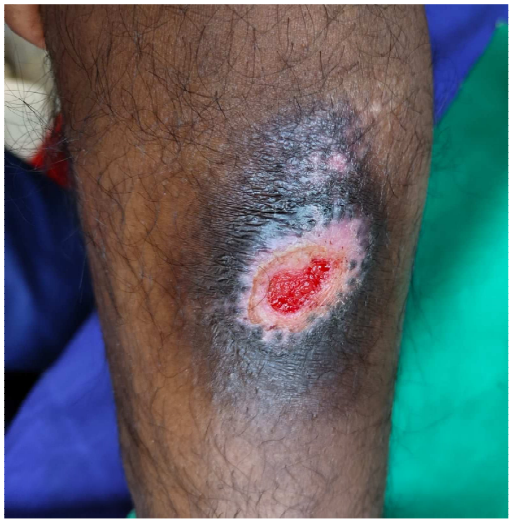
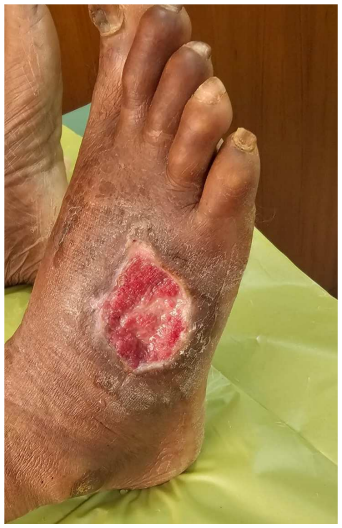
Group Alloted:

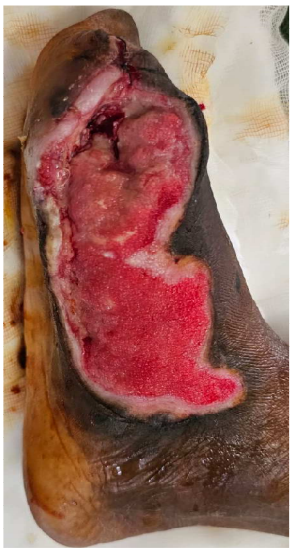
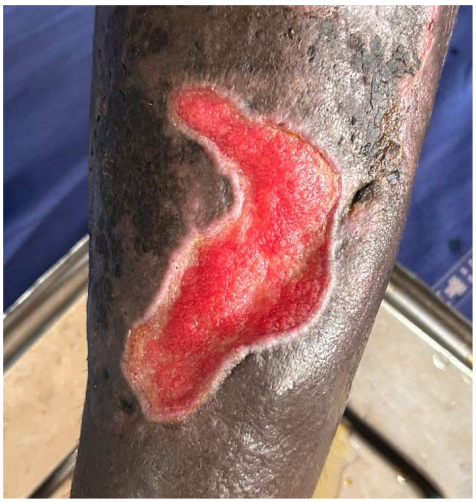
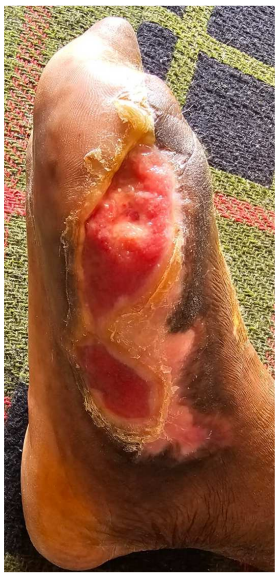
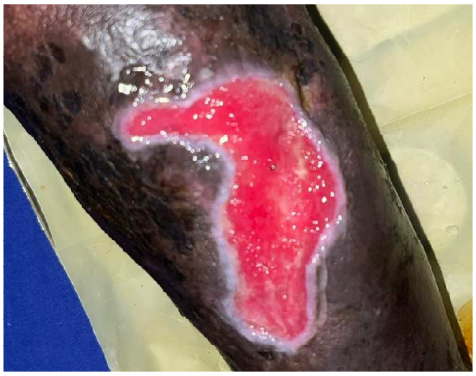
Ulcer measurement

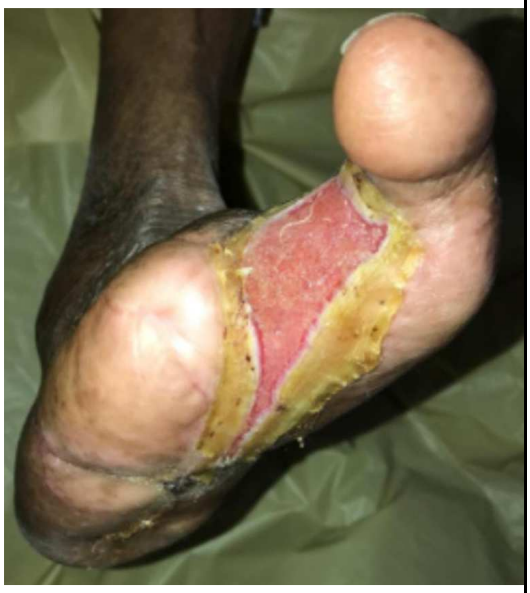
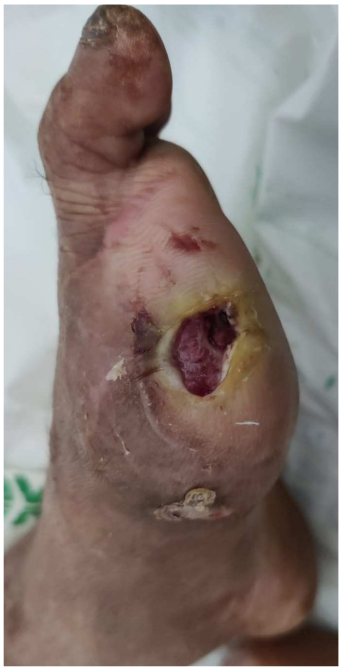
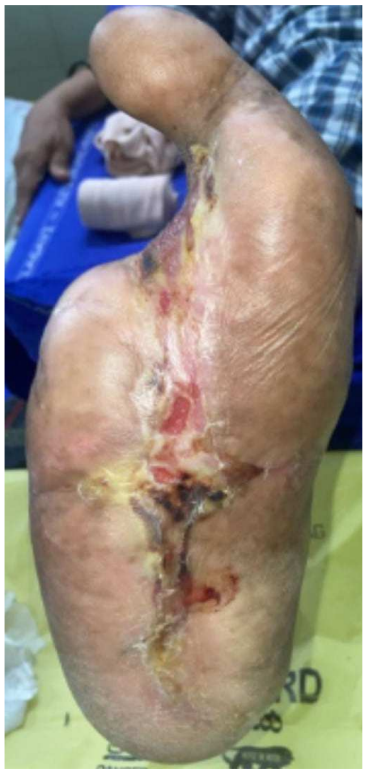
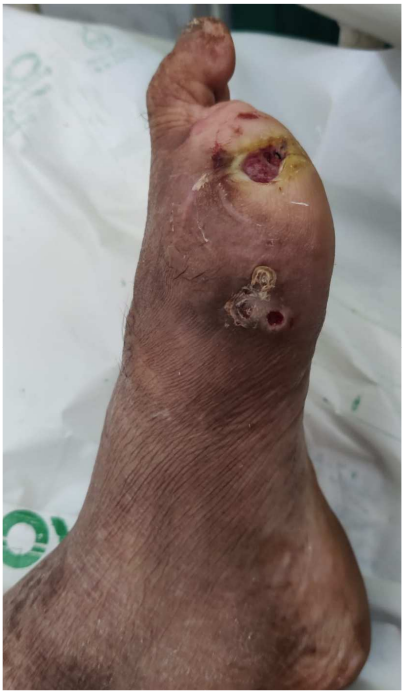
Time	Length	Width	Area	%reduction
Day 0				
Day 7				
Day 14				
Day 21				
Day 28				

% area reduction(Day 0 to day 28)=

ANNEXURE III: ULCER PHOTOS

	Ulcer treated with Timolol	Ulcer treated with Hydrogel+silver colloid gel
DAY 0		
DAY 28		

Day 0		
Day 28		

Day 0		
Day 28		

ANNEXURE 4: MASTER CHART

Sl no.	study group: A or B	Age	Sex	IP Number	Complaints	Past history	drug history	Smoker/non-smoker	alcohol history	drug allergies	Hba1c	peripheral pulsations	varicosities	exposed bone/ tendon/ fascia	evidence of infection	Wound size day 0(area)			wound size day 7(area)			wound size day 14(area)			wound size day 21(area)			wound size day 28(area)			Reduction in wound size (%)	Granulation tissue
																lenght	width	area	lenght	width	area	lenght	width	area	lenght	width	area	lenght	width	area		
1	B	65	male	10072136	ulcer over back since 3 months	diabetic x 5 years	t. metformin 500 mg 1-0-1	yes	no	no	8.8	present	no	no	absent	5.6	4.8	26.88	5.4	4.7	25.38	5.2	4.5	23.4	5	4.4	22	4.7	4.2	19.74	26.56%	present
2	A	66	male	13172024	ulcer over left foot x 3 months	diabetic x 10 years	t. metformin 1gm 1-0-1	yes	yes	no	9.7	present	yes	yes	absent	9.5	11	104.5	9.3	10.8	100.4	9.2	10.6	97.52	9.1	10.3	93.73	8.9	10	89	14.83%	present
3	B	39	Male	10056946	ulcer over lt foot x 3months	diabetic x 8 years	t. glycomet gp1 1-0-0	no	no	no	10	present	no	no	absent	7.1	5.2	36.92	6.8	5	34	6.49	4.8	31.152	6.12	4.6	28.152	5.86	4.64	27.19	26.35%	present
4	B	55	male	2426266	ulcer over lt thighx 2 months	diabetic x 8 years	insulin HA 8-8-8	yes	yes	no	7.8	present	yes	yes	no	8	10	80	7.7	9.8	75.46	7.5	9.6	72	7.4	9.4	69.56	7.2	9.1	65.52	18.10%	present
5	A	61	female	10077525	ulcer between toes since 6 weeks	diabetic x 15 years	Inj H/M 14-10-6	no	no	no	9	present	no	no	no	1.4	0.9	1.26	1.3	0.9	1.17	1.1	0.8	0.88	0.9	0.7	0.63	0.8	0.7	0.56	55.56%	present
6	A	59	male	10077704	ulcer at plantar aspect left foot	diabetes x 15 years	inj. H/M 10-0-6	no	yes	no	9.6	present	no	no	no	7.2	5.7	41.04	6.9	5.5	37.95	6.6	5.3	34.98	6.4	5.2	33.28	6.1	5	30.5	25.68%	present
7	B	55	female	10084506	ulcer over back since 3 months	diabetes x 12 years	Inj. HA 12-6-6	no	no	no	8.8	present	no	no	no	5.6	5.1	28.56	5.2	4.9	25.48	5	4.7	23.5	4.7	4.5	21.15	4.4	4.3	18.92	33.75%	present
8	B	70	female	10047151	ulcer over left foot x 6 months	diabetes sunce 8 years	tab. metformin 1 gm 1-0-1	no	no	no	7.6	present	present	no	no	7.4	5.6	41.44	7.1	5.5	39.05	6.9	5.3	36.57	6.7	5.1	34.17	6.6	5	33	20.37%	present
9	A	70	male	10062354	ulcer over right leg anterior aspect x 4 months	diabetes x 6 months	t. metformin 500mg 1-0-1	yes	yes	no	8.8	present	no	no	no	5.5	2.5	13.75	5.3	2.3	12.19	4.9	2.1	10.29	4.6	1.9	8.74	4.3	1.6	6.88	49.96%	present
10	B	42	female	10056769	ulcer palmar aspect lt foot x 3 months	diabetes x 5 years	tab metformin 1gm 1-0-1	no	no	no	7.9	present	no	no	no	2.8	2.6	7.28	2.7	2.6	7.02	2.7	2.5	6.75	2.6	2.4	6.24	2.5	2.3	5.75	21.02%	present
11	A	61	female	10068538	ulcer over lt foor since 2 months	diabetes x 10 years	t. glycomet gp 1-0-1	no	no	no	6.8	present	no	no	no	4.6	1.6	7.36	4.4	1.7	7.48	4.3	1.6	6.88	4.1	1.5	6.15	4	1.4	5.6	23.91%	present
12	B	34	male	10063085	ulcer over right foot x 2 months	diabetes x 2 months	t. metformin 500 mg 1-0-1	no	yes	no	7.8	present	no	no	no	4.2	4	16.8	3.9	3.8	14.82	3.8	3.7	14.06	3.6	3.6	12.96	3.4	3.5	11.9	29.17%	present
13	B	57	male	10057961	ulcer over left heel x 2 months	diabetes x 5 years	Inj, HA 10-6-6	yes	yes	no	9.2	present	no	no	no	4.6	5.1	23.46	4.6	5	23	4.5	4.9	22.05	4.4	4.7	20.68	4.3	4.5	19.35	17.52%	present
14	A	75	male	10065565	ulcer over left heel x 1 year	doabetes x 16 years	inj HA 12-8-8	no	yes	no	11	present	present	no	no	6.1	3.4	20.74	5.8	3.3	19.14	5.6	3.2	17.92	5.4	3	16.2	5.1	2.8	14.28	31.15%	present
15	B	74	male	10059081	ulcer over left heel	diabetes x 15 years	Inj HM 14-10-8	no	yes	no	9	present	no	no	no	4.1	3.2	13.12	4	3.1	12.4	3.9	3	11.7	3.8	2.9	11.02	3.6	2.8	10.08	23.17%	present
16	A	68	male	6792266	ulcer over right foot x 3 months	diabetes x 4 years	tab metformin 1 gm 1-0-1	yes	no	no	8.2	present	no	no	no	5.9	3.4	20.06	5.7	3.3	18.81	5.5	3.1	17.05	5.3	3	15.9	5.1	2.8	14.28	28.81%	present
17	A	50	female	10013976	ulcer right foot x 3 months	diabetes x 6 years	tab metformin+gp 1-0-1	no	no	no	8.6	present	no	no	no	6.2	4.5	27.9	6.1	4.4	26.84	5.9	4.3	25.37	5.7	4.1	23.37	5.5	3.9	21.45	23.12%	present
18	B	73	male	10066912	ulcer over diasrticulated 1,2 toe left foot	diabetes x 15 years	Inj HM 20-10-25	yes	no	no	10	present	no	no	no	4.1	6.2	25.42	4	6	24	3.9	5.9	23.01	3.9	5.8	22.62	3.8	5.7	21.66	14.79%	present
19	B	48	Male	1176857	ulcer left foot x 3 months	diabetes x 6 years	tab metformin 500 mg 1-0-1	no	yes	no	8	present	no	no	no	9.1	6.2	56.42	8.9	6.1	54.29	8.8	6	52.8	8.6	5.9	50.74	8.3	5.8	48.14	14.68%	present
20	B	50	male	10020018	ulcer over disarticulated right toe x 6 months	diabetes x 8 years	tab metformin + GP 1-0-1	yes	no	no	9	present	no	no	no	4.2	3.9	16.38	4.1	3.8	15.58	3.8	3.6	13.68	3.7	3.5	12.95	3.6	3.5	12.6	23.08%	present
21	B	44	female	10066114	ulcer over right diarticulated 3,4 toe since 2 months	diabetes x 8 years	tab glycomet gp 1-0-0	no	no	no	10.6	present	no	no	no	9.2	5.4	49.68	9.1	5.3	48.23	9	5.3	47.7	8.9	5.3	47.17	8.8	5.2	45.76	7.89%	present
22	A	61	male	10054125	ulcer over left foot	Diabetic x 6 years	tab metformin 500mg + tab GP 1	yes	yes	no	7	present	no	no	no	5.4	4.1	22.14	5.2	4	20.8	5	3.8	19	4.8	3.7	17.76	4.6	3.5	16.1	27.28%	present
23	A	47	female	10051486	ulcer over left foot	Diabetic x 5 years	tab metformin 500mg		no	no	8	present	no	no	no	3.2	3.3	10.56	3.1	3.2	9.92	3	3	9	2.8	2.9	8.12	2.6	2.7	7.02	33.52%	present
24	B	33	male	1185353	ulcer over lt foot x 3 months	diabetes x 5 years	tab metformin 500mg 1-0-1	yes	no	no	9	present	no	no	no	10	7	70	9.6	6.8	65.28	9.3	6.6	61.38	9.1	6.3	57.33	8.9	6	53.4	23.71%	present
25	B	60	male	10025700	ulcer over back since 3 months	recently diagnosed diabetes	inj HA 10-10-10	no	yes	no	11	present	no	no	no	5.3	4.6	24.38	5.1	4.5	22.95	4.8	4.3	20.64	4.5	4.1	18.45	4.2	3.9	16.38	32.81%	present
26	B	38	male	1100245	ulcer over right lateral malleolus x 4 months	diabetic x 8 years	inj HM 12-0-10	yes	yes	no	9.5	present	yes	no	no	2.1	1.9	3.99	1.8	1.7	3.06	1.7	1.5	2.55	1.5	1.3	1.95	1.4	1.2	1.68	57.89%	present
27	B	54	male	1168420	ulcer over lt shin x 6 weeks	diabetes x 5 years	t. glycomet gp 1-0-0	yes	yes	no	7.9	present	no	no	no	4.5	2.9	13.05	4.2	2.7	11.34	4	2.6	10.4	3.9	2.4	9.36	3.7	2.2	8.14	37.62%	present
28	A	44	male	107246	ulcer over back x 2 months	diabetes x 22 years	inj hm 16-0-10	yes	yes	no	8.8	present	no	no	no	6.8	8.2	55.76	6.4	7.9	50.56	6.12	7.2	44.064	5.8	7	40.6	5.4	6.7	36.18	35.11%	present
29	A	55	male	1100456	ucler over plantar aspect of right foot between 4-5th webspace	diabetic x 20 years	inj HM 20-0-10-0	no	no	no	9.8	present	no	no	no	4.9	2.8	13.72	4.7	2.6	12.22	4.4	2.3	10.12	4.1	2	8.2	3.1	1.8	5.58	59.33%	present
30	B	39	male	10085746	ulcer over left leg x 2 months	diabetic x 7 years	tab metformin 500mg 1-0-1	no	yes	no	10	present	no	no	no	11.6	6.8	78.88	11.3	6.6	74.58	11	6.4	70.4	10.7	6.2	66.34	10.5	6	63	20.13%	present
31	B	44	female	107724	ulcer over left great toe x 3 months	diabetic x 6 years	inj HA 8-8-6-0	no	no	no	6.7	present	no	no	no	3.6	3.2	11.52	3.5	3.1	10.85	3.4	3.1	10.54	3.2	3	9.6	3	2.9	8.7	24.48%	present
32	B	38	female	10084500	ulcer over left lower limb x 2 months	diabetic x 5 years	Tab metformin 500mg 1-0-1	no	no	no	7.4	present	no	no	no	9.6	5.1	48.96	9.2	5	46	8.8	4.8	42.24	8.6	4.7	40.42	8.4	4.5	37.8	22.79%	present
33	A	54	male	10084862	ulcer over back of neck x 2 months	diabetic x 10 years	inj HA 10-0-6-0	yes	yes	no	6.8	present	no	no	no	4.1	3.8	15.58	3.9	3.7	14.43	3.6	3.5	12.6	3.4	3.3	11.22	3.1	3.2	9.92	36.33%	present
34	A	82	male	10083048	ulcer over dorsum of right foot x 2 months	diabetic x 15 years	inj HM 20-10-14	yes	yes	no	7.8	present	no	no	no	7.6	4.1	31.16	7.1	4	28.4	6.8	3.9	26.52	6.5	3.7	24.05	6.1	3.5	21.35	31.48%	present
35	B	75	male	10084742	ulcer over dorsum of right foot x 2 months	diabetic x 20 years	inj HA 10-0-8-0	yes	yes	no	7.2	present	no	no	no	11.7	6.6	77.22	11.5	6.5	74.75	11.3	6.4	72.32	11.1	6.3	69.93	10.8	6.2	66.96	13.29%	present

36	A	56	male	10070105	ulcer over medial aspect of right foot x 2 months	diabetic x 5 years	Tab metformin 500mg 1-0-1	no	yes	no	8.1	present	no	no	no	11.2	6.1	68.32	10.9	5.9	64.31	10.6	5.7	60.42	10.2	5.5	56.1	9.8	5.3	51.94	23.98%	present
37	B	56	male	10050956	ulcer over right foot x 3 months	diabetic x 5 years	Tab metformin 500mg 1-0-1	yes	no	no	6.9	present	no	no	no	16.2	5.1	82.62	15.9	5	79.5	15.6	4.8	74.88	15.2	4.7	71.44	4.8	4.5	21.6	73.86%	present
38	A	50	male	10085926	ulcer over left foot x 2 months	diabetic x 5 years	Tab metformin 500mg 1-0-1	no	yes	no	7.6	present	no	no	no	13.1	6.8	89.08	12.8	6.6	84.48	12.3	6.4	78.72	12	6.3	75.6	11.7	5.9	69.03	22.51%	present
39	B	65	male	10072136	ulcer over heel of left foot	diabetic x 10 years	tab Metformin 500mg + tab GP1	yes	yes	no	9.2	present	no	no	no	8.6	6.1	52.46	8.3	6	49.8	8	5.8	46.4	7.7	5.6	43.12	7.5	5.5	41.25	21.37%	present
40	B	38	male	10059157	ulcer over right arm x 2 months	diabetic x 2 years	Tab metformin 500mg 1-0-1	yes	yes	no	8.3	present	no	no	no	7.6	4.1	31.16	7.4	4	29.6	7.1	3.9	27.69	6.9	3.8	26.22	6.7	3.6	24.12	22.59%	present
41	B	71	male	10068124	ulcer over dorsum of left foot x 3 months	diabetic x 8 years	inj HA 12-10-10	yes	yes	no	7.4	present	no	no	no	7.6	5.5	41.8	7.4	5.4	39.96	7.1	5.3	37.63	6.8	5.1	34.68	6.6	4.9	32.34	22.63%	present
42	A	55	male	10062790	ulcer over right leg x 3 months	diabetic x 8 years	tab Metformin 500mg + tab GP1	yes	yes	no	9.6	present	no	no	no	5.6	3.9	21.84	5.5	3.8	20.9	5.3	3.6	19.08	5.1	3.4	17.34	5	3.3	16.5	24.45%	present
43	A	66	male	10045113	ulcer over anterior aspect of left foot x 2 months	diabetic x 3 years	Tab metformin 500mg 1-0-1	yes	no	no	7.7	present	no	no	no	7.6	5.4	41.04	7.4	5.3	39.22	7.2	5.1	36.72	7	4.9	34.3	6.8	4.8	32.64	20.47%	present
44	B	45	female	10050282	ulcer over medial aspect of right foot x 2 months	diabetic x 11 years	inj HM 14-0-14	no	no	no	7.9	present	no	no	no	11.6	9.6	111.36	11.3	9.2	103.96	10.9	9	98.1	10.6	8.8	93.28	10.4	8.2	85.28	23.42%	present
45	B	69	male	10045361	ulcer over dorsum of right foot x 4 months	diabetic x 6 years	Tab metformin 500mg 1-0-1	no	no	no	10	present	no	no	no	11	7.6	83.6	10.6	7.4	78.44	10.3	7.4	76.22	10.1	7.1	71.71	9.8	6.9	67.62	19.11%	present
46	B	60	female	10041164	ulcer over anterior aspect of left foot x 2 months	diabetic x 3 years	Tab metformin 500mg 1-0-1	no	no	no	9.8	present	no	no	no	16.8	5.4	90.72	16.4	5.2	85.28	16.1	5.1	82.11	15.8	4.9	77.42	15.4	4.7	72.38	20.22%	present
47	B	50	male	10034265	ulcer over left leg x 2 months	diabetic x 10 years	tab glycomet gp 1 1-0-1	yes	no	no	8.8	present	no	no	no	7.6	6.8	51.68	7.4	6.7	49.58	7.1	6.5	46.15	6.9	6.2	42.78	6.6	6	39.6	23.37%	present
48	A	73	male	10081535	ulcer over medial aspect right foot x 3 months	diabetic x 8 years	inj HA 8-8-8	no	no	no	9.2	present	no	no	no	10.6	4.9	51.94	10.3	4.8	49.44	10	4.6	46	9.8	4.5	44.1	9.5	4.3	40.85	21.35%	present
49	A	71	male	10081526	ulcer over right foot x 4 months	diabetic x 5 years	Tab metformin 1g 1-0-1	yes	yes	no	7.9	present	no	no	no	12.7	8.1	102.87	12.4	8	99.2	12.1	7.9	95.59	11.8	7.8	92.04	11.6	7.6	88.16	14.30%	present
50	A	82	male	10052353	ulcer over heel of right foot x 6 months	diabetic x 15 years	inj HM 15-10-10-0	no	no	no	8.2	present	no	no	no	4.8	2.6	12.48	4.5	2.5	11.25	4.4	2.4	10.56	4.1	2.2	9.02	3.9	1.9	7.41	40.63%	present
51	A	60	male	10072645	ulcer over left hand x 4 months	diabetic x 20 years	inj HA 14-10-10	yes	yes	no	7.1	present	no	no	no	8.2	4.6	37.72	8.1	4.5	36.45	8	4.5	36	7.8	4.5	35.1	7.5	4.3	32.25	14.50%	present
52	B	65	male	10078153	ulcer over left foot stump site x 1 year	diabetic x 8 years	Tab metformin 500mg 1-0-1	yes	no	no	8.8	present	no	no	no	13.2	9.7	128.04	13	9.5	123.5	12.8	9.3	119.04	12.5	9.1	113.75	12.1	8.9	107.69	15.89%	present
53	A	59	male	10077491	ulcer over medial aspect of left leg x 4 months	newly diagnosed diabetic	inj HA 10-10-10	yes	no	no	10.9	present	no	no	no	9.7	8.8	85.36	9.5	8.6	81.7	9.1	8.4	76.44	8.9	8.2	72.98	8.7	8	69.6	18.46%	present
54	A	60	female	10055229	ulcer over dorsum of right foot x 3 months	diabetic x 15 years	inj Ha 14-10-10	no	no	no	9.5	present	no	no	no	4.7	5.1	23.97	5	4.5	22.5	4.8	4.3	20.64	4.1	4.1	16.81	4.3	3.9	16.77	30.04%	present
55	A	64	male	10065748	ulcer over plantar aspect of left foot x 6 months	diabetic x 20 years	tab glycomet gp1 1-0-1	no	no	no	10	present	yes	no	no	5.4	4.9	26.46	5.3	4.8	25.44	5.1	4.7	23.97	5	4.5	22.5	4.8	4.4	21.12	20.18%	present
56	B	56	male	10069424	ulcer over left leg x 3 months	diabetic x 10 years	Tab metformin 1g 1-0-1	no	yes	no	8.9	present	no	no	no	11.4	7.6	86.64	11.1	7.4	82.14	10.9	7.3	79.57	10.5	7.1	74.55	9.8	6.8	66.64	23.08%	present
57	B	60	male	10081415	ulcer over upper 1/3rd of left leg x 3 months	diabetic x 8 years	Tab metformin 500mg 1-0-1	yes	yes	no	7.5	present	no	no	no	12.6	10	128.52	11.9	9.9	117.81	11.6	9.7	112.52	11.2	9.4	105.28	10.8	9	97.2	24.37%	present
58	A	49	male	10050662	ulcer over right lumbar region x 4 months	diabetic x 7 years	tab glycomet gp1 1-0-1	yes	yes	no	7.1	present	no	no	no	5.8	6.3	36.54	5.6	6.1	34.16	5.2	5.9	30.68	4.8	5.5	26.4	4.4	5.1	22.44	38.59%	present
59	A	74	male	10075438	ulcer over right foot amputation stump x 1 year	diabetic x 20 years	Tab metformin 1g 1-0-1	yes	yes	no	8.8	present	yes	no	no	9.1	5.4	49.14	8.8	5.2	45.76	8.5	5	42.5	8.1	4.8	38.88	7.8	4.6	35.88	26.98%	present
60	A	52	male	10075433	ulcer over right 2nd toe amputation site	diabetic x 15 years	inj HM 10-0-6-0	no	yes	no	9.3	present	no	no	no	7.6	4.1	31.16	7.5	4	30	7.3	3.8	27.74	7	3.6	25.2	6.7	3.5	23.45	24.74%	present
61	B	72	male	10076524	ulcer over heel of right foot x 4 months	diabetic x 10 years	tab glycomet gp1 1-0-1	no	no	no	7.8	present	no	no	no	4.4	2.1	9.24	4.3	2.1	9.03	4.2	2	8.4	4	1.9	7.6	3.7	1.8	6.66	27.92%	present
62	A	48	male	10075493	ulcer over right leg x 3 months	diabetic x 7 years	tab glycomet gp1 1-0-1	no	no	no	9.2	present	no	no	no	11.1	5.4	59.94	10.8	5.3	57.24	10.5	5.1	53.55	10.1	4.9	49.49	9.7	4.8	46.56	22.32%	present
63	B	60	male	10073574	ulcer over medial aspect of right foot x 6 months	diabetic x 20 years	inj HM 16-10-10-0	no	no	no	6.6	present	no	no	no	7.6	4.3	32.68	7.4	4.1	30.34	7.2	4	28.8	6.8	3.8	25.84	6.5	3.7	24.05	26.41%	present
64	A	74	male	10075438	ulcer over medial aspect of right foot x 6 months	diabetic x 20 years	inj HA 16-10-4	yes	no	no	7.4	present	no	no	no	12.2	5.6	68.32	12.1	5.4	65.34	11.9	5.2	61.88	11.7	5	58.5	11.5	4.8	55.2	19.20%	present
65	A	56	male	10075433	ulcer over plantar aspect of right foot x 6 months	diabetic x 10 years	inj HM 14-10-8-0	no	no	no	8.5	present	no	no	no	5.8	3.2	18.56	5.5	2.9	15.95	5.1	2.8	14.28	4.5	2.5	11.25	4.1	2.1	8.61	53.61%	present
66	B	56	male	10084956	ulcer over heel of right foot x 3 months	diabetic x 12 years	tab metformin 1g 1-0-1	no	no	no	9.2	present	no	no	no	4.6	5.3	24.38	4.4	5.1	22.44	4.2	4.9	20.58	4	4.7	18.8	3.8	4.4	16.72	31.42%	present
67	A	44	male	10076956	ulcer over right leg x 2 months	diabetic x 5 years	tab metformin 500mg 1-0-1	no	yes	no	6.9	present	no	no	no	8.1	3.9	31.59	7.8	3.7	28.86	7.4	3.6	26.64	6.9	3.4	23.46	6.6	3.2	21.12	33.14%	present
68	A	53	female	10053574	ulcer over plantar aspect of left foot x 4 months	diabetic x 12 years	tab glycomet gp1 1-0-1	no	no	no	7.1	present	no	no	no	6.9	5.4	37.26	6.6	5.2	34.32	6.3	5	31.5	6	4.8	28.8	5.7	4.5	25.65	31.16%	present
69	B	46	male	10070998	ulcer over left leg x 3 months	diabetic x 10 years	tab glycomet gp1 1-0-1	no	no	no	8.9	present	no	no	no	4.6	4.3	19.78	4.4	4.2	18.48	4.1	3.9	15.99	3.8	3.6	13.68	3.5	3.4	11.9	39.84%	present
70	A	41	male	10117292	ulcer over right leg x 6 months	diabetic x 7 months	tab metformin 500mg 1-0-1	no	no	no	10.1	present	no	no	no	17	4.6	78.2	16.6	4.5	74.7	16.1	4.3	69.23	15.7	4.1	64.37	15.3	3.9	59.67	23.70%	present
71	A	55	male	10067999	ulcer over dorsum of right foot x 3 months	diabetic x 8 years	tab glycomet gp1 1-0-1	no	no	no	7.8	present	no	no	no	11.4	5.6	63.84	11.1	5.4	59.94	10.8	5.2	56.16	10.5	5.1	53.55	10.1	4.8	48.48	24.06%	present

72	B	68	male	10072925	ulcer over right leg x 6 months	diabetic x 12 years	inj HA 14-10-10	yes	yes	no	6.7	present	no	no	no	5.6	3.4	19.04	5.4	3.2	17.28	5	3	15	4.7	2.8	13.16	4.4	2.7	11.88	37.61%	present
73	B	60	male	10054545	ulcer over right leg x 4 months	diabetic x 3 years	tab glycomet gp1 1-0-1	no	yes	no	8.4	present	no	no	no	3.8	2.7	10.26	3.6	2.5	9	3.3	2.3	7.59	3.1	2.1	6.51	2.8	1.9	5.32	48.15%	present
74	A	85	male	10125226	ulcer over medial aspect of right lower limb x 2 months	diabetic x 15 years	tab glycomet gp1 1-0-1	no	yes	no	9.9	present	no	no	no	24.6	8.1	199.26	23.8	7.8	185.64	23.1	7.5	173.25	22.6	7.1	160.46	21.9	6.8	148.92	25.26%	present
75	B	48	male	10129082	ulcer over lateral plantar aspect of right foot x 3 months	diabetic x 7 years	tab glycomet gp1 1-0-1	no	yes	no	8.5	present	no	no	no	9.8	5.8	56.84	9.6	5.6	53.76	9.2	5.4	49.68	8.9	5.2	46.28	8.6	5	43	24.35%	present
76	B	40	male	10125574	ulcer over right leg x 6 months	diabetic x 3 years	tab metformin 500mg 1-0-0	yes	yes	no	7.6	present	no	no	no	4.7	4.1	19.27	4.5	3.9	17.55	4.3	3.7	15.91	4	3.5	14	3.7	3.1	11.47	40.48%	present
77	A	40	male	10125547	ulcer over left leg x 6 months	diabetic x 5 years	tab glycomet gp1 1-0-1	yes	yes	no	8.4	present	no	no	no	4.7	4.6	21.62	4.5	4.5	20.25	4.3	4.4	18.92	4	4.1	16.4	3.8	3.8	14.44	33.21%	present
78	A	65	female	10121754	ulcer over left foot 4th toe amputation site x 3 months	diabetic x 20 years	inj HM 14-10-8	no	no	no	8.8	present	no	no	no	4.1	2.4	9.84	3.8	2.3	8.74	3.4	2.1	7.14	3.1	1.9	5.89	2.8	1.7	4.76	51.63%	present
79	B	67	male	10127697	ulcer over medial aspect of left leg x 3 months	diabetic x 8 years	tab glycomet gp1 1-0-1	no	no	no	7.3	present	no	no	no	2.3	2.1	4.83	2.1	1.9	3.99	1.8	1.7	3.06	1.5	1.5	2.25	1.3	1.2	1.56	67.70%	present
80	A	48	male	10097211	ulcer over heel of left foot x 3 months	diabetic x 5 years	tab glycomet gp1 1-0-1	no	no	no	9.3	present	no	no	no	5.9	5.1	30.09	5.6	4.9	27.44	5.4	4.7	25.38	5	4.5	22.5	4.7	4.3	20.21	32.83%	present
81	A	34	male	10106866	ulcer over right lower limb x 3 months	diabetic x 3 years	tab metformin 500mg 1-0-0	no	no	no	9.9	present	no	no	no	11.2	5.1	57.12	11	4.9	53.9	10.6	4.7	49.82	10.2	4.5	45.9	9.7	4.1	39.77	30.37%	present
82	B	65	male	10110477	ulcer over 3-4th toe amputation site of right foot x 2 months	diabetic x 15 years	inj HA 10-10-10	no	no	no	7.9	present	no	no	no	4.6	3.4	15.64	4.4	3.3	14.52	4.1	3.1	12.71	3.7	2.9	10.73	3.4	2.8	9.52	39.13%	present
83	B	41	male	10112745	ulcer over left leg x 4 months	diabetic x 5 years	tab metformin 500mg 1-0-0	no	no	no	8.3	present	no	no	no	5.4	4.2	22.68	5.1	4	20.4	4.8	3.9	18.72	4.6	3.7	17.02	4.3	3.5	15.05	33.64%	present
84	A	56	male	10121642	ulcer over left forefoot amputation site x 3 months	diabetic x 15 years	inj HM 16-10-8	no	no	no	7.1	present	no	no	no	8.8	5.6	49.28	8.4	5.4	45.36	8.1	5.2	42.12	7.8	5	39	7.4	4.9	36.26	26.42%	present
85	A	72	female	10116787	ulcer over right thigh x 3 months	diabetic x 20 years	inj HM 14-10-10	no	no	no	6.7	present	no	no	no	5.6	5.4	30.24	5.4	5.2	28.08	5.1	5	25.5	4.8	4.7	22.56	4.5	4.4	19.8	34.52%	present
86	B	55	female	10119934	ulcer over left 4th toe amputation site x 2 months	diabetic x 15 years	tab glycomet gp1 1-0-1	no	no	no	8.9	present	no	no	no	6.8	4.3	29.24	6.5	4.1	26.65	6.1	4	24.4	5.6	3.8	21.28	5.1	3.6	18.36	37.21%	present
87	A	58	male	10110478	ulcer over right lower limb x 3 months	diabetic x 10 years	tab metformin 1g 1-0-0	no	no	no	9.3	present	no	no	no	16.1	9.6	154.56	15.5	9.4	145.7	15.1	9.1	137.41	14.6	8.7	127.02	14	8.3	116.2	24.82%	present
88	A	82	male	10113411	ulcer over right 2-3rd toe amputation site x 3 months	diabetic x 20 years	inj HM 20-14-10-0	no	yes	no	8.8	present	no	no	no	6.1	4.8	29.28	5.8	4.6	26.68	5.5	4.4	24.2	5.3	4.2	22.26	5.1	4.1	20.91	28.59%	present
89	B	55	male	10062790	ulcer over left foot x 3 months	diabetic x 15 years	inj HA 15-10-10	yes	no	no	9.2	present	no	no	no	8.6	6.1	52.46	8.2	5.9	48.38	7.8	5.7	44.46	7.5	5.5	41.25	7.1	5.1	36.21	30.98%	present
90	B	50	male	10034264	ulcer over right leg x 3 months	diabetic x 7 years	tab glycomet gp1 1-0-1	no	no	no	9.4	present	no	no	no	3.4	3.3	11.22	3.2	3.1	9.92	3	2.9	8.7	2.8	2.7	7.56	2.6	2.5	6.5	42.07%	present
91	A	42	male	10127350	ulcer over right leg x 3 months	diabetic x 7 years	tab glycomet gp1 1-0-1	no	no	no	7.9	present	no	no	no	7.6	4.7	35.72	7.2	4.4	31.68	6.9	4.2	28.98	6.4	3.9	24.96	5.9	3.6	21.24	40.54%	present
92	B	66	male	10045113	ulcer over right 1-4 toe amputation site x 4 months	diabetic x 15 years	tab glycomet gp1 1-0-1	no	no	no	10	present	no	no	no	11.7	6.7	78.39	11.4	6.5	74.1	11.1	6.3	69.93	10.6	5.9	62.54	10.2	5.6	57.12	27.13%	present
93	A	33	male	10059157	ulcer over dorsal aspect of right foot x 4 months	diabetic x 6 months	tab metformin 500mg 1-0-0	no	no	no	8.9	present	no	no	no	6.6	4.9	32.34	6.3	4.7	29.61	5.9	4.5	26.55	5.5	4.3	23.65	5.1	4.1	20.91	35.34%	present
94	A	56	male	10050956	ulcer over left leg x 4 months	diabetic x 15 years	tab glycomet gp1 1-0-1	no	no	no	10.3	present	no	no	no	15.6	9.1	141.96	15.1	8.8	132.88	14.4	8.4	120.96	13.9	8.1	112.59	13.4	7.9	105.86	25.43%	present
95	B	61	male	10114618	ulver over left forefoot amputation site x 3 months	diabetic x 15 years	inj HM 20-14-12-0	no	no	no	7.5	present	no	no	no	6.8	9.4	63.92	6.6	9.1	60.06	6.4	8.8	56.32	6.2	8.6	53.32	6	8.5	51	20.21%	present
96	B	50	male	7559395	ulcer over left leg x 3 months	diabetic x 8 years	tab metformin 1g 1-0-1	yes	yes	no	9.1	present	no	no	no	4.6	4.1	18.86	4.3	3.9	16.77	3.9	3.7	14.43	3.7	3.5	12.95	3.4	3.2	10.88	42.31%	present
97	A	56	male	10067393	ulcer over right foot 2-3rd toe amputation site x 3 months	diabetic x 15 years	Inj HM 14-10-10	no	no	no	8.3	present	no	no	no	5.6	4.2	23.52	5.4	4	21.6	5.2	3.9	20.28	5	3.7	18.5	4.7	3.5	16.45	30.06%	present
98	A	56	male	10086688	ulcer over right leg x 4 months	diabetic x 7 years	Inj HA 10-8-8-0	no	no	no	8.8	present	no	no	no	16.1	7.6	122.36	15.7	7.3	114.61	15.3	7	107.1	14.8	6.7	99.16	14.4	6.4	92.16	24.68%	present
99	A	48	male	1185104	ulcer over right leg x 4 months	diabetic x 7 years	tab metformin 1g 1-0-1	no	no	no	9.4	present	no	no	no	5.4	4.7	25.38	5.1	4.5	22.95	4.8	4.2	20.16	4.4	4	17.6	4.2	4	16.8	33.81%	present
100	B	56	male	10091250	ulcer over right leg x 4 months	diabetic x 5 years	tab metformin 1g 1-0-1	yes	yes	no	7.3	present	no	no	no	6.3	5.4	34.02	6.1	5.2	31.72	5.8	5	29	5.5	4.8	26.4	5.1	4.6	23.46	31.04%	present
101	B	56	female	1180175	ulcer over heel of left foot x 4 months	diabetic x 12 years	tab glycomet gp1 1-0-1	no	no	no	9.2	present	no	no	no	6.3	5.4	34.02	6	5.2	31.2	5.8	5	29	5.5	4.8	26.4	5.1	4.6	23.46	31.04%	present
102	B	44	female	1172565	ulcer over right leg x 3 months	diabetic x 6 years	tab metformin 1g 1-0-1	no	no	no	8.7	present	no	no	no	9.1	5.4	49.14	8.8	5.1	44.88	8.4	4.9	41.16	8.1	4.7	38.07	7.8	4.5	35.1	28.57%	present
103	A	56	male	10016861	ulcer over right thigh x 4 months	diabetic x 12 years	tab glycomet gp1 1-0-1	no	yes	no	9.2	present	no	no	no	4.7	3.8	17.86	4.5	3.7	16.65	4.3	3.5	15.05	4.1	3.3	13.53	3.8	3	11.4	36.17%	present
104	A	55	female	1011922	ulcer over left 4th toe amputation site x 2 months	diabetic x 15 years	tab glycomet gp1 1-0-1	no	no	no	8.9	present	no	no	no	6.8	4.3	29.24	6.5	4.1	26.65	6.1	4	24.4	5.6	3.8	21.28	5.1	3.6	18.36	37.21%	present
105	A	66	male	10081326	ulcer over right foot x 4 months	diabetic x 5 years	Tab metformin 1g 1-0-1	yes	yes	no	7.9	present	no	no	no	12.7	8.1	102.87	12.4	8	99.2	12.1	7.9	95.59	11.8	7.8	92.04	11.6	7.6	88.16	14.30%	present
106	B	57	male	10110477	ulcer over 3-4th toe amputation site of right foot x 2 months	diabetic x 15 years	inj HA 10-10-10	no	no	no	7.9	present	no	no	no	4.6	3.4	15.64	4.4	3.3	14.52	4.1	3.1	12.71	3.7	2.9	10.73	3.4	2.8	9.52	39.13%	present
107	A	58	male	13172324	ulcer over left foot x 3 months	diabetic x 10 years	t. metformin 1gm 1-0-1	yes	yes	no	9.7	present	yes	yes	absent	9.5	11	104.5	9.3	10.8	100.4	9.2	10.6	97.52	9.1	10.3	93.73	8.9	10	89	14.83%	present

108	B	49	male	10125147	ulcer over left leg x 6 months	diabetic x 5 years	tab glycomet gp1 1-0-1	yes	yes	no	8.4	present	no	no	no	4.7	4.6	21.62	4.5	4.5	20.25	4.3	4.4	18.92	4	4.1	16.4	3.8	3.8	14.44	33.21%	present
109	A	34	male	10109690	ulcer over right lower limb x 3 months	diabetic x 3 years	tab metformin 500mg 1-0-0	no	no	no	9.9	present	no	no	no	11.2	5.1	57.12	11	4.9	53.9	10.6	4.7	49.82	10.2	4.5	45.9	9.7	4.1	39.77	30.37%	present
110	A	56	male	10127688	ulcer over medial aspect of left leg x 3 months	diabetic x 8 years	tab glycomet gp1 1-0-1	no	no	no	7.3	present	no	no	no	2.3	2.1	4.83	2.1	1.9	3.99	1.8	1.7	3.06	1.5	1.5	2.25	1.3	1.2	1.56	67.70%	present
111	B	52	male	10117296	ulcer over right leg x 6 months	diabetic x 7 months	tab metformin 500mg 1-0-1	no	no	no	10.1	present	no	no	no	17	4.6	78.2	16.6	4.5	74.7	16.1	4.3	69.23	15.7	4.1	64.37	15.3	3.9	59.67	23.70%	present
112	B	54	male	10084853	ulcer over back of neck x 2 months	diabetic x 10 years	inj HA 10-0-6-0	yes	yes	no	6.8	present	no	no	no	4.1	3.8	15.58	3.9	3.7	14.43	3.6	3.5	12.6	3.4	3.3	11.22	3.1	3.2	9.92	36.33%	present
113	A	58	male	10053185	ulcer over left foot	Diabetic x 6 years	tab metformin 500mg + tab GP 1	yes	yes	no	7	present	no	no	no	5.4	4.1	22.14	5.2	4	20.8	5	3.8	19	4.8	3.7	17.76	4.6	3.5	16.1	27.28%	present
114	B	48	male	10073227	ulcer over right 2nd toe amputation site	diabetic x 15 years	inj HM 10-0-6-0	no	yes	no	9.3	present	no	no	no	7.6	4.1	31.16	7.5	4	30	7.3	3.8	27.74	7	3.6	25.2	6.7	3.5	23.45	24.74%	present