"CADEXOMER IODINE OINTMENT VS POVIDINE IODINE OINTMENT IN DIABETIC ULCER DRESSING-A RANDOMISED CONTROL TRIAL AT A TERITIARY CARE CENTER"

BY

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LIST OF ABBREVIATIONS

CI	:	Cadexomer Iodine
DAMPs	:	Damage-Associated Molecular Patterns
DCs	:	Dendritic Cells
DETCs	:	Dendritic Epidermal T Cells
ECM	:	Extracellular Matrix
ELR	:	Glutamic Acid-Leucine-Arginine
EPCs	:	Endothelial Precursor Cells
FGF	:	Fibroblast Growth Factor
GPCRs	:	G Protein-Coupled Receptors
H2O2	:	Hydrogen Peroxide
HSCs	:	Hematopoietic Stem Cells
ICAM	:	Intercellular Adhesion Molecule
IL	:	Interleukin
MMPs	:	Matrix Metalloproteinases
NETs	:	Neutrophil Extracellular Traps
NO	:	Nitric Oxide
PI	:	Povidone Iodine
PDGF	:	Platelet-Derived Growth Factor
SMA	:	Smooth Muscle Actin
TGF-β	:	Transforming Growth Factor Beta
TNF-α	:	Tumor Necrosis Factor Alpha
VEGF	:	Vascular Endothelial Growth Factor
vWF	:	von Willebrand Factor
VCAM	:	Vascular Cell Adhesion Molecule

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ABSTRACT

Background: Iodine has been a cornerstone in antiseptic wound care for over a century. Lugol's solution is the basic form of iodine but has notable drawbacks such as stinging and caustic properties. Advances in wound management have led to the development of iodine complexes like povidone iodine (PI) and cadexomer iodine (CI), which offer controlled iodine release, enhancing their safety and efficacy. In the Indian context, diabetic ulcers are a significant health burden, necessitating effective and tailored treatment strategies. This study aims to compare the efficacy of cadexomer iodine ointment and povidone iodine ointment in the management of diabetic ulcers, focusing on wound healing, infection control, and patient outcomes.

Materials and Methods: A randomized controlled trial was conducted from 2022 to 2023 with 100 patients with diabetic ulcers, admitted to a tertiary healthcare center in India. Patients were randomly assigned to two groups: one receiving cadexomer iodine ointment (n=50) and the other povidone iodine ointment (n=50). Ulcer dimensions were measured at baseline and after 28 days. Wound area reduction, granulation tissue formation, pain scores, and hospital stay duration were assessed. Data were analyzed using unpaired t-tests and chi-square tests, with a p-value <0.05 considered statistically significant.

Results: The cadexomer iodine group exhibited a significantly greater reduction in ulcer area at 28 days compared to the povidone iodine group ($p<0.05$). The quality of the ulcer floor, indicated by granulation tissue, was notably better in the cadexomer iodine group ($p<0.05$). Although the cadexomer iodine group reported lower pain scores, this difference was not statistically significant. The mean hospital stay was

significantly shorter for patients treated with cadexomer iodine (18.8±5.4 days) than for those treated with povidone iodine (22.8±4.6 days) ($p<0.05$).

Conclusion: Cadexomer iodine ointment is more effective than povidone iodine ointment in managing diabetic ulcers. It promotes greater reduction in ulcer size, enhances wound bed quality, and reduces hospital stay duration, making it a superior option for diabetic ulcer management.

Keywords: Cadexomer iodine, Povidone iodine, Diabetic ulcers, Wound healing, Randomized controlled trial, Wound management.

INTRODUCTION

For more than a century, iodine has been utilized as one of the most potent antiseptics to lessen the effects of infections, and topical iodine formulations have been applied to wound treatment.[1] The most basic form of iodine is called Lugol's solution, and it has caustic and stinging qualities.[2] The field of wound treatment has made significant strides in the past 20 years.[3]

There are several topical treatments on the market, and each has advantages and disadvantages of its own. For instance, when iodine-based medicines come into contact with exudates from wounds, they often produce free iodine, which functions as antiseptic and controls infection, helps wound healing.[4]

Iodine complexes as cadexomer iodine (CI) and povidone iodine (PI) are utilized to get around the problem. PI is a mixture of polyvinylpyrrolidone and triiodide. Triiodide is released as the paste is assimilated into the wound exudates, it adeptly preserves the equilibrium between triiodide and the PI complex.

Iodine molecules help in trapping a hydrophilic modified-starch polymer bead known as cadexomer iodine (CI). The wound exudates cause the polymer beads in CI to swell up, which gently releases integrated iodine and prevents its buildup. This prevents iodine-related problems including allergic contact dermatitis and systemic acidosis, among others.[5]

In light of these circumstances, the goal of this study is to diffrentiate the effectiveness of PI and CI ointments managing wounds to get around the drawbacks of PI ointments that are currently in use. These drawbacks include decreased epithelial regeneration, de-sloughing agent, and facilitating the promotion of granulation tissue formation, wound contractility, and neovascularization.

In the Indian context, where diabetes is reaching epidemic proportions, there's a pressing need for effective management strategies to address diabetic ulcers. Diabetic ulcers pose significant health burdens, often leading to complications such as infections, amputations, and decreased quality of life. With a large diabetic population in India, there's a critical demand for evidence-based interventions to improve ulcer management outcomes and reduce healthcare costs associated with diabetic complications. Despite the availability of various wound dressing options, there's limited comparative research on the effectiveness of specific treatments tailored to Indian patients' needs.

The aim of the study comparing cadexomer iodine ointment versus povidone iodine ointment in diabetic ulcer dressing is to provide empirical evidence on the efficacy, safety, and cost-effectiveness of these two commonly used treatments in the Indian diabetic population. Specifically, the study seeks to determine which of the two ointments yields better outcomes in terms of ulcer healing rates, reduction of infection risk, improvement in wound bed preparation, and overall patient satisfaction. By comparing these two treatments head-to-head, the study aims to inform clinicians, healthcare providers, and policymakers about the most suitable option for diabetic ulcer management in the Indian context, ultimately enhancing patient care and optimizing healthcare resources.

AIMS & OBJECTIVES

Primary objective:

To compare efficacy of wound healing between cadexomer iodine and povidine iodine

Secondary objective:

To check the ability of cadexomer iodine in decreasing the median hospital stay time.

REVIEW OF LITERATURE

Diabetes Mellitus[6]

Diabetes mellitus finds its roots in the Greek word "diabetes," which translates to "to pass through," combined with the Latin term "mellitus," meaning "sweet." This term was coined by Apollonius of Memphis around 250 to 300 BC, influenced by the observation of the sweet taste of urine by ancient Greek, Indian, and Egyptian civilizations. The role of the pancreas in the etiology of diabetes was acknowledged by Mering and Minkowski in 1889. Despite substantial advancements in management, diabetes remains a widespread chronic condition worldwide.[6]

Epidemiology:

Diabetes has become a global epidemic, with India emerging as the world's diabetes capital, hosting around 41 million individuals diagnosed with the condition. Projections suggest that the prevalence of diabetes across all age groups was anticipated to rise from 2.8% in 2000 to 4.4% by 2030.[7,8] According to the International Diabetes Federation (2017), the prevalence of diabetes in 2017 and 2045 is expected to be 8.8 and 11.4%, respectively. Diabetic eye disease is getting more prevalent.[9] As per the latest epidemiological data from 2019, India currently has approximately 77 million individuals affected by diabetes, a number projected to escalate to nearly 134 million by 2045. India ranks second only to China in the global diabetes crisis. Among these figures, 12.1 million individuals are aged 65 or above, and this demographic is expected to swell to 27.5 million by 2045. Moreover, an estimated 57% of diabetes cases in India, equivalent to roughly 43.9 million people, remain undiagnosed.[10]

Classification of diabetes mellitus

The new classification identifies four types of diabetes mellitus:

1. Type 1: Results from autoimmune destruction of β-cells, leading to a complete lack of insulin.
2. Type 2: Characterized by insulin resistance in peripheral tissues and a deficiency in insulin secretion by β-cells.
3. Other Specific Types: Includes conditions like MODY (Maturity onset diabetes of young
4. Diabetes in pregnancy

Wound healing

One of the most intricate processes in the human body is wound healing. Numerous cell types with different functions in the stages of hemostasis, inflammation, growth, re-epithelialization, and remodeling are synchronized both spatially and temporally. The development of single-cell technology has made it feasible to identify functional and phenotypic variation within a number of these cell types.

Individuals with diabetes and elderly, and those with genetic conditions such as sickle cell disease are particularly prone to experiencing impaired wound healing, leading to long-lasting complications. Surprisingly, existing interventions have not made a significant impact on this issue. Although various methods for wound healing are available, their effectiveness remains only moderate. Therefore, there is a need for more efficient treatments to address wound healing.

"The process of skin repair necessitates the coordinated interaction of multiple cell types across different layers in a sequential manner. In uninjured skin, the outer layer, known as the epidermis, serves as a protective barrier against external factors and houses structures like sebaceous glands, sweat glands, and hair follicles. Beneath the epidermis lies the dermis, which is abundant in extracellular matrix (ECM), blood vessels, and mechanoreceptors, providing the skin with structural support, nutrients, and defense mechanisms. Adjacent to the dermis is the subcutaneous adipose tissue, which not only acts as an energy reservoir but also serves as a continual source of growth factors for the dermal layer. Each of these layers also contains resident immune cells that constantly monitor the skin for any signs of damage."

Upon injury, various cell types within these layers must coordinate their activities at specific stages to initiate the healing process. These stages include hemostasis, inflammation, angiogenesis, proliferation, re-epithelialization, and remodeling. Although these stages occur sequentially, they also overlap, making skin repair one of the most intricate processes in the human body.

- "Injured blood arteries constrict and a fibrin clot forms as the body's first reaction to a wound; this stops blood flow and provides a framework for inflammatory cells."[12,13]

- "Neutrophils are the first immune cells recruited to the wound to combat bacterial infection."[12]

- After that, monocytes are drawn in and develop into tissue-activated macrophages, which help with tissue restoration.

To protect against both external and self-inflicted antigens, the immune system—which includes T cells, cutaneous dendritic cells, and Langerhans cells—is triggered.

- Understanding the diversity in immune cell populations is crucial, particularly their roles in debris clearance and infection resolution.[14,15]

- Angiogenesis, which involves the multiplication of endothelial cells and the activation of pericytes to give structural support to newly formed blood vessels, follows the inflammatory phase.

- Progenitor cells that circulate from the bone marrow also aid in the development of new blood vessels.

- To help with wound closure, resident fibroblasts multiply and infiltrate the clot to generate contractile granulation tissue. Some of these fibroblasts go on to differentiate into myofibroblasts.[16–18]

- The extracellular matrix (ECM) that fibroblasts produce causes the wound microenvironment to change from an inflammatory to a growing state.

- The dedifferentiation of terminally differentiated epidermal cells and the proliferation of epidermal stem cells take place concurrently with re-epithelialization.

- Tissue-resident stem cells for skin appendages exhibit great flexibility during wound healing, activating local appendage repair in response to damage.

- Subcutaneous adipose tissue's stromal vascular cells produce cytokines and growth factors that are essential for wound healing and neovascularization.

- Increased inflammation caused by inflammatory cells in subcutaneous tissue, especially in obesity and type 2 diabetes, might affect the course of wound healing.

- Adult wound healing usually leads to fibrotic scarring instead of the natural skin architecture that is restored in the case of prenatal wound healing.

Hypertrophic scarring and keloid development can result from excessive scarring, and these conditions are frequently impacted by differentiating cellular reactions to mechanical stress.[19,20]

- Impairments in wound healing can result in chronic wounds, which are common in conditions like diabetes, vascular disease, aging, and hemoglobinopathies, potentially leading to limb amputations and mortality.

Cellular responses during wound healing

A. Hemostasis
B. Inflammatory phase
C. Growth phase
D. Re-epithelialization
E. Tissue maturation and remodeling in wound healing

A. Hemostasis:

Hemostasis, the initial phase of wound healing, plays a crucial role in halting bleeding following vascular injury. This process involves three steps: vasoconstriction, primary hemostasis, and secondary hemostasis. Platelets are key players in hemostasis, while fibrinogen is a critical component of the matrix. Under normal conditions, platelets remain inactive due to the protective endothelial cell layer lining the blood vessels. However, upon injury, vasoconstriction occurs to stop bleeding, followed by primary and secondary hemostasis pathways.[21,22] Primary hemostasis involves platelet aggregation and plug formation triggered by collagen exposure, while secondary hemostasis activates the coagulation cascade, converting soluble fibrinogen into insoluble fibrin strands to form a mesh. The combined action

of platelet plugs and fibrin meshes forms a thrombus, stopping bleeding and providing a scaffold for cells necessary for wound healing.[22]

- Vasoconstriction
- Formation of platelet plug which is primary hemostasis
- Coagulation and reinforcement of the platelet plug

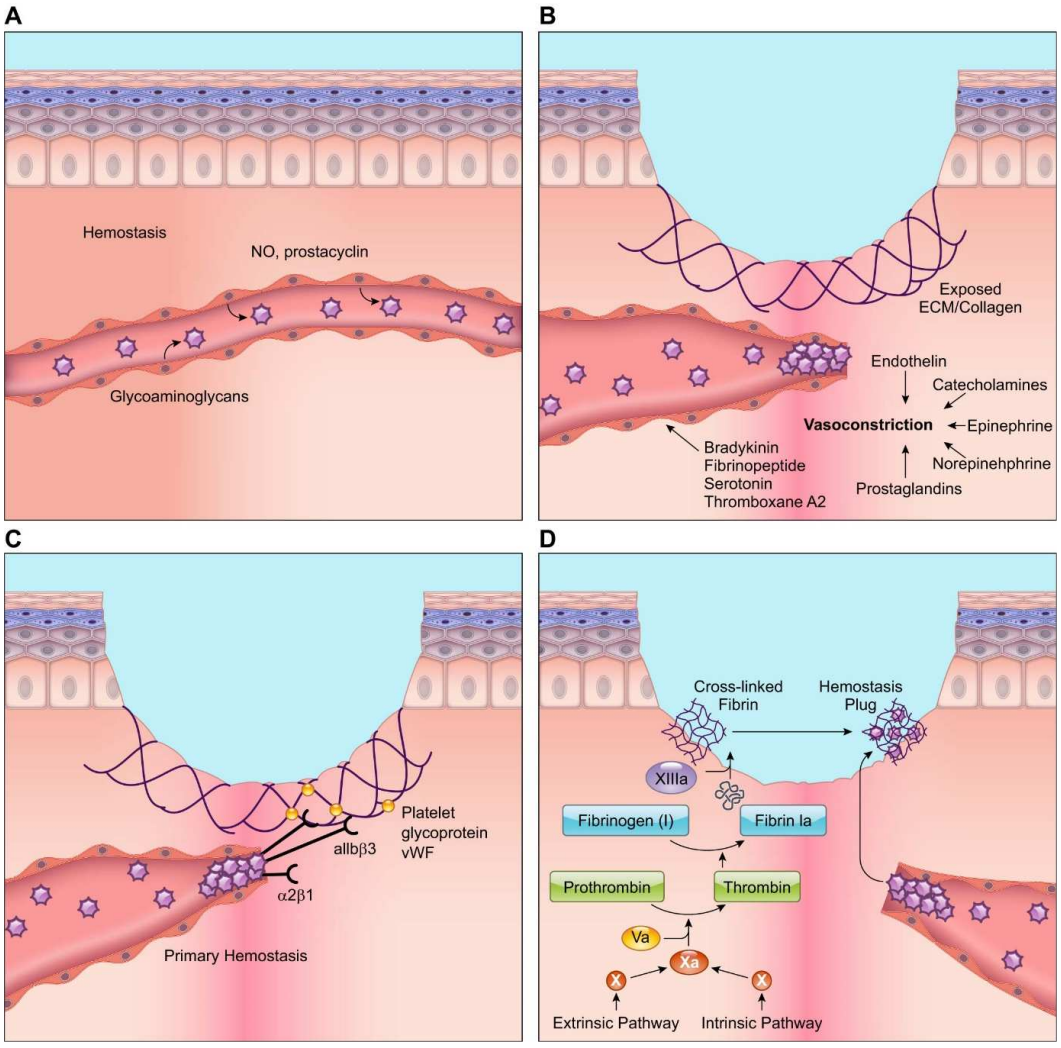

Figure 1: Cellular response during the hemostatis phase of wound healing[23]

"During hemostasis, platelets are normally prevented from attaching to the vessel wall and aggregating by anti-thrombotic agents like nitric oxide (NO) and prostacyclin released from endothelial cells. When a wound occurs, injured cells release vasoconstrictors, causing temporary cessation of bleeding by contracting smooth muscles. Blood vessel rupture exposes the subendothelial matrix, where platelets bind using surface receptors and glycoproteins, along with von Willebrand factor (vWF) released by platelets. This strengthens the platelet plug. The activation of Factor X through extrinsic and intrinsic pathways leads to the conversion of fibrinogen to fibrin. Cross-linked fibrin binds the aggregated platelet plug, forming a thrombus that halts blood flow and provides a scaffold for healing. This summary simplifies the process of hemostasis and wound healing based on current understanding."

B. Inflammatory phase of wound healing

a. Mechanisms of inflammatory cell recruitment:

Wound healing initiates with the activation of cellular response through transcription-independent pathways like Ca2+ waves, reactive oxygen species (ROS) gradients, and purigenic molecules.

Damage-associated molecular patterns (DAMPs), hydrogen peroxide (H2O2), lipid mediators, and chemokines released from injured cells recruit inflammatory cells, particularly neutrophils.

Chemokines are small proteins that bind to G protein-coupled receptors (GPCRs), attracting various immune cells. ELR+ chemokines preferentially attract neutrophils, while ELR- chemokines attract lymphocytes.

Mast cells release inflammatory mediators upon injury, enhancing immune cell recruitment. Mast cell enzymes like mast cell proteases 4 and 5 play a crucial role in neutrophil recruitment during wound healing.

b. Neutrophils in wound healing:

Neutrophils, typically absent in normal skin, are recruited from the bone marrow in response to "find me" signals released from injured areas.

Neutrophils express various surface receptors that aid in detecting injury signals and constitute a significant portion of cells in the wound early in the healing process.

Activated neutrophils eliminate pathogens through toxic granules, oxidative burst, phagocytosis, and production of neutrophil extracellular traps (NETs).

Neutrophils develop different granules containing antimicrobial agents like proteases, human cationic antimicrobial protein (hCAP-18), and matrix metalloprotease (MMPs) during their maturation in the bone marrow.

Proteases in neutrophil granules play a crucial role in antimicrobial activity and tissue remodeling but can also cause tissue damage if produced excessively, as observed in chronic wounds.

NETs, released by neutrophils, capture and eliminate pathogens through chromatin filaments coated with histones, cytosolic proteins, and proteases. NETs are released either through suicidal NETosis or vital NETosis, depending on the activation pathways involved.

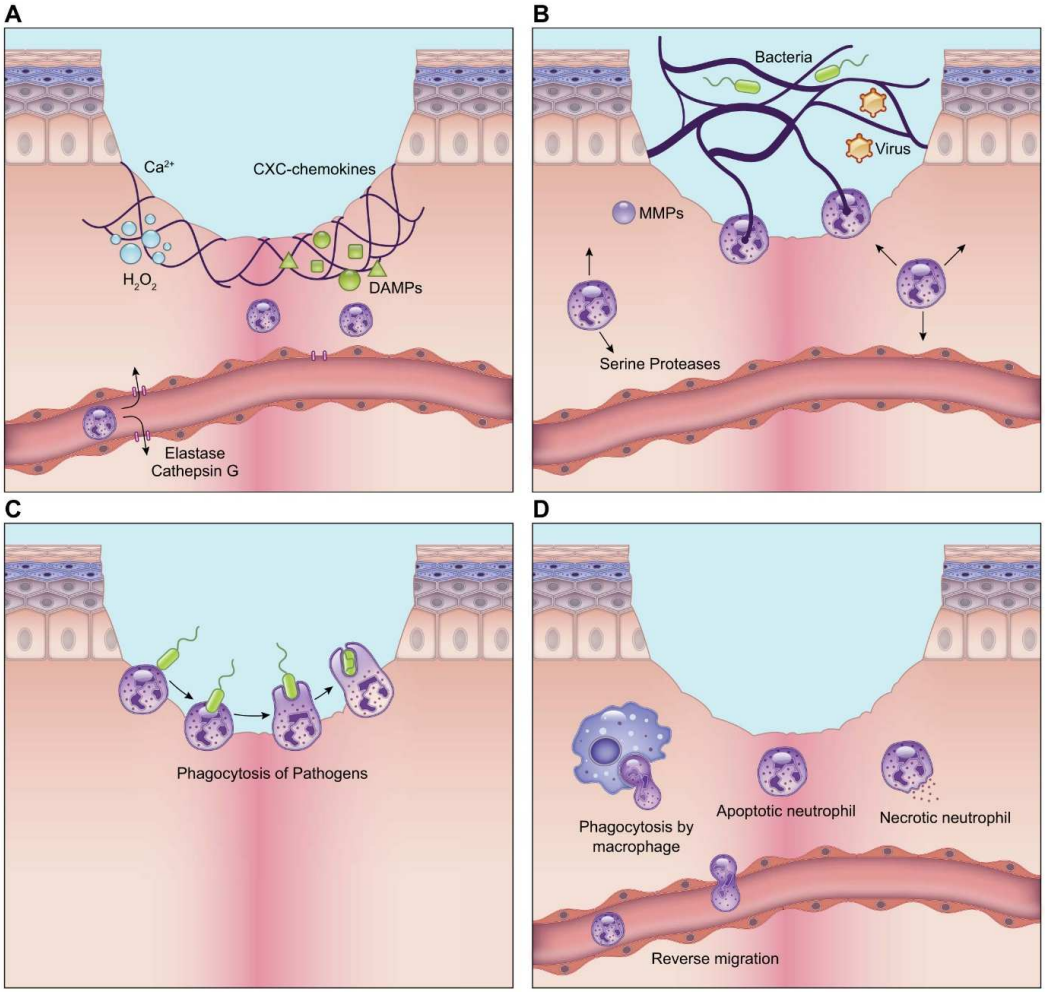

Figure 2: Role of neutrophils in wound healing[23]

c. Macrophages in wound healing

"Macrophages play a crucial role in wound healing, identified by surface markers like CD45+/ CD11b+/ F480+ in mice and CD45+/ Cd11b+/ CD66B- in humans. Within 24-48 hours post-injury, macrophages accumulate at the wound site, peaking around day 3 and declining by day 10. They originate from both local tissue-resident macrophages and recruited monocytes from the bone marrow. Depletion of macrophages delays wound closure, while increasing their numbers accelerates healing in various organisms, including mice and salamanders."[24,25]

In the early stages of healing, macrophages exhibit a microbicidal and pro-inflammatory phenotype known as M1, expressing TNF-α, IL-6, and IL-1β. They engulf pathogens, synthesize MMPs to digest the extracellular matrix (ECM), and perform efferocytosis to eliminate spent neutrophils. This pro-inflammatory response aids in clearing pathogens and promoting tissue repair. However, prolonged inflammation due to improper neutrophil clearance can lead to tissue damage.[26,27]

"Macrophages also transition to a reparative phenotype, facilitating tissue regeneration during the later stages of healing. They induce the transition of fibroblasts to myofibroblasts, contributing to collagen deposition and wound contraction. Additionally, macrophages participate in tissue remodeling by phagocytizing excess cells and matrix components. Dysregulated macrophage functions are implicated in fibrotic diseases like keloids and hypertrophic scars, as well as impaired wound healing in conditions like diabetes. Understanding the diverse roles of macrophages in wound healing is crucial for developing effective therapeutic strategies."

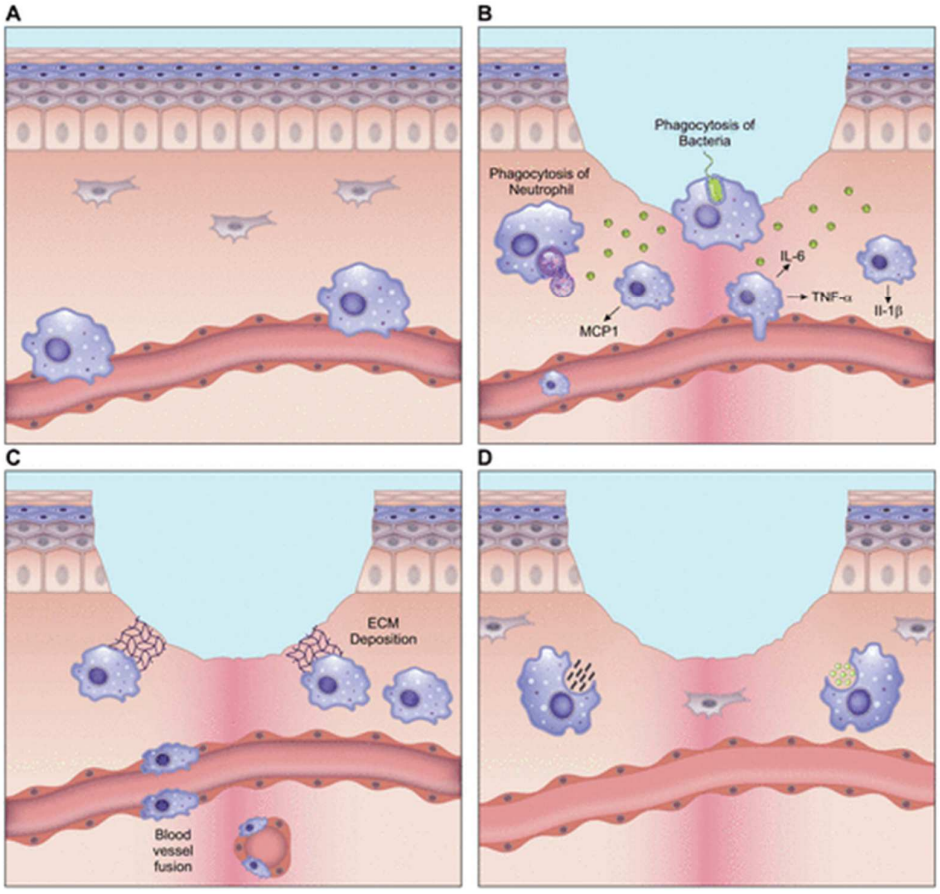

Figure 3: Macrophage phenotypes in wound healing[23]

d. Mast cell in wound healing

"Paul Ehrlich first identified mast cells in 1878. These cells come from progenitors in the bone marrow and move to perivascular areas of the skin and mucosa, where they undergo differentiation. Due to contradictory results in mast cell-deficient animals, their function in wound healing is up for discussion. But during wound healing, they interact with different cell types and are linked to reactions that cause scarring, such as scleroderma and hypertrophic scarring."[28]

Mast cells generate histamines, VEGF, chymase and tryptase, antimicrobial peptides, and other substances that facilitate vascular permeability and keratinocyte proliferation during the early phases of wound healing. Histamine enhances

keratinocyte proliferation, whereas tryptase and histamine boost fibroblast proliferation and collagen production, facilitating wound contraction.[29,30]

Skin fibrosis and scarring are linked to elevated mast cell counts. Research employing a fetal wound healing model indicates that mast cells impact the development of scars; injections of mast cell lysate are shown to change scarless healing into the production of scars. The precise processes, however, remain unknown, and further research is needed to fully understand the function of mast cells in chronic wounds, particularly in diseases like diabetes. The microenvironment of mast cells influences their functional variability. There may be distinct mast cell subgroups in wounds, each with their own roles, requiring more investigation.[31,32]

e. Dendritic cells in wound healing

Dendritic cells (DCs) are important antigen-presenting cells involved in T-cell responses. They exist in the epidermis as Langerhans cells, named after Paul Langerhans, and in the dermis. Although some debate exists about their classification as macrophages due to shared characteristics, they are distinct based on their primary functions. DCs have a stronger antigen-presenting ability than macrophages and migrate to draining lymph nodes to activate T-cell responses.

In murine dermis, two resident DC subtypes are typically found: CD11b+ DCs and CD103+ DCs, analogous to CD141+ DCs in humans. CD103+ dermal DCs are responsible for cross-presenting antigens to induce CD8+ T-cell responses and play roles in viral immunity. They recognize DAMPs on dying cells and viruses through specific surface receptors. CD11b+ DCs in mice correspond to CD1c+ and CD14+ DC subsets in humans and preferentially present antigens to CD4+ T cells during infection, regulating the adaptive immune response.[33,34]

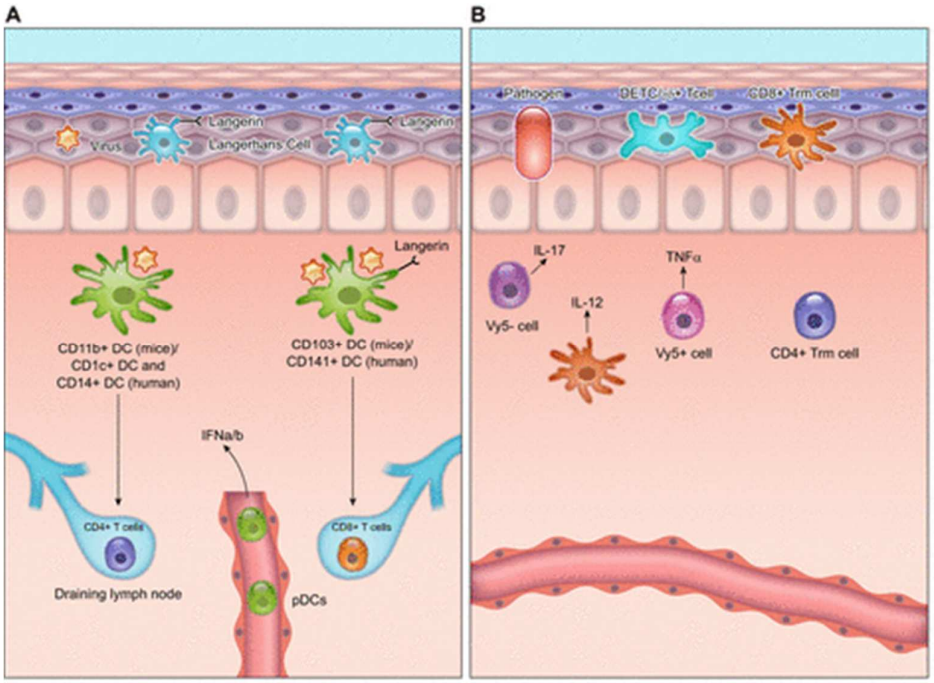

Figure 4: Dendritic cells (DCs) and T cells in the wound healing response[23]

f. Role of T cells in wound healing

There are two types of T cells found in the skin layers of humans: γδ+ T cells and αβ+ T cells. While the dermis of human skin primarily contains αβ+ T cells, the epidermis of mice is predominantly populated by γδ+ T cells, also known as DETCs, due to cellular structure differences. DETCs originate in the fetal thymus and migrate to the epidermis, where they slowly grow in number in response to signals like interleukins, particularly IL-15. Positioned in the basal layers of the epidermis, they extend their dendrites into the suprabasal layers to actively monitor for certain molecules that signal epidermal stress, such as infections or abnormal cell presence. Unlike other T cells, DETCs typically remain stationary in the skin. Research on T cells in wound healing often focuses on DETCs because they are the only T cell subtype known to release cytokines and growth factors that aid in skin cell regeneration. Additionally, studies show that mice lacking DETCs experience

significant delays in wound healing, and DETCs possess a unique T-cell receptor, Vγ3Vδ1, specific to skin T cells.

3. Growth phase of wound healing

a. formation of granulation tissue and neovascularisation

"During the proliferative phase of wound healing, various processes occur simultaneously, including the formation of new connective tissue known as granulation tissue, alongside re-epithelialization, neovascularization, and immunomodulation. Granulation tissue, first described by John Hunter in the late 18th century and further characterized by Alexis Carrel in the 19th century, is primarily composed of activated fibroblasts. These fibroblasts produce new extracellular matrix (ECM) and aid in wound contraction. In addition, granulation tissue serves as a framework for newly created blood vessels and inflammatory cells, among other cellular and structural elements. In the course of the wound remodeling phase, granulation tissue eventually gives way to normal connective tissue."

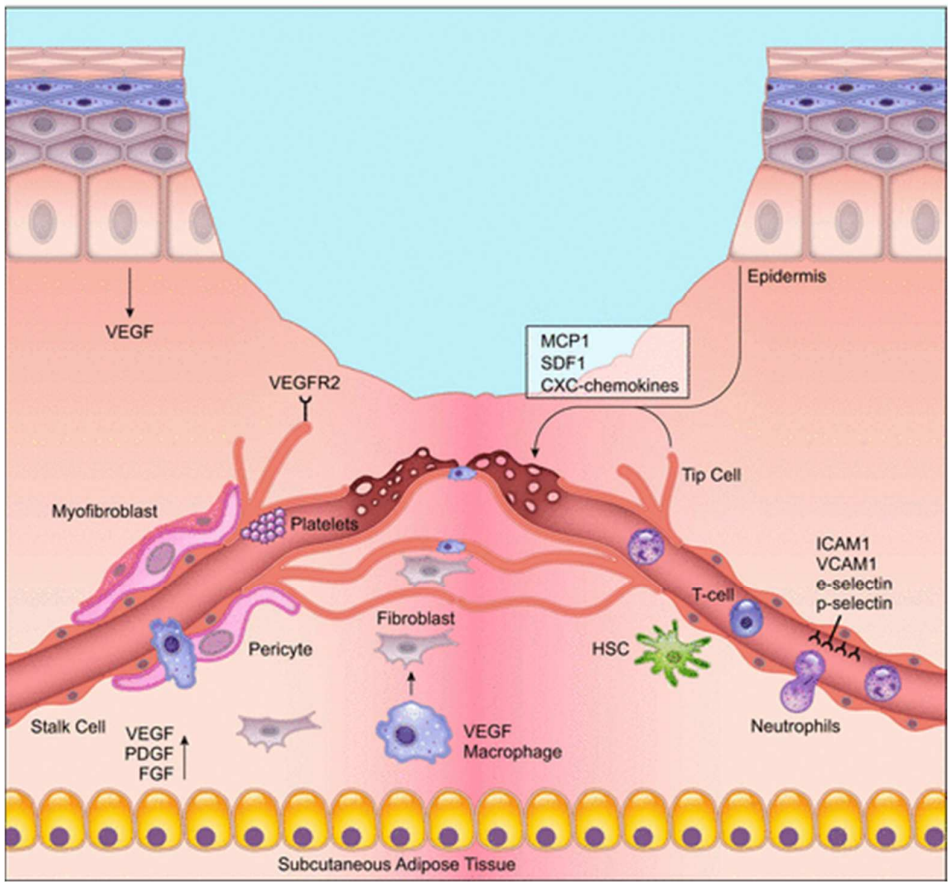

Figure 5: Angiogenesis during wound healing. [23]

Neovascularization, crucial for effective wound healing, facilitates nutrient delivery and oxygen balance necessary for cellular proliferation and tissue regeneration. Vasculogenesis is the process by which angioblasts, endothelial progenitor cells (EPCs), give birth to primitive blood arteries during embryonic development. Despite the fact that it was once believed that adult tissue healing included vasculogenesis through EPCs produced from bone marrow, later research on mice showed that the putative EPCs are mostly macrophages and monocytes that facilitate neovascularization. Adults produce new blood vessels mostly by angiogenesis, a process in which local microvascular endothelial cells (ECs) activate growth hormones such as PDGF and VEGF in response to hypoxia. Activated endothelial cells (ECs) break down extracellular matrix (ECM), multiply, move, and

create new capillaries, which improves tissue regeneration by promoting oxygen and nutrient supply. This process involves endothelial cells and pericytes. Additionally, we explore circulating progenitor cells' role in wound healing and discuss fibroblast subtypes supporting granulation tissue formation.[35,36]

b. Endothelial cell and new vessel formation

"Angiogenesis, the process of generating new blood vessels, is greatly aided by microvascular endothelial cells (ECs), which line the inside of blood vessels. Growth factors include VEGF, FGF, PDGF-B, TGF-β, and angiopoietins stimulate ECs, causing them to proliferate and migrate into fibrin/fibronectin-rich clots. ECs develop into stalk cells, which follow and preserve the structure, and tip cells, which drive the growth, during angiogenesis. These cells combine with existing vessels to produce new endothelial tubules. Endothelial cell receptors are essential for angiogenesis. Normally, ECs have few surface receptors, preventing interactions with platelets and immune cells, but allowing monocyte surveillance. Upon injury, ECs express glycoprotein receptors like P-selectin and E-selectin, facilitating leukocyte adhesion and infiltration. They also upregulate ICAM-1 and VCAM-1, which help stop leukocyte movement. The absence of these receptors impairs both new blood vessel formation and wound healing, highlighting their role in skin repair."[37–39]

c. Role of pericytes play in neovascularization and wound healing

"Mature pericytes are defined as cells embedded in the vascular basement membrane; this description makes it difficult to identify them in the context of ongoing neovascularization. This problem stems from the fact that the perivascular region is also inhabited by various cell types, including fibroblasts, macrophages, circulating progenitor cells, and vascular smooth muscle cells. Furthermore, pericytes cannot be

easily distinguished from these other cells by a specific molecular signature. As a result, it is challenging to recognize pericytes in tissue slices, and it is yet unknown whether systemic recruitment of pericytes from a common reservoir during vessel construction or local proliferation of preexisting pericytes forms new pericytes."[40,41]

"Various surface markers such as nestin, NG2, PDGFR-β, and desmin have been used to define pericytes, but these markers may not be uniformly expressed on all pericytes."[42]

d. Circulating progenitor cell role in neovascularization and wound healing

Primarily endothelial progenitor cells (EPCs), help the blood vessel regeneration. These cells follow a three-step process to reach ischemic tissue: mobilization from the bone marrow into circulation due to chemokine release at the injured site, migration through circulation , increasing chemokine gradients, and preferential homing to the ischemic region where they integrate into the sprouting endothelium and differentiate into endothelial cells.[43,44,45].

e. Role of fibroblasts play in wound healing

They , present throughout body's tissue, play crucial roles in extracellular matrix (ECM) deposition and remodeling. They exhibit notable diversity based on tissue origin, developmental stage, and activation status, leading to varied regulations in wound healing, which include ECM organization, growth factor, and immunomodulation. Historically, characterizing fibroblasts has been challenging due to a lack of distinct markers, but recent advancements of the marker identification and assays help us understand better. Fibroblast diversity can be positional, determined by their location relative to the epidermis, and anatomical, based on their location within

the body.Skin, differences exist between fibroblasts in the upper and lower dermis, with lower lineage fibroblasts initially contributing to dermal repair and scar formation. These scar-forming fibroblasts express myofibroblast markers and can be isolated using specific surface markers, with inhibition of these markers showing potential in reducing scar formation, carrying clinical implications.[46,47]

f. Role of Myofibroblasts in wound healing

Vital component in wound healing, ulcer contraction increases mechanical strength by aligning collagen fibrils perpendicular to the wound edges, reducing the surface area of the wound that requires re-epithelialization. Because of this changed stiffness, fibroblasts become myofibroblasts that are positive for α-SMA, which causes them to momentarily deposit extracellular matrix (ECM) and exhibit contractile characteristics. Growth factors, mechanosensory signals in granulation tissue, and interactions between cells and the extracellular matrix drive this process. Although local fibroblasts are the primary source of myofibroblasts, their number may also be augmented during wound healing by fibrocytes, mesenchymal stem cells (MSCs), pericytes, and epithelial cells.

After enough tissue integrity has been restored, myofibroblasts finally die off in the wound region. Eventhough still unclear whether myofibroblasts can return to the fibroblast phenotype seen in epidermis that is not damaged after healing. Myofibroblasts frequently avoid apoptosis in a variety of fibrotic diseases, including hypertrophic scarring, which aids in the formation of scar tissue. This idea is supported by research done on mice with hypertrophic scarring, which shows that more myofibroblast survival causes scar formation to spread out after mechanical loading. As a result, myofibroblasts are an attractive target for the development of

fibrosis and scarring therapies since they are essential to the latter phases of granulation tissue production.

4. Re-epithelialization

The skin provides protection against mechanical stress, bacteria , UV radiation, water loss, and high temperatures. It comprises a layered epithelium consisting primarily of, which is linked with adjacent keratinocytes through desmosomes. The basal layer, the lowest layer, connects to a specialized extracellular matrix (ECM) known as basement membrane via hemidesmosomes and focal adhesions. Above basal layer are : spinous layer, granular layer, and outermost layer, stratum corneum, composed of impermeable cells which are continuously shed. Apart from keratinocytes, the epidermis includes immune cells that reside there, along with hair follicles, sebaceous glands, and sweat glands. Due to its susceptibility for injury, stem cells are essential in maintaining homeostasis and help in repair. Stem cell division and differentiation replenish lost cells, aiding in both regular maintenance and healing processes of the skin.[48,49]

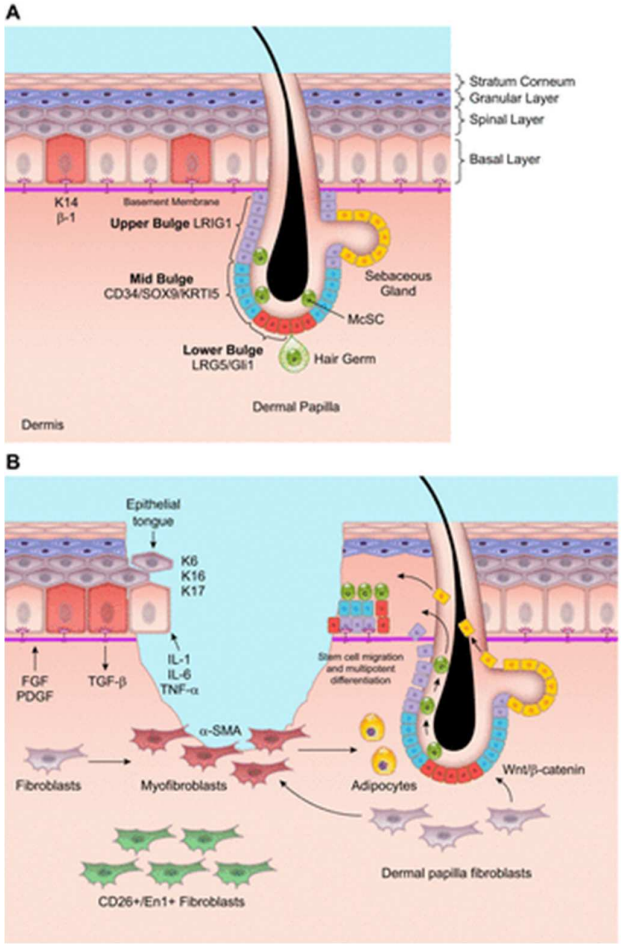

Figure 6: The process of re-epithelialization and the interactions between fibroblasts and epidermal cells play crucial roles in the intricate orchestration of wound healing.

"Extrinsic signals from the stem cell niche, consisting of cues from the extracellular matrix (ECM), growth factors, and neighboring cells, are crucial in determining the fate of stem cells. In the interfollicular epidermis (IFE), stem cells are grouped rather than dispersed individually and exhibit higher adhesiveness due to elevated integrin expression compared to transit amplifying cells. During homeostasis, integrins are primarily found in basal layer cells. Key integrins present on basal cells include α2β1, which binds collagen, α3β1 and α6β4, binding laminin, and αvβ5, binding vitronectin. α6β4 is concentrated distally on the basement membrane, while α3β1 is located at the

leading apical edge. Other integrins are distributed across the basal cells' basal, lateral, and apical surfaces."

Regeneration of hair follicles

Melanocytes in wound healing

"Because of changes in melanocyte proliferation and activation, partial thickness and deep full thickness injuries—especially those brought on by burns—often result in skin discoloration, either hyperpigmentation or hypopigmentation. Specialized dendritic cells called melanocytes are formed from the neural crest and are in charge of creating melanin, a pigment that protects the skin from oxidative damage and UV light. Melanocytes are found in hair follicles and the interfollicular epidermis (IFE) in humans, whereas they are mostly found in hair follicles in mice, with the exception of few places like the ear and tail skin, where they are also found in the IFE. In the area of the hair follicle bulge, melanocyte stem cells (McSCs) replace melanocytes during normal skin function. Numerous growth factors, including TGF-β and endothelin-2, as well as signaling molecules, such WNT and Notch, generated by nearby hair follicle stem cells, have an impact on these McSCs. Melanocyte repopulation takes place in tandem with the growth phase of the hair cycle".[50,51]

5. Tissue maturation and remodeling in wound healing

"In wound healing, closure of acute and chronic wounds is typically considered the endpoint, but the process continues with tissue remodeling or maturation, which may last for months or even years. This phase is crucial as it determines whether scarring will occur or if the wound will recur. During the remodeling phase, neovasculature regresses, and there is periodic deposition and reconstitution of the extracellular

matrix (ECM), transforming granulation tissue into scar tissue. Initially rich in collagen III, granulation tissue gradually transitions to contain more collagen I, which is stronger. This shift results from concurrent collagen I synthesis and collagen III breakdown, followed by ECM reorganization.[35]

During angiogenesis, newly formed blood vessels in the wound area lack tight cell-cell contacts and pericyte coverage, facilitating immune cell infiltration. In the remodeling phase, neovessels undergo pruning to establish stable, well-perfused vessels that can restore homeostasis. This process involves endothelial cell apoptosis, though the exact mechanisms are unclear. Re-epithelialization may also contribute to vessel pruning by reducing hypoxia in the healed wound bed, promoting endothelial cell quiescence".

Vasohibin and sprouty proteins are examples of negative-feedback systems found in endothelial cells that function as "anti-angiogenic switches" by controlling the cell's sensitivity to VEGF. "Furthermore, endothelial cells produce CXCR3, which, when attached to its ligand, CXCL10, suppresses the development of endothelial tubes during the late stages of wound healing. CXCR3 is essential for wound remodeling, as demonstrated by the hypertrophic scarring seen in mice devoid of the protein. Comprehending alternative cellular signaling pathways that exhibit preferential expression during wound remodeling might potentially clarify the reasons behind dystrophic healing in some wounds, such keloids and hypertrophic scarring."

Relation of diabetes and wound healing:

The relationship between diabetes and wound healing is a complex and well-studied phenomenon in the medical field. Diabetes, particularly when poorly managed, can significantly impair the body's ability to heal wounds effectively. This

impairment is attributed to a combination of physiological factors that interfere with the normal wound healing process. In this discussion, we'll delve into the scientific factors underlying this relationship, supported by references from relevant studies.

1. Delayed Inflammatory Response:

"In diabetic individuals, the inflammatory phase of wound healing is often delayed or impaired. This phase is crucial for clearing debris, preventing infection, and initiating the subsequent phases of healing. Research by Mirza et al. (2015) demonstrated that diabetes can disrupt the recruitment of inflammatory cells to the wound site, leading to prolonged inflammation and delayed healing".

2. Impaired Angiogenesis:

Angiogenesis, is formation of new blood vessels, is essential for delivering oxygen, nutrients, and neutrophil cells to the wound area. However, in diabetes, angiogenesis is often impaired due to various factors, including reduced levels of growth factors like vascular endothelial growth factor (VEGF). A study by Loots et al. (1998) found that diabetic wounds exhibit decreased angiogenesis, which contributes to poor wound healing outcomes.[52]

3. Microvascular Complications:

Diabetes is associated with microvascular complications, such as endothelial dysfunction and reduced capillary density. These complications impair blood flow to the wound site, depriving it of essential nutrients and oxygen necessary for healing. According to a review by Schäffer et al. (2011), microvascular dysfunction in diabetes hinders the delivery of oxygen and nutrients to the wound, prolonging the healing process.[53]

4. Impaired Extracellular Matrix Remodeling:

The extracellular matrix (ECM) provides structural support and scaffolding for cells involved in wound healing. In diabetes, alterations in ECM composition and function impair its remodeling during wound repair. Studies by Galiano et al. (2004) have shown that diabetes alters the balance of matrix metalloproteinases (MMPs) and their inhibitors, leading to excessive degradation of the ECM and impaired wound closure.

5. Defective Fibroblast Function:

" Fibroblasts play a crucial role in synthesizing collagen and promoting wound contraction during the proliferative phase of healing. However, in diabetes, fibroblast function is often compromised. Research by Falanga et al. (1992) demonstrated that fibroblasts isolated from diabetic wounds exhibit reduced proliferation and collagen production compared to those from non-diabetic wounds, contributing to delayed healing".[54]

6. Increased Susceptibility to Infection:

Diabetes predisposes individuals to infections due to immune dysfunction and impaired wound defense mechanisms. Elevated blood glucose levels create a favorable environment for bacterial growth, increasing the risk of wound contamination and infection. A study by Lipsky et al. (2012) highlighted the heightened susceptibility of diabetic patients to wound infections, which further impedes the healing process.[55]

The relationship between diabetes and wound healing is multifactorial, involving disruptions in inflammatory responses, angiogenesis, microvascular function, ECM remodeling, fibroblast activity, and susceptibility to infection. Understanding these underlying mechanisms is crucial for developing targeted therapeutic strategies to improve wound healing outcomes in diabetic patients.

Wound dressing in diabetic ulcers:

Diabetic wounds pose a significant challenge due to the impaired healing process associated with diabetes. Proper wound dressing methods are essential to facilitate healing, prevent infections, and manage complications. Here, I'll delve into various diabetic wound dressing methods, providing scientific insights into each:

Moist Wound Healing: Moist wound healing is a widely accepted approach that maintains a moist environment around the wound. Research suggests that moist conditions promote faster epithelialization, reduce the risk of infection, and minimize scarring. Hydrogel dressings, foam dressings, and hydrocolloid dressings are commonly used in moist wound healing. These dressings help to keep the wound bed moist while absorbing excess exudate.

Antimicrobial Dressings: Diabetic wounds are prone to infections due to compromised immune responses. Antimicrobial dressings contain agents such as silver, iodine, or honey, which exhibit antimicrobial properties. Silver dressings, for example, release silver ions that inhibit bacterial growth. They are effective against a broad spectrum of pathogens, including antibiotic-resistant strains.

Alginate Dressings: Alginate dressings are derived from seaweed and contain calcium alginate fibers. When in contact with wound exudate, alginate dressings form

a gel-like substance, which helps maintain a moist environment and facilitates autolytic debridement. These dressings are particularly useful for wounds with moderate to heavy exudate.

Foam Dressings: Foam dressings are highly absorbent and provide cushioning and protection to the wound. They are suitable for wounds with moderate to heavy exudate and can help manage pressure ulcers commonly seen in diabetic patients. Foam dressings also maintain a moist environment conducive to wound healing.

Collagen Dressings: Collagen is a key component of the extracellular matrix and plays a crucial role in tissue repair. Collagen dressings provide a scaffold for cell migration and proliferation, promoting granulation tissue formation and wound closure. They are particularly beneficial for chronic wounds with impaired healing.

Negative Pressure Wound Therapy (NPWT): NPWT involves the application of sub-atmospheric pressure to the wound bed through a sealed dressing system. This technique promotes wound healing by reducing edema, improving blood flow, and stimulating the formation of granulation tissue. NPWT is effective for managing complex diabetic wounds, including those with exposed bone or tendon.

Biological Dressings: Biological dressings, such as amniotic membrane or growth factor-based dressings, harness the regenerative potential of biological materials. Amniotic membrane dressings contain growth factors and cytokines that promote tissue regeneration and modulate inflammation. They are particularly useful for diabetic wounds with delayed healing.

Compression Therapy: Compression therapy is essential for managing diabetic foot ulcers and venous ulcers, which are common complications of diabetes.

Compression dressings or stockings improve venous return, reduce edema, and promote wound healing by enhancing tissue perfusion.

Diabetic wound management requires a multifaceted approach, including appropriate wound dressing methods are made for the individual patient's needs. These methods aim to create an optimal environment for wound healing while addressing underlying factors help to impaired healing in diabetic patients. Through a combination of advanced wound care technologies and evidence-based practices, healthcare professionals can effectively manage diabetic wounds and improve patient outcomes.

Various studies discussing cadexomer iodine ointment versus povidine iodine ointment in diabetic ulcer dressing;

In a review study by Noda Y et al., (2009) "to assess the critical evaluation of cadexomer iodine ointment and povidone iodine ointment in wound dressing. "The quantities of iodine had an opposite effect on the interactions between PI sugar ointment and CI ointment with L-tyrosine. Whereas PI sugar ointment reacted with lecithin in a constant, iodine concentration-independent manner, CI ointment reacted with lecithin in a manner that was dependent on the concentration of iodine." However, PI sugar ointment interacted efficiently with L-tyrosine and less efficiently with lecithin at the clinically relevant iodine content (0.1, w/v%), whereas CI ointment reacted well with lecithin and less efficiently with L-tyrosine. These results suggest that PI sugar ointment and CI ointment have different characteristics for iodine reactivity and water absorption".[56]

In a review article by Murdoch R et al., (2013)" aato assess the role of povidone and cadexomer iodine in management of acute and chronic wound. Both povidone and cadexomer iodine are effective antibacterial agents that do not cause bacterial resistance, according to the literature. Reduced concentrations may be necessary in patients with severe immunocompromised individuals, renal failure, thyroid dysfunction, and major burns, hence caution is suggested while using them in these patients. In conclusion, the research supports the positive effects of povidone and cadexomer iodine on tissue and cells, especially in their most recent formulations. While povidone iodine is known for its usefulness in treating acute wounds that are infected, cadexomer iodine is excellent in healing chronic wounds. However, there are still unanswered questions, particularly when it comes to contrasting more recent povidone iodine formulations with older ones. Therefore, more study is necessary to give doctors using these antimicrobial medicines in wound care more precise information".[57]

In a study by Raju R et al., (2019)" to assess the efficacy of cadexomer iodine in treatment of chronic ulcer. "Both formulations of cadexomer iodine, ointment and powder, exhibited a significantly higher percentage reduction in ulcer size compared to standard care alone over the 12-week study period. Specifically, the reduction was 94.3% ± 10.6% for ointment and 90.4% ± 14.9% for powder, compared to 67.8% ± 21.8% for standard care. Additionally, a higher percentage of patients achieved complete wound healing with cadexomer iodine ointment (65.8%) and powder (58.1%) compared to standard care alone (20.0%) at the end of the 12 weeks." These findings indicate that cadexomer iodine enhances ulcer size reduction and promotes complete wound healing in chronic ulcers when compared to standard care alone.[58]

In a systematic review study by Woo K et al., (2021):" to assess the efficacy of topical cadexomer iodine treatment in chronic wounds. A total of 436 papers were found, 13 of which were comparison trials with an emphasis on study-relevant outcomes. When compared to standard of care (SOC), chronic wounds treated with cadexomer iodine ointment (CIOD) shown substantial decreases in exudate, pus/debris, slough, bioburden, and infection. In comparison to SOC, meta-analyses showed that CIOD therapy improved mean wound area reduction at eight weeks and enhanced total wound healing events. In particular, wounds treated with CIOD had a more than twofold healing rate compared to those not getting treatment, such as pressure ulcers, diabetic foot ulcers, and venous leg ulcers. These results highlight how well CIOD works to remove obstacles to the healing process in order to facilitate the healing of chronic wounds. Consequently, after preparing the wound bed and following treatment protocols".[59]

In a study conducted by Gupta S et al., (2021) "to assess the povidone iodine versus cadexomer iodine ointment in management of wound of chronic duration. Individuals who receive treatment with cadexomer iodine ointment show a markedly increased pace of wound healing ($p < 0.05$), as well as a marked reduction in bacterial overload and improved granulation tissue formation promotion. The use of cadexomer as a delivery system in conjunction with iodine ointment shows a higher rate of biofilm, slough, and debris reduction in addition to improving the stimulation of granulation tissue development. This results in both more efficient and successful wound healing as well as more affordable chronic wound care".[60]

In a study conducted by Gupta S et al., (2022) "to assess the outcome of cadexomer idodine and povidone iodine in wound management. A marked enhancement ($p < 0.05$) in the formation of granulation tissue was noted following the application of cadexomer ointment when contrasted with the use of povidone-iodine ointment. Both groups exhibited statistically significant decreases in ulcer dimensions and discharge; however, clinically, cadexomer ointment demonstrated superior efficacy in reducing ulcer size and minimizing discharge compared to povidone-iodine ointment. Cadexomer iodine ointment exhibited superior performance over povidone-iodine ointment in managing ulcers, as evidenced by higher rates of granulation tissue formation, greater reductions in ulcer size, and decreased discharge volume from the ulcers". [61]

In a review study conducted by Gupta S et al., (2022) to assess topical management of wound. "Due to differences in preparations and research methodologies, a number of studies that have looked at both povidone iodine (PI) and cadexomer iodine (CI) have produced inconsistent results. PI has a wide range of effects, low cytotoxicity, good tolerance, and antibacterial and anti-inflammatory qualities. A hydrophilic modified-starch polymer bead containing immobilized iodine, called CI, absorbs exudate from wounds and releases iodine molecules to provide long-lasting bactericidal effects. Both treatments promote wound healing and reduce the amount of germs in burns, ulcers, and chronic wounds." In terms of how well they work to reduce biofilm, shrink wounds, and encourage the production of granulation tissue, this review contrasts CI with PI. [62]

In a study conducted by Sharma R et al., (2023) "to assess the role of cadexomer iodine as debriding agent. Most of the patients, approximately 88%, showed no visible slough within a week, and by two weeks, all patients, 100%, were devoid of visible slough. Within a four-week period, 74% of patients achieved complete wound closure, while 22% experienced a reduction in total wound surface area ranging from 75% to 99%. In conclusion, in controlled settings, cadexomer iodine proves to be an effective topical agent for debriding infected wounds with visible slough and pus discharge, while also aiding in wound healing". [63]

In a study by Raj A et al., (2023) " to cadexomer versus povidone iodine in dressing of chronic leg ulcer. Patients treated with cadexomer iodine ointment demonstrated a significantly higher rate of wound healing ($p < 0.05$), along with a notable reduction in bacterial overload and enhanced granulation tissue formation. The combination of cadexomer as a delivery vehicle with povidone iodine ointment led to superior outcomes in reducing biofilm, slough, and debris, while promoting granulation tissue formation, ultimately accelerating wound healing and reducing the burden of managing chronic wounds. Given the prevalence of leg ulcers among diabetic patients, with over 60 individuals at risk in the study, it is recommended to further investigate the efficacy of cadexomer and povidone iodine ointments for the proper healing of diabetic leg ulcers".[64]

MATERIALS AND METHODS

Source of Data: The source of data were the patients with diabetic ulcer admitted in general surgery wards at a tertiary health care center

Study Design: Study design: Randomized control trial.

Study Period: From 2022 to 2023- 1 year

Sample Size: Sample size formula:

The minimum sample size formula based on two proportions is

$$n = \frac{(z_\alpha + z_\beta)^2 \bar{p}(1-\bar{p})}{d^2}$$

Where p_1 and p_2 are the proportions of the A group and B group.

$p = \frac{p_1 + p_2}{2}$ and $d = p_1 - p_2$

z_α is linked with the level of significance and z_β is linked with the power of the test. For 5% level of the significance $z_\alpha = 1.96$ and $z_\beta = 0.84$ for 85% power of the test.

The parameter considered in the calculation is the percentage of cases having decrease in wound surface area by $10cm^2$

By taking, p_1 = 38.8% and p_2 = 44.4% the sample size obtained is 50.

There would be two groups with size of **50** in each group.

Sampling technique: group A (CADEXOMER IODINE dressing) and group B (POVIDINE IODINE dressing) selected by simple random sampling.

Inclusion Criteria:

- Patient accepting to participate in study
- Patient in the age group of 18-75 years both sexes
- Patient with a diabetic ulcer.
- Ulcer size should be less than 10cm2

  Wegner grade 1 and 2 ulcers

Exclusion Criteria:

- Patient suffering from cardiovascular disease or on anticoagulant therapy.
- Patients having wound with exposure of tendon or bone.
- Patient with any immunosuppressive disease or on immunosuppressant therapy.
- Pregnancy
- Hypersensitivity to iodine formulations
- Uncontrolled diabetes hba1c >9%
- Renal failure s.creatinine ->3mg/dl
- Anemia <8gm/dl

Study protocol:

100 patients with chronic ulcers were taken. The testing group of 50 were given cadexomer iodine and the control group of 50 continued treatment with povidine iodine. In the first group, cadexomer iodine can be given 7 times/week, in 2nd group povidine iodine is applied 7times/week and patient wound healing is followed up regularly for both groups to analyze the results at 1, 2, 3, 4 weeks and area of the ulcer taken as main parameter of comparison.

Calculation of wound area:

The dimensions of the ulcer i.e. length, width and area were measured by outlining the ulcer over a sterile transparent film placed over it. This was followed by placing the film over graph paper and counting the number of squares also referred to as 'grid tracing'. The length of the smallest square is 1mm

The measurement of ulcer dimensions on day 0(x) = initial wound area and day 28(y) = final wound area. The reduction in area and percentage reduction in area are calculated as follows:

Wound area as on Day0 = x

Wound area as on Day28 = y

wound area reduction = x-y

% wound area reduction = $\frac{x-y}{x} x100$

Data collection procedure:

*****One-year randomized control trail

* an informed consent was obtained from the patients

*in patient individuals with diabetic foot ulcer were identified

* detailed history and examination would be done. History including =age, sex, h/o smoking, h/o diabetes, h/o hypertension treatment

Detailed examination and investigations

Fbs

Hba1c,viral markers, culture and sensitivity

Hb

Mini renal profile

Data of each patient were collected on a proforma which includes the following:

STATISTICAL ANALYSIS

The information was gathered using a standardized proforma and subsequently entered into an Excel spreadsheet. Statistical summaries such as means, standard deviations, frequencies, and percentages were computed. These summarized data were visually depicted through tables, figures, bar diagrams, and pie charts. Mean differences in continuous variables were assessed using the unpaired t-test, while categorical variables were analyzed using the chi-square test. A significance threshold of $p < 0.05$ was applied to all statistical analyses to determine statistical significance.

OBSERVATION & RESULTS

Present study included 100 patients fulfilling inclusion criteria. Among them 50 are grouped as cadexomer and 50 patients in povidine iodine group. The mean age of patients were comparable with not much difference between the groups.

Table 1: Comparison of mean age of patients between the groups

	Cadexomer		Povidine Iodine		p-value
	Mean	SD	Mean	SD	
AGE	59.1	11.5	61.1	10.9	0.52

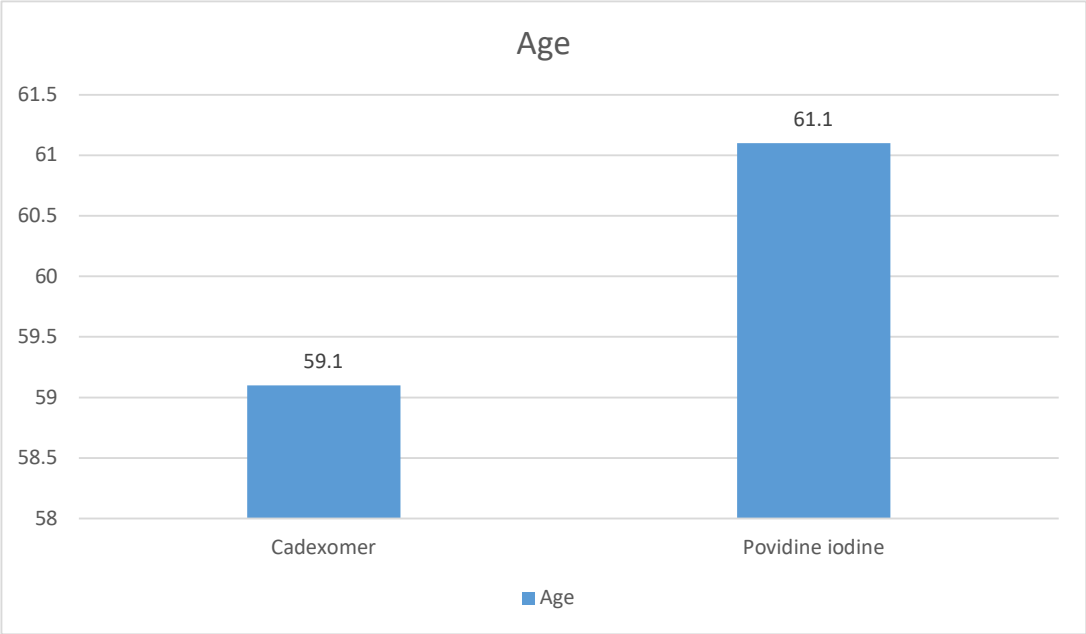

Figure 1: Comparison of mean age of patients between the groups

Table 2: On comparison of the gender, there is no significant difference between the groups

		Cadexomer		Povidine Iodine	
		Count	N %	Count	N %
Gender	Female	18	36.0%	14	28.0%
	Male	32	64.0%	36	72.0%

There is no significant difference in gender distribution between the group, however overall male preponderance is observed in the study participants.

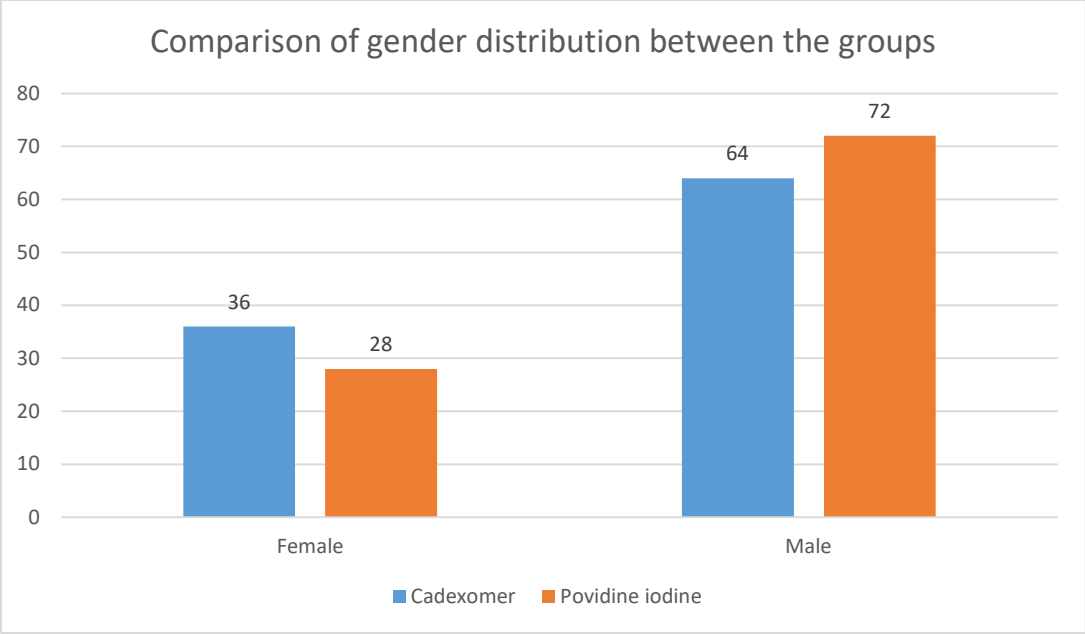

Figure 2: Comparison of gender distribution between the groups

Table 3: Comparison of the duration of diabetes mellitus between the groups

		Cadexomer		Povidine Iodine		Chi-square (p-value)
		Count	N %	Count	N %	
Duration of diabetes	1.0	12	24.0%	13	26.0%	2.33 (0.61)
	2.0	12	24.0%	17	34.0%	
	3.0	12	24.0%	9	18.0%	
	4.0	8	16.0%	8	16.0%	
	5.0	6	12.0%	3	6.0%	

There is no significant difference noted in the duration of diabetes mellitus among the patients between the groups.

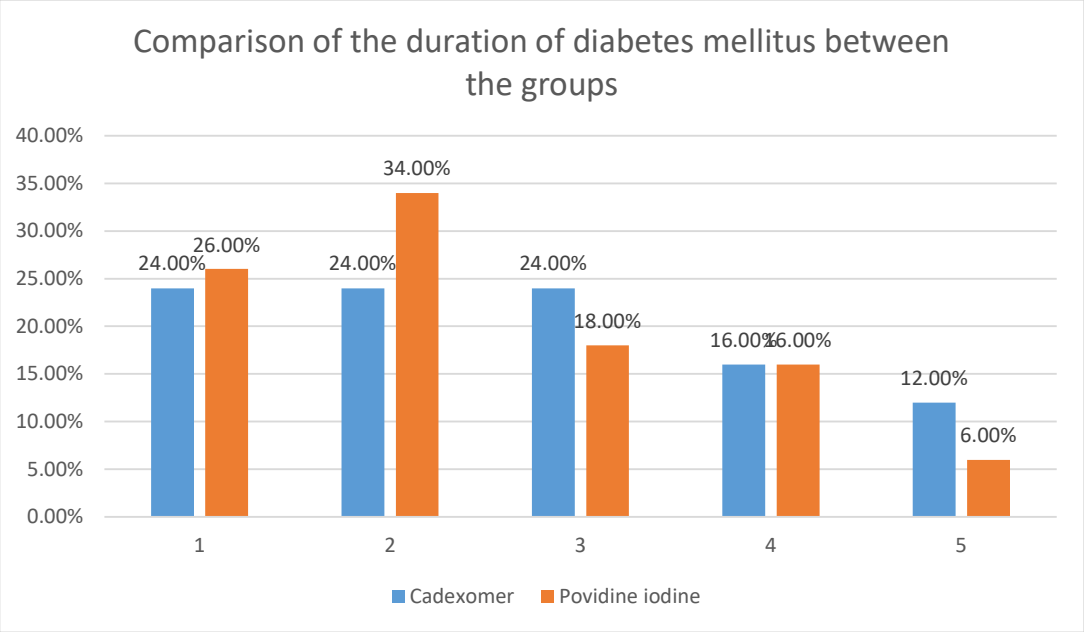

Figure 3: Comparison of the duration of diabetes mellitus between the groups

Table 4: Comparison of the site between the groups

		Cadexomer		Povidine Iodine		Chi-square
		Count	N %	Count	N %	(p-value)
SITE	DLF	20	40.0%	15	30.0%	3.21 (0.66)
	DRF	14	28.0%	18	36.0%	
	HLF	2	4.0%	2	4.0%	
	HRF	1	2.0%	3	6.0%	
	PLF	4	8.0%	6	12.0%	
	PRF	9	18.0%	6	12.0%	

There is no significant difference noted in distribution of site among the patients between the groups.

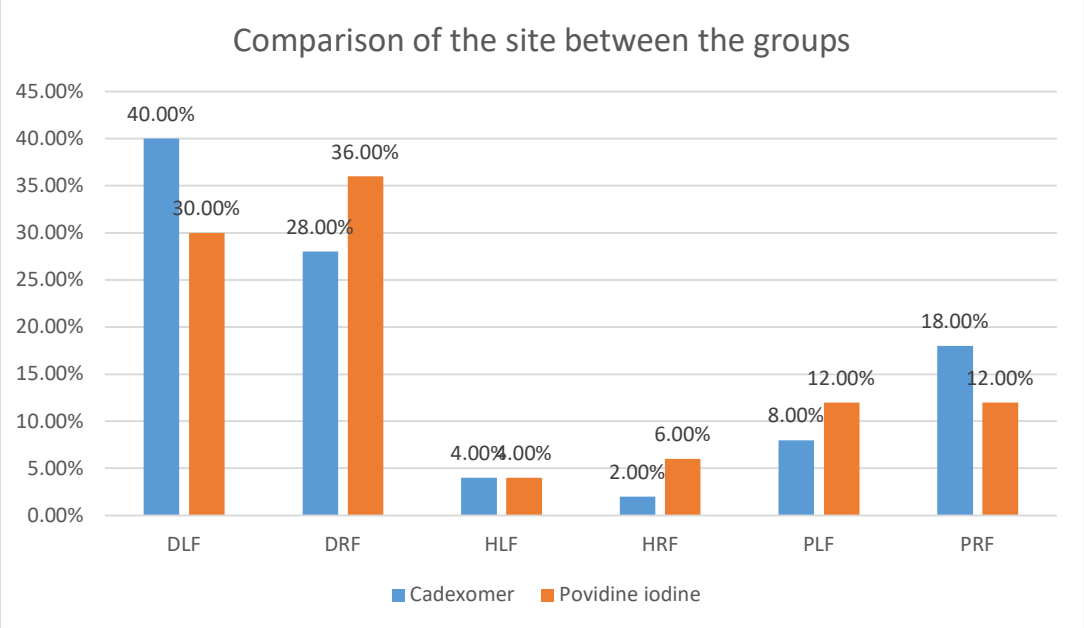

Figure 4: Comparison of the site between the groups

Table 5: Comparison of mean HbA1c level between the groups

	Cadexomer		Povidine Iodine		p-value
	Mean	SD	Mean	SD	
HBA1C	7.9	1.0	8.0	1.1	0.622

Comparison of mean HbA1c between the group, the mean level were comparable between the group with no significant difference.

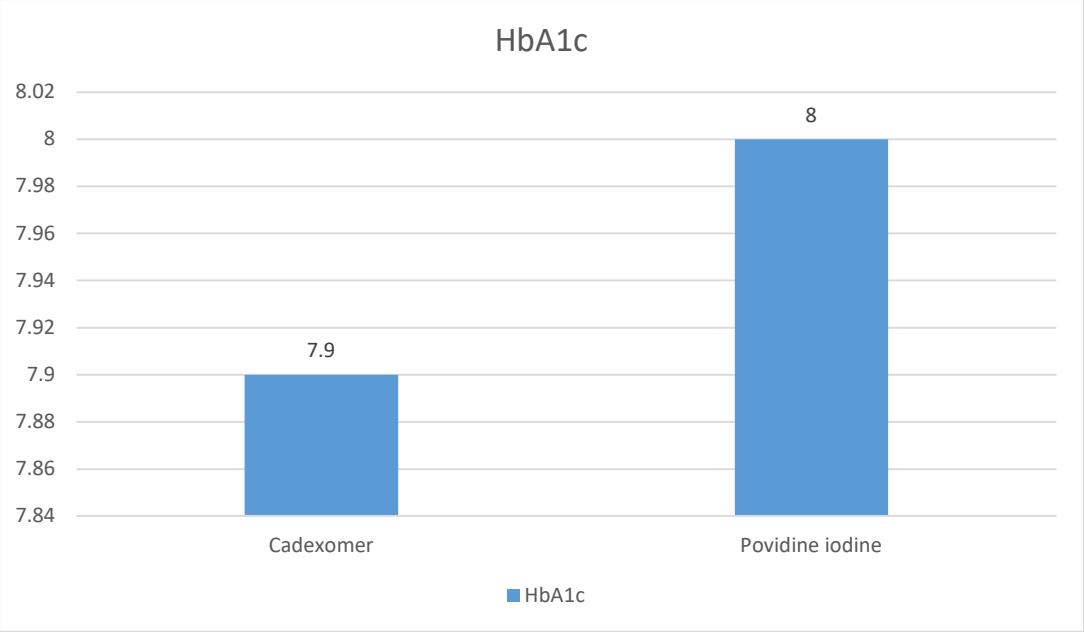

Figure 5: Comparison of mean HbA1c level between the groups

Table 6: Comparison of the area of wound at different point of time between groups

	Cadexomer		Povidine Iodine		p-value
	Mean	SD	Mean	SD	
Area day 0	26.81	6.28	24.82	7.92	0.166
Area day 28	19.37	4.38	21.42	7.40	0.01*

on comparison of the area between the group, there is significant lower area on day 28 in cadexomer group compared to the patients in povidine iodine group. ($p<0.05$)

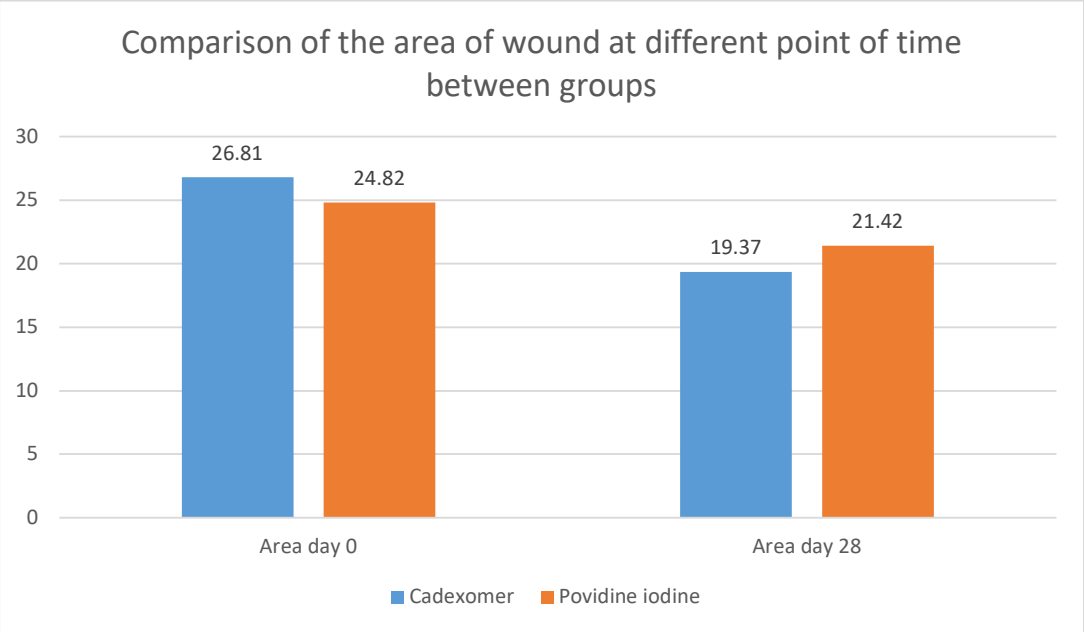

Figure 6: Comparison of the area of wound at different point of time between groups

Table 7: Comparison of the mean area reduction between the groups

	Cadexomer		Povidine Iodine		p-value
	Mean	SD	Mean	SD	
Reduction in area	7.44	3.50	3.39	1.47	0.01*
Reduction in area (%)	26.95	9.28	14.35	6.18	0.01*

Assessment of the reduction in area, there was significant rate of reduction of area in cadexomer group compared to povidine iodine.($p<0.05$)

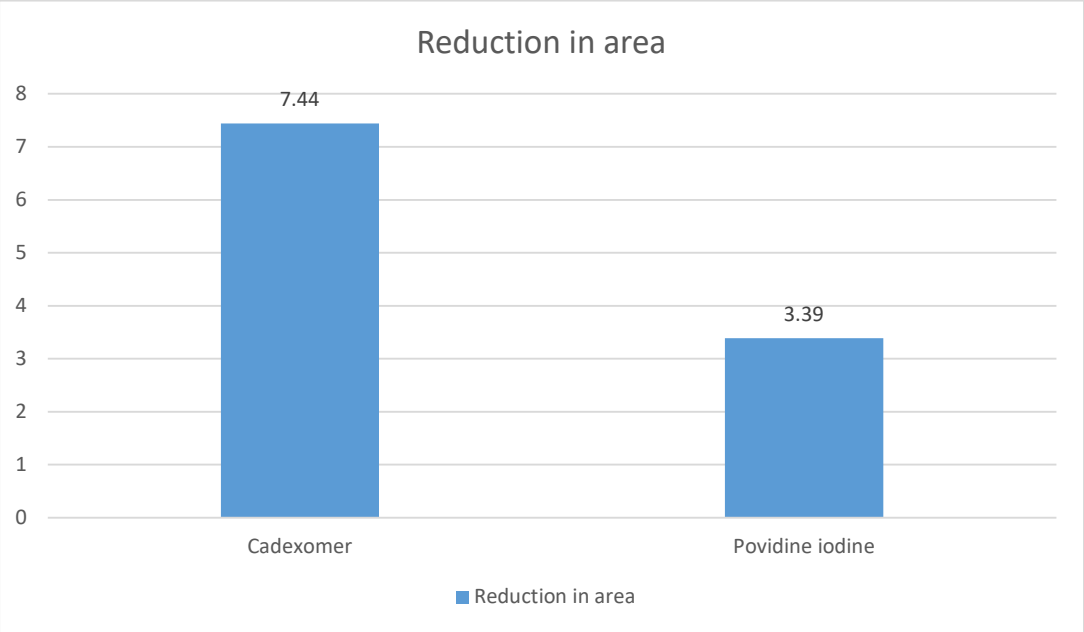

Figure 7: Comparison of the mean area reduction between the groups

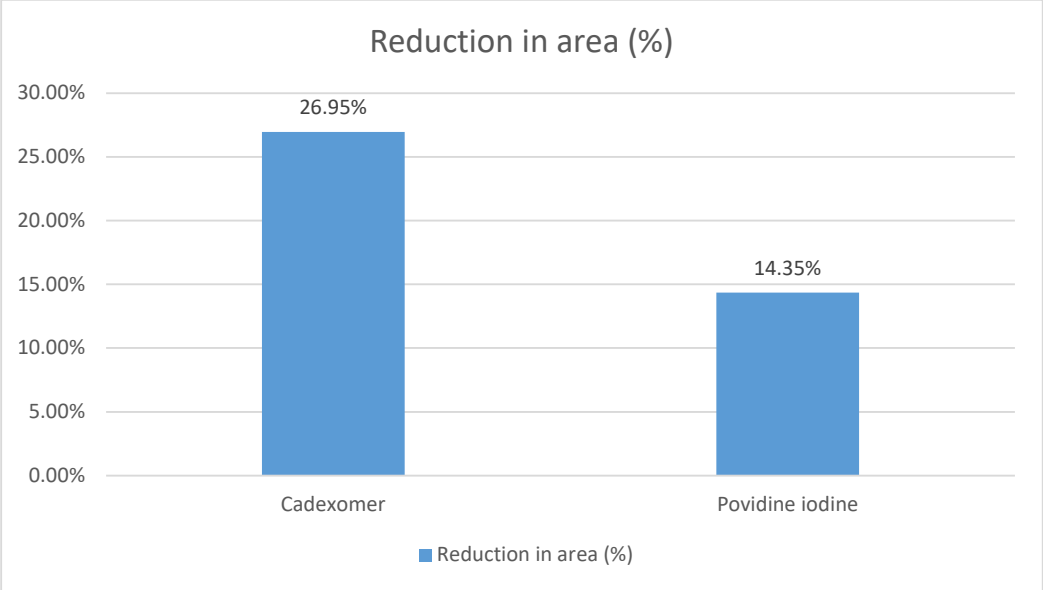

Figure 8: Comparison of the mean area reduction between the groups

Table 8: Comparison of the status of floor of wound between the groups

		Group			
		Cadexomer		Povidine Iodine	
		Count	Column N %	Count	Column N %
Floor day 0	S	50	100.0%	50	100.0%
Floor day 28	G	41	82.0%	28	56.0%
	S	9	18.0%	22	44.0%

The floor of ulcer was significant better in the patients with Cadexomer group showing granulation tissue compared to the patients in povidine iodine group. ($p<0.05$)

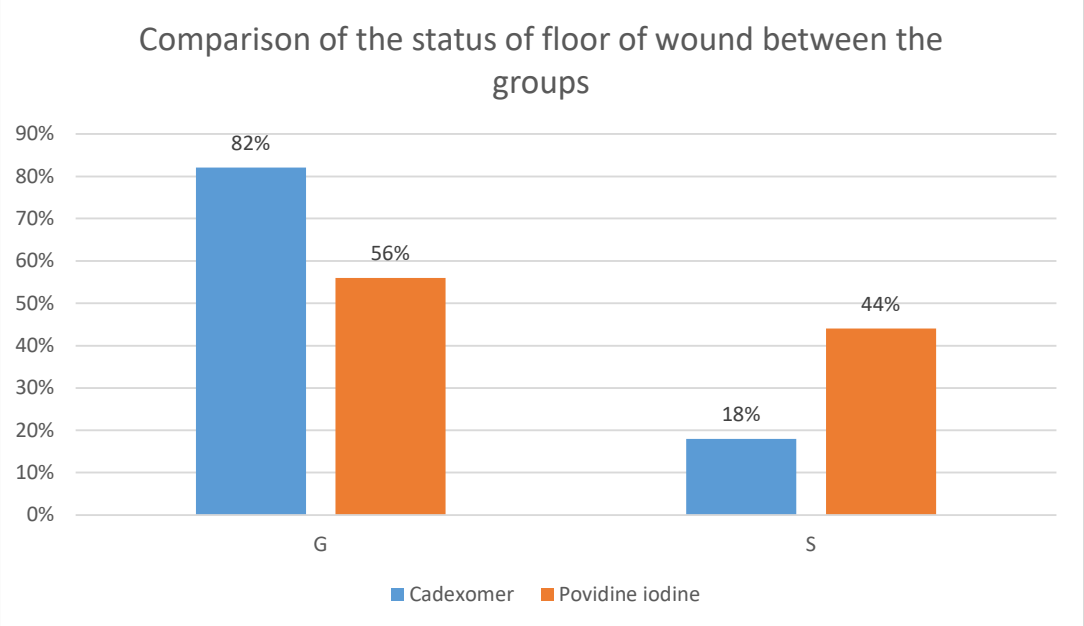

Figure 9: Comparison of the status of floor of wound between the groups

Table 9: Comparison of the mean pain score and total hospital stay between the groups

	Cadexomer		Povidine Iodine		p-value
	Mean	SD	Mean	SD	
Pain	1.5	.6	1.7	.7	0.143
Length of hospital stay	18.8	5.4	22.8	4.6	0.01*

On assessment of the mean pain score, there was lower pain score in Cadexomer group however this finding was not statistically significant.

The mean length of hospital stay in Cadexomer group (18.8±5.4) was significantly shorter compared to patients in povidine iodine group (22.8±4.6).($p<0.05$)

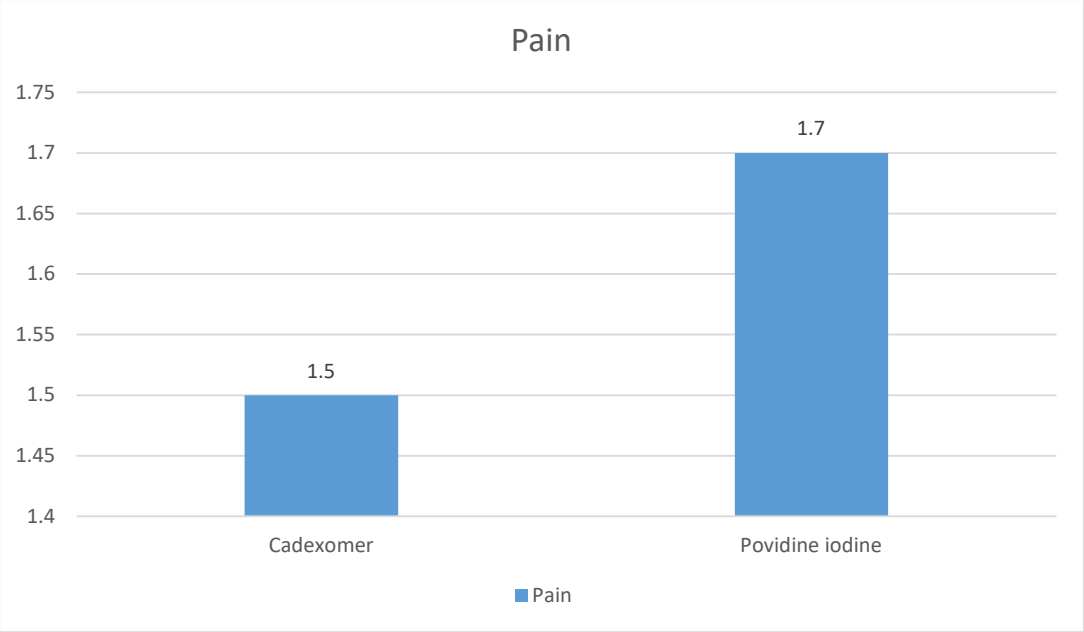

Figure 10: Comparison of the mean pain score between the groups

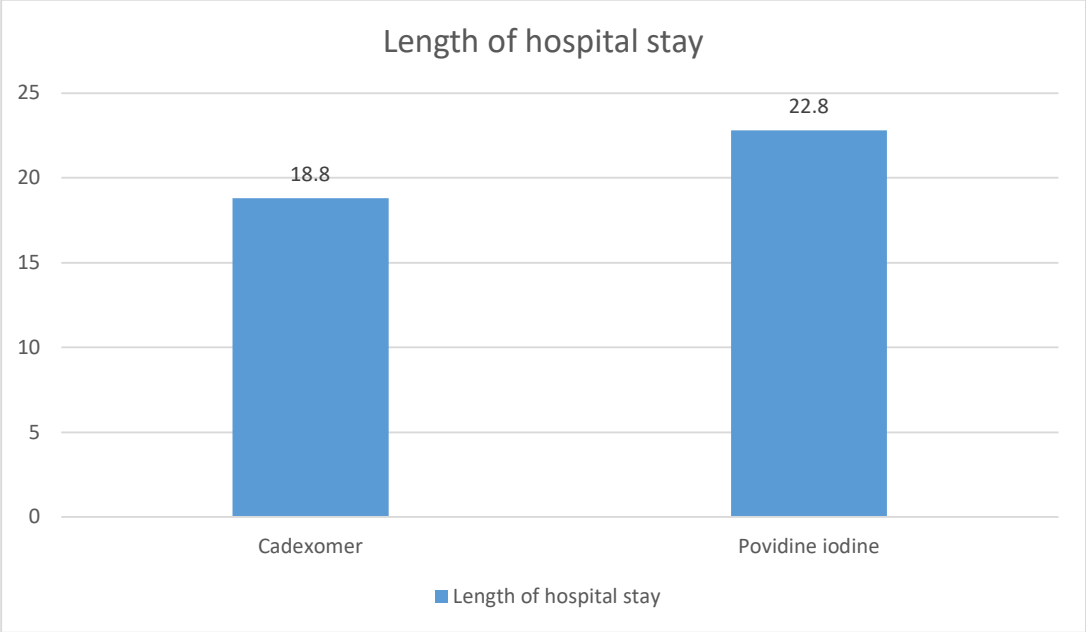

Figure 11: Comparison of the mean total hospital stay between the groups

DISCUSSION

Diabetic ulcers are a prevalent and severe complication of diabetes mellitus, posing a significant health burden globally and particularly in India, where the diabetic population is burgeoning. Effective management of these ulcers is crucial to prevent complications such as infections, amputations, and decreased quality of life. Among the various treatments, iodine-based formulations have long been recognized for their antiseptic properties in wound care.

Povidone iodine (PI) is a widely used antiseptic due to its broad-spectrum antimicrobial activity and ease of application. It functions by releasing free iodine when in contact with wound exudates, effectively controlling infections and aiding in wound healing. However, its use can be limited by potential drawbacks, including irritation and delayed healing due to iodine accumulation.

In contrast, cadexomer iodine (CI) represents an advancement in wound management. CI comprises iodine molecules encapsulated in a hydrophilic modified-starch polymer bead. These beads absorb wound exudates and gradually release iodine, ensuring a controlled and sustained antiseptic action. This mechanism reduces the risks associated with iodine toxicity and offers additional benefits such as enhanced desloughing, increased epithelial regeneration, and improved granulation tissue formation.

Despite the established use of PI and the promising attributes of CI, comparative research specifically tailored to diabetic ulcer management in the Indian population remains limited. This study aims to fill this gap by evaluating the efficacy, safety, and overall patient outcomes of cadexomer iodine ointment versus povidone iodine ointment in treating diabetic ulcers. The findings will provide empirical evidence to guide clinicians in selecting the most effective and patient-friendly

treatment option for diabetic ulcers, thereby improving patient care and optimizing healthcare resources.

Present study included total of 100 patients fulfilling inclusion criteria. Among them 50 were grouped in cadexomer and 50 patients in povidine iodine group. The mean age of patients were comparable (59.1yrs in group cadexomer and 61.1yrs in povidine iodine group) with no significant difference between the groups. There is no significant difference in gender distribution between the group, however overall male preponderance is observed in the study participants.

In similar to present study Raj A et al., documented majority in age group of 55 to 65yrs. Among them male preponderance was seen with baseline characteristics matched in both the groups.[64]

On comparison of the area between the group, there is significant lower area on day 28 in cadexomer group compared to the patients in povidine iodine group. ($p<0.05$) Also the reduction in area, there was significant rate of reduction of area in cadexomer group compared to povidine iodine.($p<0.05$) The floor of ulcer was significant better in the patients with Cadexomer group showing granulation tissue compared to the patients in povidine iodine group. ($p<0.05$)

In line with present study findings, Raju R et al., documented reduction of wound size was 94.3% ± 10.6% for ointment and 90.4% ± 14.9% for powder, compared to 67.8% ± 21.8% for standard care. Additionally, a higher percentage of patients achieved complete wound healing with cadexomer iodine ointment (65.8%) and powder (58.1%) compared to standard care alone (20.0%) at the end of the 12 weeks. These findings indicate that cadexomer iodine enhances ulcer size reduction and promotes complete wound healing in chronic ulcers when compared to standard care alone.[58]

In concordance to present study Murdoch R et al., documented Cadexomer iodine demonstrates effectiveness in treating chronic wounds, whereas povidone iodine is noted for its efficacy in infected acute wounds. Nevertheless, research gaps exist, notably in comparing newer formulations of povidone iodine with traditional preparations. Hence, further research is essential to provide clearer evidence for clinicians utilizing these antimicrobial agents in wound management.[57] In meta-analysis the findings underscore the efficacy of CIOD in promoting healing of chronic wounds by addressing barriers to healing. Therefore, CIOD should be considered in wound bed preparation and treatment protocols.[59]

In a different research by Gupta S et al., patients who received cadexomer iodine ointment showed a markedly faster rate of wound healing ($p < 0.05$), along with a considerable reduction in bacterial overload and improved granulation tissue formation promotion. The use of cadexomer as a delivery system in conjunction with iodine ointment shows a higher rate of biofilm, slough, and debris reduction in addition to improving the stimulation of granulation tissue development. This results in both more efficient and successful wound healing as well as more affordable chronic wound care.[60] In line to present study Gupta S et al., found that Cadexomer iodine ointment exhibited superior performance over povidone-iodine ointment in managing ulcers, as evidenced by higher rates of granulation tissue formation, greater reductions in ulcer size, and decreased discharge volume from the ulcers. [61]

Sharma R et al., documented approximately 88%, showed no visible slough within a week, and by two weeks, all patients, 100%, were devoid of visible slough. Within a four-week period, 74% of patients achieved complete wound closure, while 22% experienced a reduction in total wound surface area ranging from 75% to 99%.

cadexomer iodine proves to be an effective topical agent for debriding infected wounds with visible slough and pus discharge, while also aiding in wound healing. [63]

In similar another study by Gupta S et al., documented a better and healthy granulation tissue in the cadexomer ointment group compared to the patients in povidine iodine powder group.[61]

The mean length of hospital stay in Cadexomer group (18.8±5.4) was significantly shorter compared to patients in povidine iodine group (22.8±4.6).($p<0.05$)

In similar to present Raj A et al., documented with significant shorter duration of hospital stay among the cadexomer group compared to povidine iodine group.[64]

In a study comparing the effectiveness of cadexomer iodine and povidone iodine ointments for diabetic ulcer treatment, 100 patients were divided equally between the two groups. Both groups were matched for age, gender, diabetes duration, ulcer location, and initial HbA1c levels to ensure a fair comparison. The findings revealed that cadexomer iodine significantly outperformed povidone iodine in reducing ulcer size over 28 days ($p<0.05$), promoting better wound healing characterized by enhanced granulation tissue ($p<0.05$), and shortening hospital stays ($p<0.05$), despite similar pain levels between treatments. These results suggest that cadexomer iodine not only accelerates ulcer reduction but also improves the quality of healing and reduces healthcare resource use, making it a more effective and preferable option for diabetic ulcer management.

CONCLUSION

This study offers a comparative analysis of the efficacy of cadexomer iodine ointment versus povidone iodine ointment in treating diabetic ulcers. The investigation included 100 patients divided equally into two groups, one receiving cadexomer iodine and the other povidone iodine. Both groups were similar in terms of age distribution and duration of diabetes, and no significant differences were observed in gender distribution, site of ulcer, or baseline HbA1c levels, ensuring a balanced comparison.

Cadexomer iodine ointment showed superior performance in reducing the ulcer area after 28 days of treatment. Patients in the cadexomer iodine group experienced a significantly greater reduction in ulcer size compared to those in the povidone iodine group. This indicates that cadexomer iodine is more effective in promoting the healing of diabetic ulcers. Additionally, the cadexomer iodine group displayed a more pronounced rate of reduction in ulcer area, underscoring its efficacy in wound healing over the study period ($p<0.05$).

Further, the quality of the ulcer floor in the cadexomer iodine group was significantly better, characterized by the presence of granulation tissue, in comparison to the povidone iodine group. This suggests that cadexomer iodine not only aids in reducing the ulcer size but also enhances the quality of the wound bed, facilitating better overall healing ($p<0.05$).

Pain assessment showed that patients treated with cadexomer iodine had a lower mean pain score, although this difference was not statistically significant. Importantly, the mean length of hospital stay was significantly shorter for the cadexomer iodine group (18.8±5.4 days) compared to the povidone iodine group

(22.8±4.6 days). This reduction in hospital stay reflects a potential advantage in terms of healthcare resource utilization and patient convenience ($p<0.05$).

In conclusion, cadexomer iodine ointment is more effective than povidone iodine ointment for the treatment of diabetic ulcers. It leads to greater reduction in ulcer size, better wound bed quality, and shorter hospital stays, making it a preferable option in clinical practice for managing diabetic ulcers. These findings highlight the benefits of cadexomer iodine, advocating for its use as a more efficient and patient-friendly treatment alternative.

SUMMARY

- Present study included total of 100 patients fulfilling inclusion criteria. Among them 50 were grouped in cadexomer and 50 patients in povidine iodine group. The mean age of patients were comparable with no significant difference between the groups.
- There is no significant difference in gender distribution between the group, however overall male preponderance is observed in the study participants.
- There is no significant difference noted in the duration of diabetes mellitus among the patients between the groups.
- There is no significant difference noted in distribution of site among the patients between the groups.
- Comparison of mean HbA1c between the group, the mean level were comparable between the group with no significant difference.
- On comparison of the area between the group, there is significant lower area on day 28 in cadexomer group compared to the patients in povidine iodine group. ($p<0.05$)
- Assessment of the reduction in area, there was significant rate of reduction of area in cadexomer group compared to povidine iodine.($p<0.05$)
- The floor of ulcer was significant better in the patients with Cadexomer group showing granulation tissue compared to the patients in povidine iodine group. ($p<0.05$)
- On assessment of the mean pain score, there was lower pain score in Cadexomer group however this finding was not statistically significant.
- The mean length of hospital stay in Cadexomer group (18.8 ± 5.4) was significantly shorter compared to patients in povidine iodine group (22.8 ± 4.6).($p<0.05$)

LIMITATIONS

Despite the promising results several limitations need to be addressed. The fact that the study was limited to a single tertiary healthcare facility made its findings less broadly applicable.

A further factor that could impact the analysis's statistical power is the sample size, which was somewhat small. Nutritional status is potential factors impacting wound healing that were not investigated in this study.

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ANNEXURES – I

INFORMED CONSENT FORM

CADEXOMER IODINE OINTMENT VS POVIDINE IODINE OINTMENT IN DIABETIC ULCER DRESSING- A RANDOMISED CONTROL TRIAL AT A TERITIARY CARE CENTER

Name of Student/Principal Investigator: BH0121015

Objective: TO COMPARE EFFICACY OF WOUND HEALING BETWEEN CADEXOMER IODINE AND POVIDINE IODINE AND THE ABILITY TO DECREASE THE MEDIAN HOSPITAL STAY TIME.

Introduction: This study is to compare the outcome of PI ointment and CI ointment for wound management and overcome the limitations of conventionally used PI ointment in terms of de-sloughing agent, increased epithelial regeneration, and promotion of granulation tissue formation, wound contractility, and neo vascularization

Explanation of procedure:

100 patients with chronic ulcers can be taken. The testing group of 50 will be given cadexomer iodine and the control group of 50 will continue treatment with povidine iodine. In the first group, cadexomer iodine can be given 7 times/week , in 2^{nd} group povidine iodine is applied 7times/week and patient wound healing is followed up regularly for both groups to analyze the results at 1, 2, 3, 4 weeks and area of the ulcer taken as main parameter of comparison.

Withdrawal from participation in the study: Participation in this study is voluntary. 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: You will/will not have nor get any benefits by participating in this study. The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

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.

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

Questions: in case of any questions -contact BH0121015. 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 "**CADEXOMER IODINE OINTMENT VS POVIDINE IODINE OINTMENT IN DIABETIC ULCER DRESSING-A RANDOMISED CONTROL 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

SCREENING:

Screening No. ☐☐

Enrollment No. /IP No. ☐☐☐☐☐☐☐

Date of Screening ☐☐ ☐☐ ☐☐☐☐

First Name ☐☐☐☐☐☐☐☐

Middle Name ☐☐☐☐☐☐☐

Last Name ☐☐☐☐☐☐☐☐

Age(Years) ☐☐

Address

H No. ☐☐☐☐☐

Street ☐☐☐☐☐☐☐☐☐

Taluka ☐☐☐☐☐☐☐☐☐

District ☐☐☐☐☐☐☐☐☐

Phone No.1 ☐☐☐☐☐☐☐☐☐☐

Phone No.2 ☐☐☐☐☐☐☐☐☐☐

Patient with diabetic leg ulcer:

- Yes ☐
- No ☐

Patient age above 18:

- Yes ☐
- No ☐

Applicant is willing to give consent

- Yes ☐
- No ☐

Patient has no associated illness or complications:

- Yes ☐
- No ☐

FINAL RESULT

- Ineligible ☐
- Eligible but refused ☐
- Eligible and participating ☐

PROFORMA

Name: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐
DOA: ☐☐ ☐☐ ☐☐☐☐
Age: ☐☐ YEARS
Sex: ☐☐
Occupation:
☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Address:

H No. ☐☐☐☐☐
Street ☐☐☐☐☐☐☐☐☐
Taluka ☐☐☐☐☐☐☐☐☐
District ☐☐☐☐☐☐☐☐☐
Phone No.1 ☐☐☐☐☐☐☐☐☐☐
Phone No.2 ☐☐☐☐☐☐☐☐☐☐

CHIEF COMPLAINTS:

Leg ulcer– ☐
Pain – ☐
Duration- ☐☐ month

H/O PRESENT ILLNESS:

ULCER- ☐
LOCATION: 1.RIGHT LOWER LIMB ☐ 2.LEFT LOWER LIMB ☐
ONSET: 1.INSIDIOUS ☐ 2.SUDDEN ☐ 3. TRAUMATIC ☐
DURATION: ☐ DAYS ☐
PROGRESSIVE ☐
DISCHARGE: 1.SEROUS ☐ 2.PURULENT ☐

FOUL SMELLING: ☐
C/O EPISODES OF FEVER- ☐
C/O PAIN-☐
DURATION OF PAIN- ☐☐ DAYS

PAST HISTORY:
K/C/O T2DM SINCE:☐☐ MONTHS/YEARS
H/O any Chronic drug use- ☐
H/O HTN - ☐
H/O previous surgery – ☐
H/O PVD -☐
H/O VARICOSE VEINS: ☐
H/O SIMILAR COMPLAINS IN THE PAST –IN SAME OR OPPOSITE ☐
LIMB-
PERSONAL HISTORY:
Smoker - ☐
Alcoholic-☐

GENERAL PHYSICAL EXAMINATION:
Nutritional status- 1.WELL BUILT☐ 2.POORLY BUILT ☐
Pallor - ☐
Icterus-☐
Cyanosis/ clubbing/ edema- ☐
Generalized/ regional lymphadenopathy - ☐
Pulse rate- ☐☐☐ BPM
Blood pressure- ☐☐☐ /☐☐☐ MMHG

LOCAL EXAMINATION:
SITE:
RIGHT LOWER LIMB ☐
LEFT LOWER LIMB ☐

SIZE: ☐☐ X ☐☐ CMS

FLOOR:
1.GRANULATING☐ 2.SLOUGH ☐

BASE:
1.BONE ☐ 2.MUSCLE☐

DISCHARGE:
1.SEROUS ☐ 2.PURULENT ☐

TENDERNESS- ☐
PERIPHERAL PULSES: ☐

SURROUNDING AREA: ☐

- ERYTHEMA- ☐
- EDEMA- ☐
- PERIPHERAL PULSES- ☐
- VARICOSE VEINS-

SYSTEMIC EXAMINATION

PER ABDOMEN- SOFT, NON TENDER ☐
CARDIO VASCULAR SYSTEM – normal- ☐
RESPIRATORY SYSTEM – normal- ☐
CENTRAL NERVOUS SYSTEM –normal ☐

DIAGNOSIS:

INVESTIGATIONS:

ROUTINE ☐
FBS ☐ <110 MG/DL ☐ >110MG/DL ☐
HbA1c ☐ >6 % ☐ <6% ☐
UKB- ☐

TREATMENT GIVEN:

CADEXOMER IODINE ☐
POVIDINE IODINE ☐

IV/ORAL ANTIBIOTICS: ☐
DIABETIC MANAGEMENT: ☐
BLOOD SUGARS UNDER CONTROL: ☐

OBSERVATIONS:

Wound area as on Day 0 - ☐☐ CM^2
Wound area on day 7-- ☐☐ CM^2
Wound area on day 14-- ☐☐ CM^2
Wound area on day 21-- ☐☐ CM^2
Wound area as on Day 28 - ☐☐ CM^2
wound area reduction - ☐☐ CM^2
% wound area reduction- ☐☐ %
Floor of ulcer as on Day 0-
1. GRANULATING ☐
2. SLOUGH ☐

Floor of ulcer as on Day 28-

1. GRANULATING ☐
2. SLOUGH ☐

C/O PAIN :

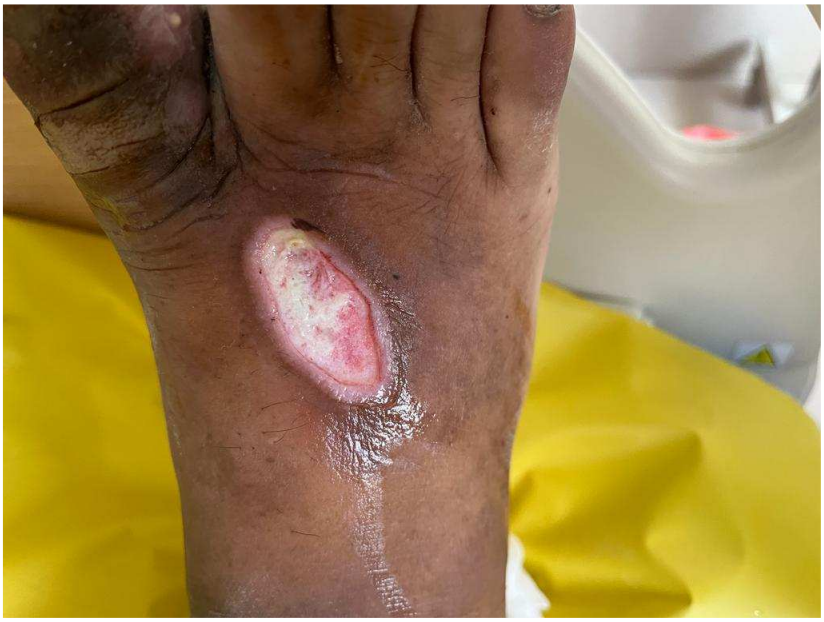
1.REDUCED ☐
2.REMAINED SAME ☐
3.INCREASED ☐
4.NOT APPLICABLE ☐

LENGTH OF HOSPITAL STAY:

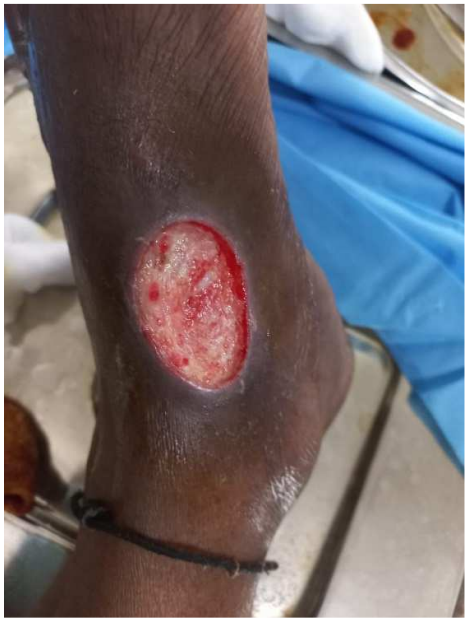
CADEXOMER IODINE ☐ DAYS
POVIDINE IODINE ☐ DAYS

ANNEXURE III

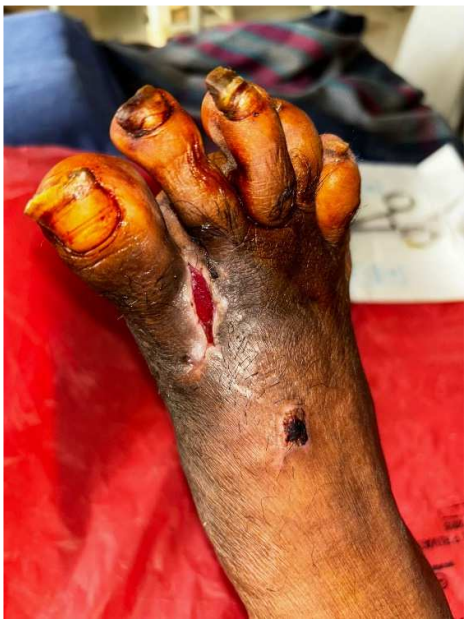
Case 1



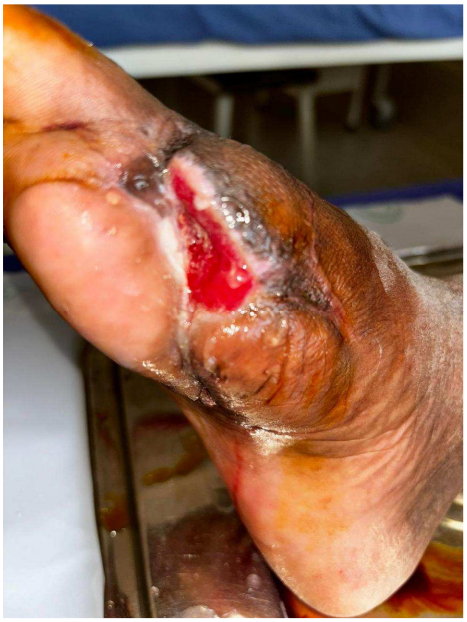
Case 2



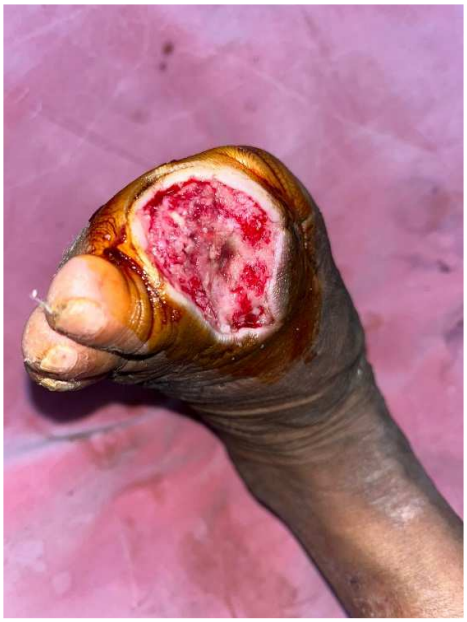
Case 3



Case 4

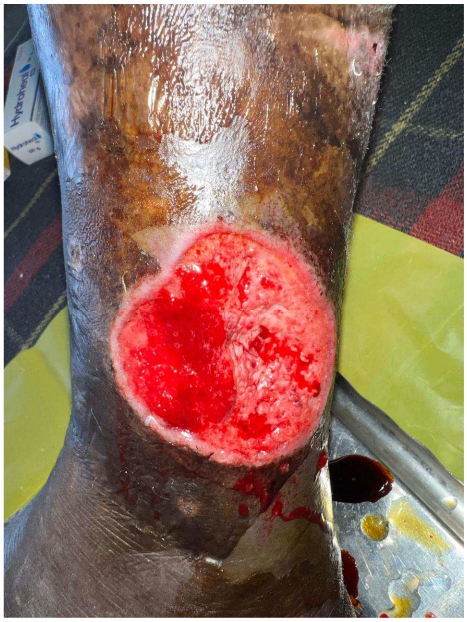


Case 4



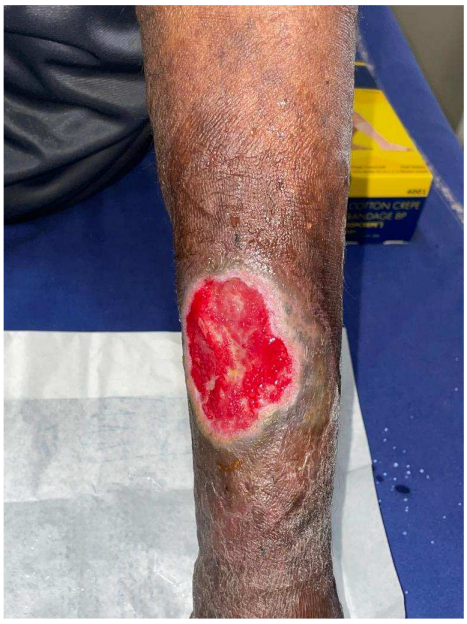
Case 5

Case 6

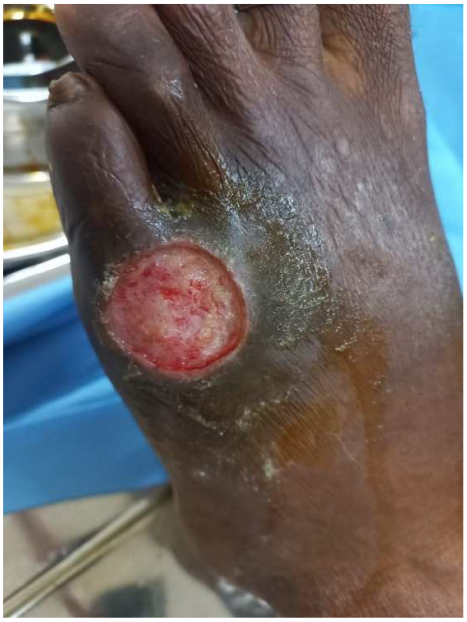


A

Case 7



Case 8



ANNEXURE IV

KEY TO MASTER CHART

DURATION OF DIABETES:

0-4 YRS - 1

5-9 YRS -2

10-14 YRS - 3

15-19 YRS - 4

>/= 20 YRS - 5

HBA1C:

6.5-7.9 = CONTROLLED

>/= 8. = UNCONTROLLED

SITE:

DRF DORSUM RIGHT FOOT

PRF PLANTAR RIGHT FOOT

DLF DORSUM LEFT FOOT

PLF PLANTAR LEFT FOOT

HRF HEEL RIGHT FOOT

HLF HEEL LEFT FOOT

MASTERCHART

S.NO	IP NO	AGE	DURATION OF DIABE	SEX	CADEX OMER	POVIDINE IODINE	SITE	HBA1C	DAY 0	DAY 28	REDUCTION IN	%REDUCTION IN AREA	FLOOR DAY0	FLOOR DAY28	PAIN	LENGTH OF HOSPITAL STAY
1	10038588	56	3	Male	YES	NO	DLF	7.1	23.50	18.96	4.54	19.31914894	S	G	1	21
2	10027855	70	4	Male	YES	NO	DRF	7.9	23.70	19.20	4.50	18.98734177	S	G	1	21
3	10043943	54	2	Male	YES	NO	DLF	6.9	32.40	20.50	11.90	36.72839506	S	G	1	14
4	6555216	63	5	Male	YES	NO	DRF	9	14.30	12.86	1.44	10.06993007	S	S	2	28
5	10035012	52	3	Male	YES	NO	PLF	8.4	15.40	12.00	3.40	22.07792208	S	G	2	21
6	10014152	64	2	Female	YES	NO	PLF	7.1	25.40	15.60	9.80	38.58267717	S	G	1	14
7	1157708	43	4	Male	YES	NO	HRF	6.8	25.25	19.50	5.75	22.77227723	S	G	1	21
8	1915996	67	1	Male	YES	NO	DRF	7.6	34.50	24.00	10.50	30.43478261	S	G	1	14
9	6473377	58	1	Male	YES	NO	PLF	9.2	25.86	22.50	3.36	12.99303944	S	S	2	28
10	6928984	53	2	Male	YES	NO	DRF	6.7	35.63	21.00	14.63	41.06090373	S	G	1	14
11	6990849	48	1	Male	YES	NO	DLF	7.4	29.66	21.84	7.82	26.36547539	S	G	2	14
12	6897024	70	5	Male	YES	NO	PRF	6.8	27.34	16.56	10.78	39.42940746	S	G	1	14
13	1158129	60	3	Male	YES	NO	DLF	7.6	31.10	22.00	9.10	29.26045016	S	G	1	14
14	1038888	62	2	Male	YES	NO	DLF	8.4	34.55	28.20	6.35	18.37916064	S	G	2	21
15	10042913	65	4	Male	YES	NO	PRF	10.7	17.83	15.96	1.87	10.48794167	S	S	3	28
16	10044291	40	3	Female	YES	NO	DLF	7.7	27.20	20.30	6.90	25.36764706	S	G	2	21
17	10043375	63	2	Male	YES	NO	PRF	7.2	33.00	21.20	11.80	35.75757576	S	G	1	14
18	10043528	72	1	Male	YES	NO	DLF	7.5	25.40	17.26	8.14	32.04724409	S	G	1	14
19	10045355	68	3	Male	YES	NO	DRF	10	21.96	19.80	2.16	9.836065574	S	S	3	28
20	10039373	75	1	Male	YES	NO	HLF	9.3	24.60	20.30	4.30	17.4796748	S	G	2	21
21	10050618	65	1	Female	YES	NO	DLF	7.6	14.30	10.10	4.20	29.37062937	S	G	2	28
22	1167694	63	5	Female	YES	NO	PRF	8.4	24.56	20.78	3.78	15.39087948	S	S	2	21
23	10053063	52	4	Male	YES	NO	DRF	7.7	15.50	11.66	3.84	24.77419355	S	G	3	21

24	10051933	66	1	Male	YES	NO	PRF	6.9	27.50	17.20	10.30	37.45454545	S	G	1	14
25	10039373	65	5	Female	YES	NO	DRF	6.8	36.00	25.70	10.30	28.61111111	S	G	1	14
26	10042023	48	3	Female	YES	NO	DLF	7.1	23.68	14.90	8.78	37.0777027	S	G	1	14
27	10050077	36	1	Female	YES	NO	DLF	8.5	34.20	22.00	12.20	35.67251462	S	G	1	14
28	10052569	40	4	Female	YES	NO	DLF	8.4	15.60	11.20	4.40	28.20512821	S	G	2	28
29	10043294	42	3	Female	YES	NO	PRF	7.2	32.80	22.00	10.80	32.92682927	S	G	1	14
30	10059117	60	2	Male	YES	NO	DLF	8.2	25.48	16.24	9.24	36.26373626	S	G	1	14
31	66232254	60	2	Female	YES	NO	DLF	9.9	25.60	22.40	3.2	12.5	S	S	2	28
32	1201805	50	3	Female	YES	NO	DRF	6.7	26.8	19.6	7.2	26.86567164	S	G	2	21
33	1199098	59	2	Male	YES	NO	DLF	8	27.55	21	6.55	23.77495463	S	G	1	21
34	6530851	51	2	Male	YES	NO	PRF	10.4	32.44	29.8	2.64	8.13810111	S	S	3	28
35	1054125	40	1	Male	YES	NO	DRF	7.8	19.4	14.2	5.2	26.80412371	S	G	2	21
36	1051486	74	3	Male	YES	NO	DLF	8.7	21.2	17.8	3.4	16.03773585	S	G	2	28
37	1156769	43	2	Male	YES	NO	DRF	7.7	33.5	23.3	10.2	30.44776119	S	G	1	14
38	6475567	75	4	Male	YES	NO	PLF	8.2	32.9	26.6	6.3	19.14893617	S	G	1	21
39	6188538	41	1	Male	YES	NO	DLF	7.7	27.7	21.2	6.5	23.46570397	S	G	1	21
40	6326114	55	3	Female	YES	NO	DRF	7.6	29.34	20.56	8.78	29.93	S	G	1	14
41	1200218	75	5	Female	YES	NO	DRF	7.2	33.00	21.20	11.80	35.75757576	S	G	1	14
42	1176857	65	4	Male	YES	NO	HLF	7.5	25.40	17.26	8.14	32.04724409	S	G	1	14
43	1166912	63	1	Female	YES	NO	DLF	9.3	24.60	20.30	4.30	17.4796748	S	S	2	21
44	4417601	52	5	Male	YES	NO	PRF	7.6	14.30	10.10	4.20	29.37062937	S	S	2	21
45	6390081	66	3	Male	YES	NO	DRF	7.6	34.50	24.00	10.50	30.43478261	S	G	1	14
46	1139736	65	1	Male	YES	NO	PRF	6.8	27.34	16.56	10.78	39.42940746	S	G	1	14
47	1199203	48	4	Female	YES	NO	DRF	6.7	35.63	21.00	14.63	41.06090373	S	G	1	14
48	7096596	80	3	Female	YES	NO	DLF	7.4	29.66	21.84	7.82	26.36547539	S	G	2	14
49	6792266	75	2	Female	YES	NO	DLF	6.8	27.34	16.56	10.78	39.42940746	S	G	1	14
50	1199675	78	2	Female	YES	NO	DLF	8.5	34.20	22.00	12.20	35.67251462	S	G	1	14

DURATION OF DIABETES	SEX	CADEXOMER	POVIDINE IODINE	SITE	HBA1C	AREA D0	AREA D 28	REDUCTION IN AREA	%REDUCTION IN AREA	FLOOR D0	FLOOR D 28	PAIN	LENGTH OF HOSPITAL STAY
3	Male	NO	YES	PLF	7.9	35.46	31.82	3.64	10.26509	S	G	2	21
4	Male	NO	YES	PLF	8.2	31.34	28.35	2.99	9.540523	S	G	2	21
2	Male	NO	YES	DRF	8.4	26.81	23.66	3.15	11.74935	S	G	2	21
5	Male	NO	YES	PRF	7.4	35.47	30.70	4.77	13.44798	S	G	1	21
2	Male	NO	YES	PLF	6.8	11.65	9.80	1.85	15.87983	S	S	2	28
3	Male	NO	YES	DRF	7.7	13.67	11.80	1.87	13.67959	S	S	2	28
1	Male	NO	YES	DRF	8.9	35.23	31.67	3.56	10.10502	S	S	3	28
3	Female	NO	YES	DLF	6.9	12.80	9.68	3.12	24.375	S	G	3	21
4	Male	NO	YES	DLF	7.1	29.00	25.37	3.63	12.51724	S	G	1	28
1	Male	NO	YES	PRF	7.8	26.78	23.45	3.33	12.43465	S	S	1	28
1	Male	NO	YES	DLF	7	25.34	21.99	3.35	13.22021	S	S	1	21
3	Male	NO	YES	HRF	9	32.18	28.94	3.24	10.06837	S	G	2	21
1	Male	NO	YES	DRF	7.2	16.78	14.16	2.62	15.61383	S	G	2	21
3	Female	NO	YES	HLF	6.8	9.80	8.20	1.60	16.32653	S	S	2	28
4	Female	NO	YES	DRF	7.4	19.20	11.10	8.10	42.1875	S	G	1	14
2	Female	NO	YES	DLF	8.8	23.56	21.34	2.22	9.42275	S	S	1	28
4	Male	NO	YES	DRF	6.7	14.72	12.56	2.16	14.67391	S	S	2	28
3	Female	NO	YES	PRF	8.6	31.80	27.91	3.89	12.2327	S	G	2	21
5	Male	NO	YES	PLF	10.2	25.60	22.86	2.74	10.70313	S	G	2	28
3	Male	NO	YES	DLF	9	19.67	17.77	1.90	9.65938	S	S	3	28
2	Male	NO	YES	DRF	7.6	33.18	29.42	3.76	11.33213	S	G	2	21
3	Male	NO	YES	HRF	9.7	34.67	29.72	4.95	14.27747	S	G	1	14
2	Male	NO	YES	PRF	7.9	22.34	18.79	3.55	15.89078	S	G	1	21
1	Male	NO	YES	DLF	7.5	34.26	29.66	4.60	13.42674	S	G	1	21

2	Male	NO	YES	DRF	8.3	25.00	20.78	4.22	16.88	S	S	2	21
1	Male	NO	YES	DRF	8.7	26.68	24.23	2.45	9.182909	S	S	2	28
3	Male	NO	YES	DRF	7	30.65	27.67	2.98	9.722675	S	S	3	28
2	Female	NO	YES	DLF	8	6.36	5.38	0.98	15.40881	S	S	3	28
1	Male	NO	YES	PRF	7.7	35.46	31.47	3.99	11.25212	S	G	1	21
2	Male	NO	YES	DLF	6.8	27.70	23.30	4.40	15.88448	S	G	1	14
2	Male	NO	YES	DRF	7.8	34.50	31.20	3.3	9.565217	S	S	1	21
1	Male	NO	YES	PLF	10.5	28.1	24.6	3.5	12.45552	S	G	2	21
2	Female	NO	YES	DRF	7.5	23.5	18.1	5.4	22.97872	S	G	1	21
4	Male	NO	YES	DLF	7.9	24.7	22.8	1.9	7.692308	S	S	3	28
2	Male	NO	YES	DRF	8.7	32.1	29.1	3	9.345794	S	G	2	21
1	Female	NO	YES	DLF	7.4	25.6	20	5.6	21.875	S	G	1	14
1	Female	NO	YES	DRF	7.8	27.92	21.77	6.15	22.02722	S	G	1	14
4	Male	NO	YES	DLF	11	26.5	24.98	1.52	5.735849	S	S	2	28
1	Male	NO	YES	DRF	6.7	26.32	19.12	7.2	27.35562	S	G	1	14
2	Male	NO	YES	DLF	7.8	30.45	24.76	5.69	18.69	S	G	1	21
5	Male	NO	YES	DLF	6.9	12.80	9.68	3.12	24.375	S	S	2	21
2	Female	NO	YES	HRF	8.7	26.68	24.23	2.45	9.182909	S	S	2	21
1	Male	NO	YES	DRF	6.8	27.70	23.30	4.40	15.88448	S	G	1	21
2	Male	NO	YES	HLF	7.9	24.7	22.8	1.9	7.692308	S	S	3	28
2	Female	NO	YES	DRF	6.8	11.65	9.80	1.85	15.87983	S	S	1	28
1	Female	NO	YES	DLF	7.7	13.67	11.80	1.87	13.67959	S	S	1	28
2	Female	NO	YES	DRF	9	32.18	28.94	3.24	10.06837	S	G	1	21
4	Male	NO	YES	PRF	7.2	16.78	14.16	2.62	15.61383	S	G	2	21
2	Male	NO	YES	PLF	10.5	28.1	24.6	3.5	12.45552	S	G	2	21
4	Female	NO	YES	DLF	7.7	13.67	11.80	1.87	13.67959	S	S	1	28