"STUDY OF EFFECTIVENESS OF TOPICAL INSULIN ON HEALING OF DIABETIC ULCERS AT TERTIARY HEALTH CARE CENTER"

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LIST OF ABBREVIATIONS USED

DM	–	Diabetes mellitus
T1DM	–	Type 1 Diabetes mellitus.
T2DM	–	Type 2 Diabetes mellitus.
GDM	–	Gestational Diabetes mellitus.
GLUT2	–	Glucose transporter 2.
FPG	–	Fasting Plasma Glucose.
OGTT	–	Oral Glucose Tolerance Test
HbA1c	–	Glycated Haemoglobin
CGM	–	Continuous glucose monitoring
CAD	–	CoronaryArtery Disease
PVD	–	Peripheral Vascular Disease
ECM	–	Extracellular matrix
VEGF	–	Vascular endothelial growth factor
TGF-β	–	Transforming Growth factor – β
ABI	–	Ankle-brachial index
MRI	–	Magnetic resonance imaging
TCC	–	Total Contact Casting
PDGF	–	Platelet-Derived Growth Factor
rhEGF	–	Recombinant Human Epidermal Growth Factor
NPWT	–	Negative pressure wound therapy
HBOT	–	Hyper Baric Oxygen Therapy
TMA	–	Trans metatarsal Amputation
BKA	–	Below-Knee Amputation
AKA	–	Above-Knee Amputation
PI3K	–	Phosphoinositide 3-kinase
DFU	–	Diabetic foot ulcer.
MAPK	–	Mitogen-Activated Protein Kinase
ERK	–	Extracellular Signal-Regulated Kinase
mTOR	–	mammalian Target Of Rapamycin
IL-10	–	Interleukin-10
TNF-α	–	Tumor Necrosis Factor – alpha
MMPs	–	Matrix Metalloproteinases

SBP	–	Systolic blood pressure
DBP	–	Diastolic blood pressure
HBsAg	–	Hepatitis B Surface Antigen
HIV	–	Human Immunodeficiency Virus
H/O	–	History of
SD	–	Standard Deviation
M W test	–	Mann -Whitney Test
IGF	–	Insulin Like Growth Factor

ABSTRACT

BACK GROUND

Diabetes mellitus presents a significant challenge to global healthcare systems, with diabetic ulcers being a major complication. Despite advances in wound care, these ulcers often resist conventional treatments, leading to prolonged patient suffering and substantial healthcare costs. Recent interest in topical insulin therapy stems from its potential to improve wound healing outcomes by addressing underlying pathophysiological mechanisms disrupted by chronic hyperglycemia. While preclinical studies suggest efficacy, clinical evidence remains limited and inconclusive due to methodological shortcomings. Rigorous, well-designed clinical trials are needed to evaluate the true effectiveness of topical insulin therapy in managing diabetic ulcers and filling current knowledge gaps.

OBJECTIVE

- To assess the effectiveness of the topical insulin application in diabetic patients and To Compare the effectiveness of topical insulin application versus normal Saline dressings in diabetic patients

METHODS

Seventy patients with diabetic ulcers were evenly divided into two groups for a trial. Group A received insulin dressing, and Group B received normal saline dressing. The trial evaluated outcomes such as reduction in wound size, presence of granulation tissue, and wound preparation time as key metrics.

RESULTS

Group A exhibited a significant 50.1% decrease in wound size throughout the study, whereas Group B showed a more modest reduction of 16.99%. This disparity in wound size reduction between the groups strongly indicates that insulin dressing is more effective in enhancing the healing of diabetic ulcers.

CONCLUSION

Research findings indicate that using insulin dressing topically notably enhances the healing of diabetic ulcers compared to normal saline dressing, mainly supported by substantial reductions in wound size.

INDEX

LIST OF IMAGES

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Diabetes mellitus poses a significant challenge to healthcare systems globally, with diabetic ulcers representing a major complication associated with the condition [1]. Despite advances in wound care, diabetic ulcers often resist conventional treatments, leading to prolonged suffering for patients and substantial healthcare costs [1,2]. In recent years, interest has grown in the potential of topical insulin therapy to enhance wound healing outcomes in diabetic ulcers [3].

The rationale behind topical insulin therapy lies in its ability to address the underlying pathophysiological mechanisms that impair wound healing in diabetes [4]. Chronic hyperglycaemia disrupts multiple aspects of the wound healing process, including inflammation, angiogenesis, and collagen synthesis [4]. Topical insulin administration offers a targeted approach to deliver exogenous insulin directly to the wound site, circumventing systemic insulin resistance and promoting tissue repair [2].

Although preclinical research has shown that topical insulin is effective in accelerating wound healing [2,3], clinical evidence supporting its use remains limited and inconclusive [5]. Existing studies suffer from methodological limitations, including small sample sizes, heterogeneity in patient populations, and variations in treatment protocols [6]. Consequently, there is a need for well-designed clinical trials to rigorously evaluate the effectiveness of topical insulin therapy in diabetic ulcer management[6].

In order to close this knowledge gap, a prospective, randomized controlled trial evaluating the impact of topical insulin on the healing of diabetic ulcers is being proposed[6]. By comparing outcomes between patients receiving topical insulin

therapy and those receiving standard wound care, the study seeks to elucidate the potential benefits of topical insulin in improving wound healing rates, reducing wound size, and preventing complications [2].

Key outcome measures will include wound size reduction, time to healing, and incidence of complications[3][5]. These measures will be assessed using standardized techniques and will be compared between the case and control groups [3]. Additionally, this study will explore potential mechanisms underlying the therapeutic effects of topical insulin, such as its impact on wound microcirculation, growth factor expression, and tissue remodelling [4] [5][6].

OBJECTIVE OF THE STUDY

- To assess the effectiveness of the topical insulin application in diabetic patients

- To Compare the effectiveness of topical insulin application versus normal Saline dressings in diabetic patients

REVIEW OF LITERATURE

Introduction to Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels, often referred to as hyperglycaemia.

This chapter provides an overview of diabetes mellitus, including its definition, types, epidemiology, risk factors, and etiology.

1.1 Definition- Diabetes mellitus is a group of diseases characterized by high blood sugar levels over a prolonged period. The condition arises due to defects in insulin secretion, insulin action, or both, leading to impaired glucose metabolism. Hyperglycaemia, the hallmark of diabetes, can cause various complications affecting multiple organ systems[7].

1.2 Types of Diabetes Mellitus

There are several types of diabetes mellitus, each with distinct etiologies and clinical presentations:

- Type 1 Diabetes Mellitus (T1DM): An autoimmune disease characterized by the destruction of pancreatic beta cells, resulting in insulin deficiency. T1DM typically presents in childhood or adolescence[8].
- Type 2 Diabetes Mellitus (T2DM): The most common form of diabetes, often associated with insulin resistance and relative insulin deficiency. T2DM primarily affects adults but is increasingly diagnosed in children and adolescents[9].

- Gestational Diabetes Mellitus (GDM): Diabetes diagnosed during pregnancy, typically resolving after childbirth. GDM increases the risk of maternal and fetal complications[10].

- Other Types: This category includes specific forms of diabetes caused by genetic mutations, pancreatic disease, drug-induced factors, and endocrine disorders[11].

1.3 Epidemiology of Diabetes Mellitus

Diabetes mellitus has reached epidemic proportions globally, with a significant impact on public health. Aging populations, sedentary lifestyles, poor diets, and obesity are among the factors that have been linked to a steady increase in the prevalence of diabetes[12]. Both developed and developing countries are affected by the diabetes burden, with substantial variations in prevalence rates among different populations[13].

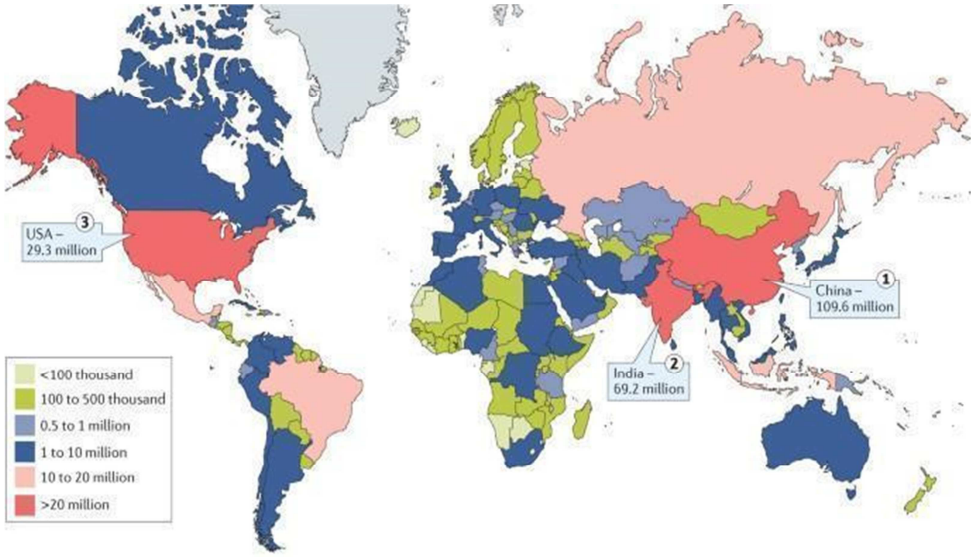

Image 1 - Epidemiology of Diabetes Mellitus

1.4 It is more likely to develop diabetes mellitus if certain risk factors are present, such as:

- Genetic Predisposition: Diabetes may be more likely to develop in families where the disease has a history of diabetes[14].
- Obesity: A major risk factor for insulin resistance and type 2 diabetes is excess body weight, especially in the case of central adiposity[15].
- Sedentary Lifestyle: Physical inactivity increases the risk of type 2 diabetes by causing obesity and insulin resistance[16].
- Unhealthy Diet: A diet heavy in sugars, refined carbohydrates, and saturated fats, with little consumption of fruits, vegetables, and fiber, is linked to a higher risk of developing diabetes[17].

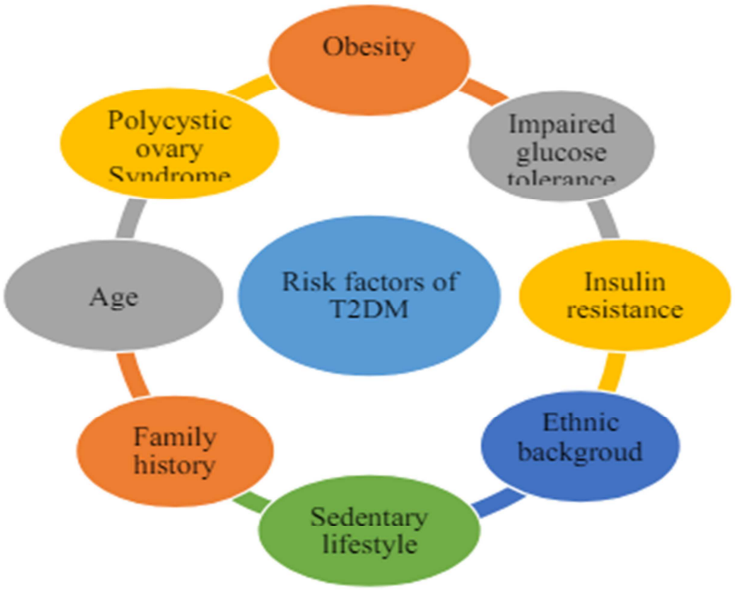

Image 2 - risk factors of diabetes mellitus

1.5 Etiology

Diabetes mellitus has a complex etiology that involves interactions between genetic, environmental, and lifestyle factors. T2DM is primarily influenced by lifestyle factors such as diet, physical activity, and obesity[18], whereas genetic predisposition plays a significant role in T1DM[19]. Other factors, including viral infections, autoimmune reactions, and gestational influences, also contribute to the development of Diabetes mellitus[20].

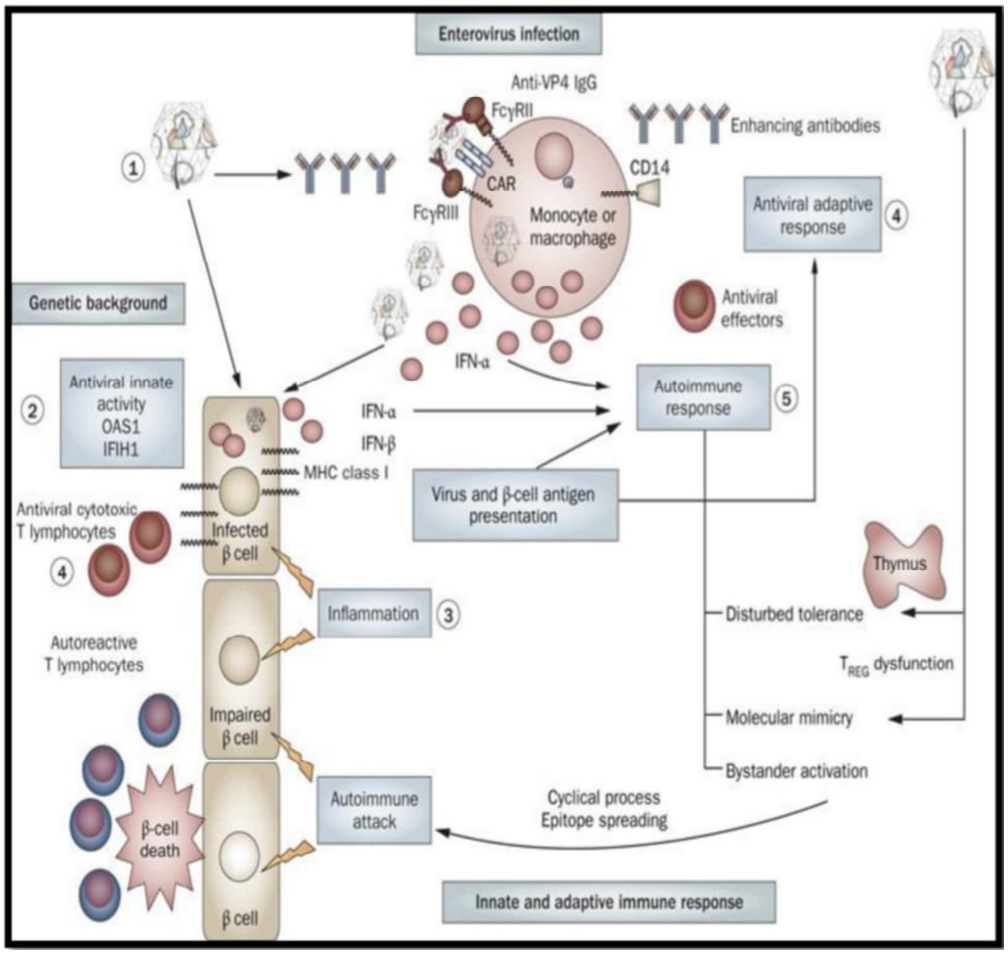

Image 3- Etiology of Diabetes Mellitus

Pathophysiology - Diabetes Mellitus

Diabetes Mellitus (DM) is characterized by dysregulation of glucose metabolism, resulting in elevated blood glucose levels. This chapter delves into the underlying pathophysiology of diabetes mellitus, elucidating the normal mechanisms of glucose metabolism, insulin secretion, and insulin action, as well as the disturbances that occur in diabetes.

2.1 Normal Glucose Metabolism

Glucose, the primary source of energy for cells, undergoes metabolism through a series of biochemical pathways. After ingestion of carbohydrates, glucose is absorbed into the bloodstream from the gastrointestinal tract. Insulin, a hormone essential for peripheral tissues to absorb and use glucose, is secreted by pancreatic beta cells in response to elevated blood glucose levels. Insulin facilitates the conversion of glucose to glycogen for storage or use in glycolysis to produce energy by promoting the uptake of glucose into cells, particularly muscle and adipose tissue [21].

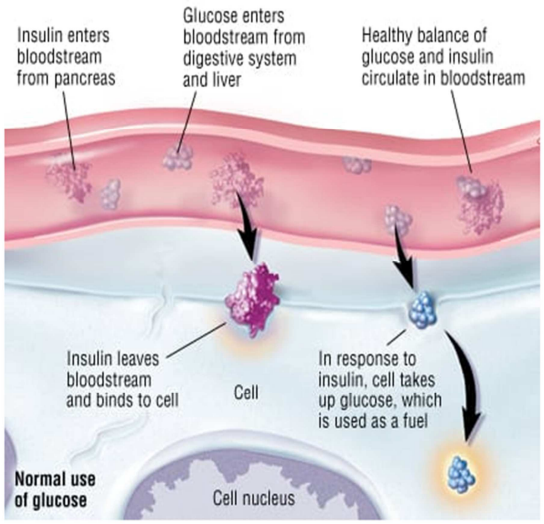

Image 4 – Normal glucose metabolism

2.2 Mechanisms of Insulin Secretion

Insulin secretion is tightly regulated by complex mechanisms involving glucose sensing and signalling pathways within pancreatic beta cells. Glucose is transported into beta cells by glucose transporters (GLUT2), where it is metabolized and produces more ATP. The depolarization of the cell membrane, closure of ATP-sensitive potassium channels, and subsequent influx of calcium ions are all caused by elevated ATP levels. Insulin-containing vesicles are exocytosed when calcium enters the bloodstream, releasing the insulin into the circulation[22].

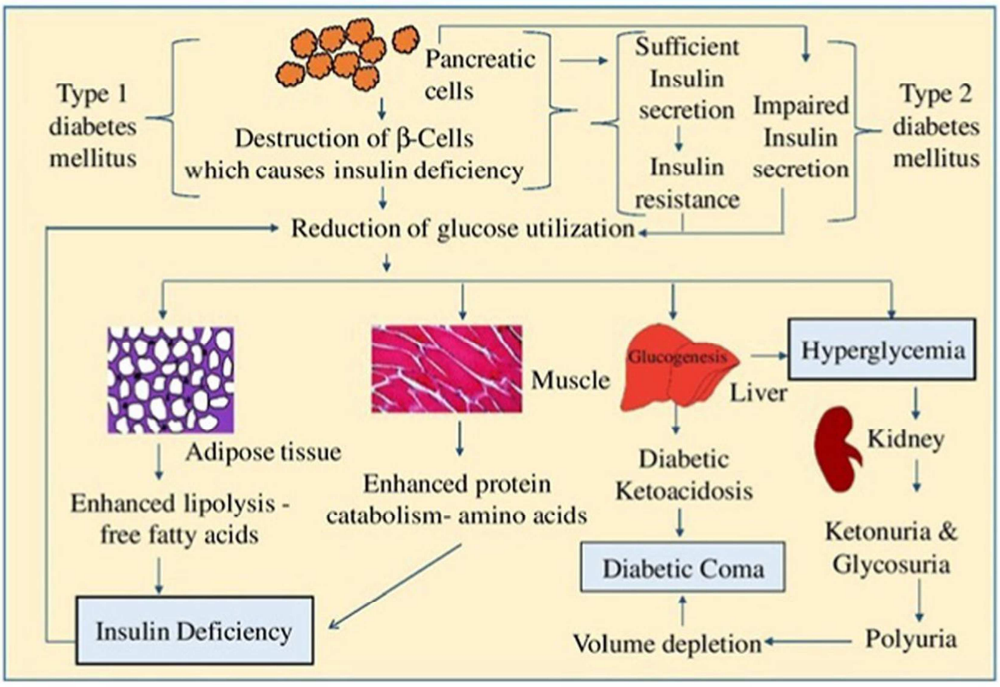

Image 5 – Mechanism of Insulin secretion

2.3 Disruption of Glucose Homeostasis in Diabetes

In diabetes mellitus, defects in insulin secretion, insulin action, or both disrupt glucose homeostasis, leading to hyperglycemia. The two primary forms of Diabetes Mellitus, type 1 and type 2, exhibit distinct pathophysiological mechanisms:

- Type 1 Diabetes Mellitus (T1DM): T1DM is defined by the autoimmune destruction of beta cells in the pancreas, which leaves the patient completely insulin deficient. Autoimmune reactions, possibly triggered by genetic and environmental factors, lead to the production of autoantibodies targeting beta cell antigens[23]. Progressive beta cell destruction impairs insulin secretion, leading to uncontrolled hyperglycemia [24].
- Type 2 Diabetes Mellitus (T2DM): T2DM is primarily attributed to insulin resistance, whereby target tissues exhibit reduced responsiveness to insulin action. Initially, compensatory hyperinsulinemia maintains normoglycemia; however, over time, beta cell dysfunction and insulin deficiency develop, exacerbating hyperglycemia [25]. Additionally, dysregulated hepatic glucose production and impaired incretin hormone signaling contribute to glucose dysregulation in T2DM[26].

Clinical Presentation and Diagnosis

Diabetes mellitus (DM) manifests clinically in a wide range of ways, from minor symptoms to serious consequences. This chapter outlines the typical signs and symptoms of diabetes, along with the diagnostic criteria and approaches used to confirm the diagnosis.

3.1 Symptoms of Diabetes Mellitus

The type, duration, and severity of the disease all affect how diabetes mellitus manifests clinically. Common signs and symptoms include:

- Polyuria: Osmotic diuresis caused by high blood glucose levels that leads to excessive urination[27].
- Polydipsia: Increased thirst, often accompanied by dry mouth, as a response to polyuria and dehydration[27].
- Polyphagia: Excessive hunger and increased food intake, driven by cellular starvation despite high blood glucose levels[27].
- Weight Loss: Some people lose weight unintentionally, especially those with type 1 diabetes or poorly controlled type 2 diabetes[27].
- Fatigue: Persistent tiredness and lack of energy, possibly due to cellular energy depletion and metabolic imbalances[27].
- Blurred Vision: Temporary visual disruptions may result from variations in blood glucose levels impacting the lens's refractive characteristics[27].
- Slow Wound Healing: Impaired wound healing and recurrent infections may occur due to compromised immune function and microvascular damage[27].

3.2 Diagnostic Criteria for Diabetes Mellitus

Diagnosis of diabetes mellitus is established based on laboratory tests and clinical criteria. The following diagnostic criteria are commonly used:

- Fasting Plasma Glucose (FPG): Diabetes mellitus is indicated by a fasting plasma glucose level of ≥126 mg/dL (7.0 mmol/L) on two different occasions[28].
- Oral Glucose Tolerance Test (OGTT): Two hours after consuming 75 grams of glucose, a plasma glucose level of ≥200 mg/dL (11.1 mmol/L) indicates the presence of diabetes mellitus[28].
- Haemoglobin A1c (HbA1c): An HbA1c level ≥6.5% (48 mmol/mol) indicates diabetes mellitus[28]. HbA1c is less affected by sudden swings and represents average blood glucose levels over the past three months[28].
- Random Plasma Glucose: Diabetes mellitus is confirmed by a random blood glucose level of ≥200 mg/dL (11.1 mmol/L) in the presence of characteristic hyperglycaemia symptoms[28].

HbA1C	≥ 6.5
Fasting Blood sugar	≥ 126mg/dl
2 hour plasma glucose	≥ 200 mg/dl
Random plasma glucose	≥ 200 mg/dl **with symptoms of hyperglycemia**

Table 1 - Criteria for diagnosis of diabetes mellitus

3.3 Screening and Diagnostic Approaches

For asymptomatic people with risk factors like obesity, a family history of diabetes, or gestational diabetes in prior pregnancies, screening for diabetes mellitus is advised[29]. Screening tests may include Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Test (OGTT), or Haemoglobin A1c (HbA1c) measurements[29]. Furthermore, continuous glucose monitoring (CGM) devices or glucometers for point-of-care testing may help in the diagnosis and management of diabetes mellitus[30].

3.4 Differential Diagnosis

Several conditions may mimic the clinical presentation of diabetes mellitus, necessitating a thorough differential diagnosis. These conditions include:

- Other Endocrine Disorders: Disorders affecting the thyroid, adrenal glands, or pituitary gland may present with symptoms similar to diabetes mellitus[31].
- Renal Disorders: Chronic kidney disease can lead to polyuria, polydipsia, and electrolyte imbalances, mimicking diabetes mellitus[32].
- Medications: Certain medications, such as corticosteroids, diuretics, and antipsychotics, can induce hyperglycemia and mimic the symptoms of diabetes mellitus[33].

Complications of Diabetes Mellitus

Complications of diabetes mellitus can affect various organ systems and significantly impact the quality of life and overall health outcomes of individuals with the condition. The microvascular and macrovascular complications, along with other potential consequences connected to diabetes, are covered in this chapter[34].

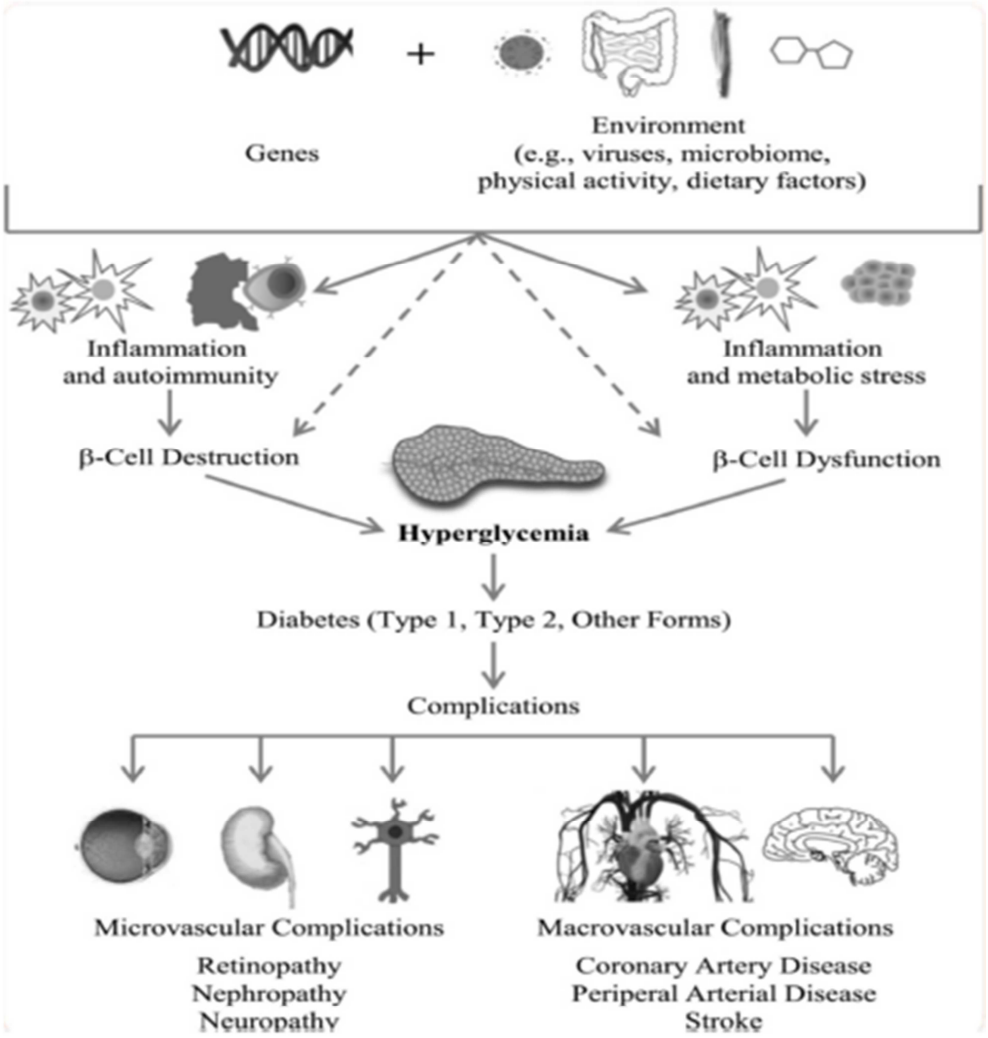

Image 6 – Complications of diabetes mellitus

4.1 Microvascular Complications

- Small blood vessels are the main target of microvascular complications, which include:
- Diabetic retinopathy: Impairment of vision and blindness due to damage to the blood vessels in the retina[35].

- Diabetic nephropathy: Proteinuria, hypertension, and ultimately end-stage renal disease are the outcomes of kidney destruction[36].
- Diabetic neuropathy: Damage to the nerves resulting in sensory, motor, and autonomic dysfunction; this can cause gastrointestinal problems, foot ulcers, and neuropathic pain[37].

4.2 Macrovascular Complications

Macrovascular complications are linked to cardiovascular disease and entail massive blood vessels, including:

- Coronary Artery Disease (CAD): Coronary artery narrowing or blockage, which can result in angina, heart failure, and myocardial infarction[38].
- Cerebrovascular Accident: Transient ischemic attacks due to impaired blood flow to the brain[39].
- Peripheral Arterial Disease: Reduced blood flow to the extremities, resulting in claudication, non-healing ulcers, and limb ischemia[40].

4.3 Other Complications

Other complications associated with diabetes mellitus include:

- Diabetic Foot Complications: Foot ulcers, infections, and gangrene due to peripheral neuropathy, poor circulation, and impaired wound healing[41].
- Skin Complications: Increased susceptibility to skin infections, necrobiosis lipoidica, and diabetic dermopathy[42].
- Oral Health Complications: Periodontal disease, dental caries, and oral candidiasis due to impaired immune function and elevated glucose levels[43].

Introduction to Diabetic Ulcers

Diabetic ulcers are a significant complication of diabetes mellitus, posing serious health risks and challenges to affected individuals. This chapter provides an overview of diabetic ulcers, including their definition, types, prevalence, risk factors, and the impact they have on quality of life and healthcare systems.

5.1 Definition and Types of Diabetic Ulcers

Diabetic ulcers refer to open sores or wounds that develop on the skin of individuals with diabetes, most commonly on the feet. A number of conditions, including peripheral neuropathy, peripheral vascular disease, and poor wound healing, contribute to the development of these ulcers. There are several types of diabetic ulcers, including neuropathic ulcers, ischemic ulcers, and neuroischemic ulcers, each with distinct pathophysiological mechanisms and clinical characteristics[44].

5.2 Epidemiology and Prevalence

A typical side effect of diabetes mellitus is diabetic ulcers, especially in those with the condition for a long time or poorly managed. Age, length of diabetes, the existence of comorbidities, and access to healthcare are some of the variables that affect the prevalence of diabetic ulcers. It is estimated that up to 25% of diabetics will develop a foot ulcer at some point in their lives. This has serious consequences for healthcare expenses, morbidity, and mortality[45].

5.3 Risk Factors for Diabetic Ulcers

Several factors increase the risk of developing diabetic ulcers, including:

- Peripheral Neuropathy: Damage to peripheral nerves reduces sensation and increases the likelihood of trauma and injury[46].
- Peripheral Vascular Disease: Impaired blood flow to the extremities hampers wound healing and tissue repair[47].
- Foot deformities: Pressure points and skin deterioration result from structural anomalies such as bunions, hammertoes, and Charcot foot deformities[48].
- Poor glycemic Control: Increased blood sugar levels weaken the body's defenses against infection and hinder wound healing[49].

5.4 Impact on Quality of Life and Healthcare Burden

Diabetic ulcers can have profound effects on the physical, emotional, and socioeconomic well-being of affected individuals. Chronic ulcers are associated with pain, reduced mobility, decreased productivity, and increased risk of infection and amputation. The management of diabetic ulcers places a significant burden on healthcare systems, requiring specialized wound care, multidisciplinary interventions, and long-term follow-up to prevent complications and improve outcomes [50].

5.5 Pathophysiology of Diabetic Ulcers

Impairment of immunological function, peripheral neuropathy, peripheral vascular disease, aberrant wound healing mechanisms, and other complicated interactions between many physiological and pathological variables are the root causes of diabetic ulcers. The basic processes behind the emergence and advancement of diabetic ulcers are examined in this chapter.

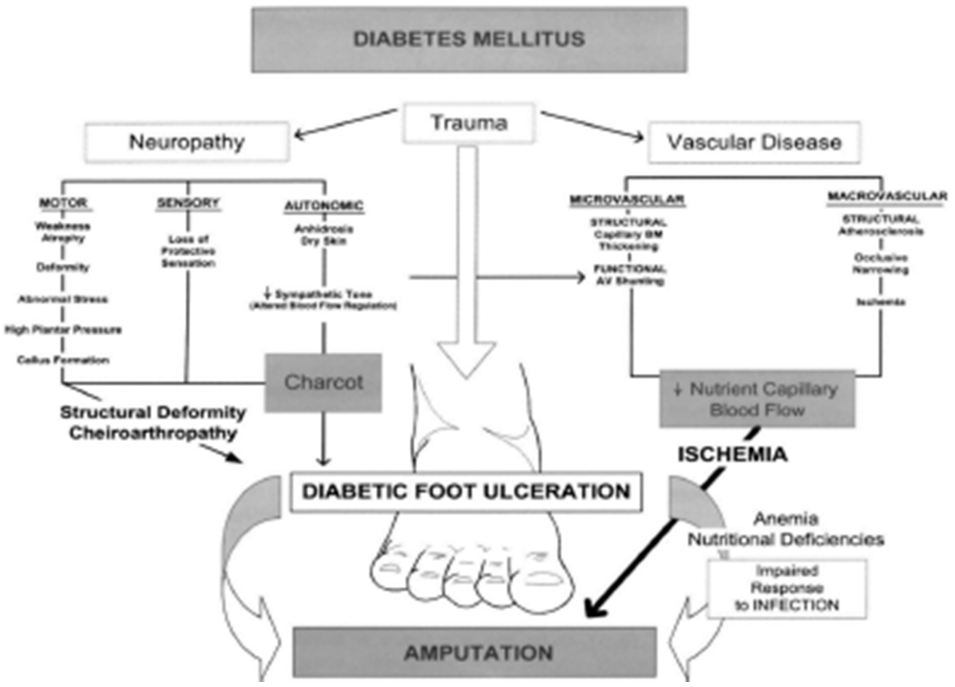

Image 7– Pathophysiology of diabetic ulcers

Peripheral Neuropathy

Diabetic ulcer development is mostly influenced by peripheral neuropathy, a common consequence of diabetes mellitus. Autonomic, motor, and sensory disorders are caused by injury to the peripheral nerves. [51-54] The loss of sensation to pain, pressure, and temperature due to sensory neuropathy makes people more vulnerable to undiscovered injuries and trauma. Affected gait patterns and foot abnormalities are partly caused by motor neuropathy, which also causes muscular weakness and imbalance. [55-61] Autonomic neuropathy affects sweat gland function, skin moisture regulation, and blood flow regulation, exacerbating skin dryness, ischemia, and susceptibility to injury

Peripheral Vascular Disease (PVD)

Peripheral vascular disease is another key contributor to diabetic ulcer formation. It encompasses a spectrum of vascular abnormalities, including arterial insufficiency, venous stasis, and microvascular dysfunction. [62-65] Arterial insufficiency diminishes blood flow to the lower extremities, impairing oxygen and nutrient delivery to tissues and compromising wound healing . Venous stasis leads to edema, inflammation, and impaired venous return, exacerbating tissue damage and delaying ulcer healing. [66,67] Microvascular dysfunction affects capillary permeability and angiogenesis, disrupting the microcirculation and exacerbating tissue hypoxia and ischemia .

Impaired Immune Function

Individuals with diabetes mellitus often exhibit impaired immune function, predisposing them to infections and delayed wound healing . Hyperglycemia impairs the function of immune cells, including neutrophils, macrophages, and lymphocytes, compromising their ability to phagocytose pathogens, produce cytokines, and mount an effective immune response . Chronic inflammation, oxidative stress, and tissue damage further disrupt the wound healing process and perpetuate a protracted inflammatory state, hindering tissue repair and regeneration. [66-69]

Abnormal Wound Healing Processes

The wound healing process in diabetic ulcers is characterized by aberrations in the normal sequence of events, including inflammation, proliferation, and remodeling . Chronic inflammation and impaired leukocyte recruitment prolong the inflammatory phase, exacerbating tissue damage and delaying the transition to the proliferative

phase. Deficient angiogenesis, fibroblast function, and extracellular matrix synthesis impair tissue granulation and wound closure, perpetuating ulcer chronicity and susceptibility to complications . Dysregulated growth factor signaling, which encompasses TGF-β and VEGF (vascular endothelial growth factor) among others, can worsen tissue repair processes and obstruct wound healing. [67-71]

5.6 Clinical Presentation and Diagnosis of Diabetic Ulcers

Diabetic ulcers present with a variety of clinical manifestations, ranging from superficial wounds to deep, necrotic lesions. Early recognition and prompt diagnosis are essential for initiating appropriate management and preventing complications.

Signs and Symptoms

Depending on the wound's location, intensity, and length of time, diabetic ulcers might show differently clinically. A few typical indications and symptoms are:

- **Skin Breakdown**: Ulcers typically manifest as open wounds or sores on the feet, particularly over pressure points and areas of repetitive trauma [72].
- **Tissue Necrosis**: Advanced ulcers may exhibit necrotic tissue, eschar, or gangrenous changes, indicating compromised blood flow and tissue viability [73].
- **Drainage and Exudate**: Ulcers may produce serous, purulent, or malodorous drainage, reflecting the presence of infection, inflammation, or necrotic tissue [74].

- **Surrounding Tissue Changes**: Periwound skin may appear erythematous, edematous, or macerated, indicating inflammation, infection, or moisture-related damage [75].

- **Pain or Discomfort**: Some ulcers may be associated with pain, burning, or discomfort, particularly if neuropathy is less severe or absent [76].

Differential Diagnosis

The differential diagnosis of diabetic ulcers includes various other skin lesions and wounds, such as:

- **Traumatic Ulcers**: Wounds resulting from mechanical trauma, friction, or pressure, including blisters, abrasions, and lacerations [77].

- **Venous Ulcers**: Ulcers secondary to chronic venous insufficiency, typically located around the ankles and characterized by hemosiderin deposition and venous stasis changes [78].

- **Arterial Ulcers**: Ischemic ulcers resulting from peripheral arterial disease, often located on the distal extremities and associated with pallor, coolness, and diminished pulses [79].

- **Neuropathic Ulcers**: Ulcers related to peripheral neuropathy, commonly found on weight-bearing areas of the feet and associated with loss of protective sensation [80].

Diagnostic Evaluation

The diagnostic evaluation of diabetic ulcers involves a comprehensive assessment of the wound and surrounding tissues, including:

- **History and Physical Examination**: Detailed history-taking, including diabetes duration, glycaemic control, and previous ulcer history, coupled with a thorough physical examination, aids in identifying potential risk factors and guiding further evaluation [81].

- **Wound Measurement and Documentation**: Accurate measurement of ulcer size, depth, and extent, along with photographic documentation, provides baseline data for monitoring wound progression and treatment efficacy [82].

- **Wound Culture and Sensitivity Testing**: Collection of wound swabs or tissue biopsies for microbiological analysis helps identify the causative pathogens and guide antibiotic selection in infected ulcers [83].

- **Vascular Assessment**: Evaluation of peripheral pulses, ankle-brachial index (ABI), and vascular imaging tools, such as Doppler ultrasound or angiography, aids in determining ischemia ulcer identification and vascular perfusion assessment [84].

- **Neuropathic Assessment**: Assessment of sensory perception, vibration sensation, and proprioception using standardized tests, such as monofilament testing and tuning fork examination, aids in detecting peripheral neuropathy and assessing ulcer risk [72].

5.7 Complications of Diabetic Ulcers

Untreated or improperly managed diabetic ulcers can result in a number of consequences that significantly impact patient outcomes and quality of life. This chapter examines the potential complications associated with diabetic ulcers and the implications for patient care and prognosis.

Infection

One of the most concerning complications of diabetic ulcers is infection, which can occur due to the compromised immune response and impaired wound healing associated with diabetes mellitus. Bacterial pathogens, such as Staphylococcus aureus, Streptococcus species, and Pseudomonas aeruginosa, can colonize and proliferate within the ulcer bed, leading to local tissue invasion, cellulitis, and systemic spread. Infected diabetic ulcers may exhibit purulent drainage, increased erythema, warmth, and tenderness, and systemic signs of infection, such as fever and leukocytosis. Delayed recognition and inadequate treatment of infected ulcers can result in abscess formation, sepsis, and limb-threatening complications necessitating urgent intervention [73].

Delayed Wound Healing

One typical consequence of diabetic ulcers is impaired wound healing, which can be caused by peripheral neuropathy, peripheral vascular disease, and changes in growth factor signaling and extracellular matrix deposition brought on by hyperglycemia. Chronic inflammation, oxidative stress, and tissue hypoxia further hinder the wound healing process, prolonging the inflammatory phase and inhibiting tissue granulation and epithelialization. Delayed wound healing increases the risk of

secondary infections, exacerbates ulcer chronicity, and heightens the likelihood of complications, such as tissue necrosis and amputation [74].

Tissue Necrosis and Gangrene

Severe diabetic ulcers may progress to tissue necrosis and gangrene, particularly in the setting of ischemia and infection. Necrotic tissue, including eschar and slough, impedes wound healing, serves as a nidus for bacterial growth, and contributes to local tissue damage and inflammation. Dry gangrene, characterized by dry, blackened tissue due to arterial occlusion, may occur in ischemic ulcers, while wet gangrene, characterized by moist, malodorous tissue due to bacterial infection, may develop in infected ulcers. Gangrenous changes signify critical limb ischemia and necessitate urgent vascular assessment and intervention to prevent irreversible tissue loss and limb amputation [75].

Osteomyelitis

Diabetic ulcers that penetrate deep into the soft tissues may lead to contiguous spread of infection to the underlying bone, resulting in osteomyelitis. Bone involvement in diabetic foot ulcers is associated with persistent infection, poor healing of wounds and increased risk of limb loss. Clinical features suggestive of osteomyelitis include localized bone tenderness, erythema, and swelling, sinus tract formation, and non-healing ulcers despite appropriate wound care. Diagnosis of osteomyelitis requires imaging studies, such as plain radiography, magnetic resonance imaging (MRI), or radionuclide bone scanning, coupled with microbiological sampling of bone tissue to confirm the presence of bacterial pathogens [76].

Amputation

Perhaps the most devastating complication of diabetic ulcers is lower extremity amputation, which may be necessitated by severe infection, ischemia, gangrene, or failed wound healing despite aggressive treatment. Major lower limb amputations, including below-knee and above-knee amputations, are associated with significant physical and psychological morbidity, impaired mobility, and reduced quality of life. Prevention of amputation requires early recognition and aggressive management of diabetic ulcers, including optimization of glycemic control, wound debridement, infection control, and revascularization when indicated, in addition to multidisciplinary foot care and patient education programs aimed at reducing ulcer recurrence and minimizing limb loss [77].

Wound Healing Process in Diabetic Ulcers

Wound healing in diabetic ulcers is intricate and often disrupted by underlying pathophysiological factors associated with diabetes mellitus. Understanding the phases of wound healing and the factors that influence tissue repair is essential for devising effective management strategies for diabetic ulcers. This chapter elucidates the stages of diabetic ulcer wound healing and factors that contribute to aberrations in this process.

6.1 Phases of Wound Healing

Wound healing typically progresses through the following sequential phases:

1. **Inflammatory Phase**: The initial response to tissue injury involves hemostasis, inflammation, and the recruitment of inflammatory cells to the site of the wound. In diabetic ulcers, chronic inflammation may occur due to

persistent tissue damage, impaired leukocyte function, and dysregulated cytokine signalling, prolonging the inflammatory phase and delaying subsequent stages of wound healing [78].

2. **Proliferative Phase**: During this phase, fibroblasts, endothelial cells, and keratinocytes migrate to the wound bed, leading to granulation tissue formation, angiogenesis, and epithelialization. Factors such as impaired angiogenesis, deficient growth factor signalling, and dysfunctional fibroblast activity in diabetic ulcers can compromise tissue granulation and hinder wound closure, resulting in chronic ulceration [79].

3. **Remodelling Phase**: In the final phase of wound healing, the extracellular matrix undergoes remodelling, collagen synthesis and degradation reach equilibrium, and wound contraction occurs. Aberrations in collagen deposition, cross-linking, and matrix metalloproteinase activity in diabetic ulcers may lead to excessive scarring, fibrosis, and impaired tissue remodelling, perpetuating ulcer chronicity and susceptibility to recurrence [80].

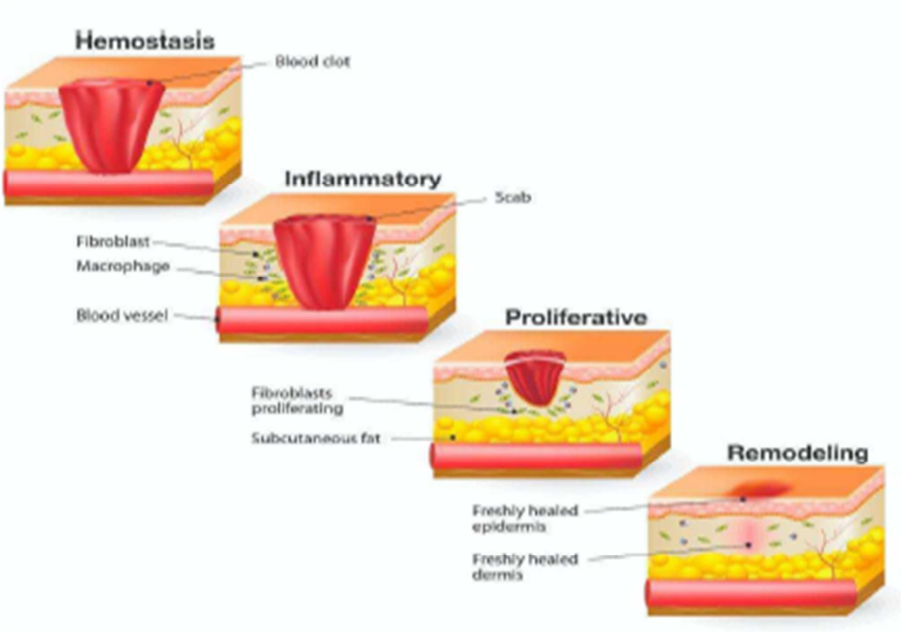

Image 8 – Phases of wound healing

PHASE	**Cellular and Bio-physiologic events**
Haemostasis	● Vasoconstriction ● Platelet plug and thrombus formation
Inflammation	● Infiltration of Neutrophil□monocyte (to Macrophage)□ lymphocyte
Proliferation	● Proliferation of epitheliocyte ● Neoangiogenesis ● Laying down of ECM and Collagen fibres (Type III)
Remodelling	● Type III□Type I collagen ● Fibroblast maturation and scar regression

Table 2 – Phases of wound healing

6.2 Factors Affecting Healing in Diabetic Ulcers

Several intrinsic and extrinsic factors influence the wound healing process in diabetic ulcers, including:

- **Peripheral Neuropathy**: Loss of sensation and proprioception impairs protective mechanisms and predisposes to trauma and injury, delaying wound detection and intervention [85].

- **Peripheral Vascular Disease**: Reduced blood flow and oxygen delivery impair cellular metabolism, nutrient transport, and waste removal, compromising tissue viability and wound healing [86].

- **Glycaemic Control**: Hyperglycaemia disrupts cellular metabolism, oxidative stress, and inflammatory pathways, impeding leukocyte function, growth factor signalling, and collagen synthesis, thereby hindering wound healing [87].

- **Infection**: Bacterial colonization and biofilm formation exacerbate tissue damage, inflammation, and delayed wound healing, necessitating aggressive antimicrobial therapy and wound debridement [88].

- **Nutrition**: Malnutrition, micronutrient deficiencies, and metabolic abnormalities compromise cellular proliferation, protein synthesis, and tissue repair, impairing wound healing and recovery [89].

- **Pressure and Shear**: Excessive pressure and friction on weight-bearing areas contribute to tissue ischemia, necrosis, and ulceration, necessitating offloading and pressure redistribution strategies to promote healing [90].

Management Strategies for Diabetic Ulcers

A multidisciplinary strategy is needed for the effective care of diabetic ulcers in order to address the underlying pathophysiological causes, promote wound healing, avoid complications, and improve patient outcomes. This chapter outlines the key components of management strategies for diabetic ulcers, including wound care techniques, offloading, and adjunctive therapies [91-95].

7.1 Wound Debridement Techniques

Because it removes necrotic tissue, biofilm, and debris and promotes the growth of healthy granulation tissue, wound debridement is essential to the healing process of wounds. Various debridement techniques may be employed, including:

- **Sharp Debridement**: Surgical removal of devitalized tissue using scalpel, scissors, or curette, performed by trained healthcare providers in a sterile setting [96].

- **Mechanical Debridement**: Non-invasive removal of necrotic tissue through irrigation, scrubbing, or wet-to-dry dressings, aiming to mechanically dislodge debris and promote wound cleansing [97].

- **Enzymatic Debridement**: Application of topical enzymes, such as collagenase or papain-urea, to enzymatically digest necrotic tissue and promote autolytic debridement, particularly in non-viable or infected wounds [98].

- **Biological Debridement**: Use of sterile maggots (larval therapy) to selectively digest necrotic tissue while sparing healthy tissue, offering a natural and effective debridement option for complex or non-healing ulcers [99].

7.2 Dressing Selection and Wound Care

Appropriate wound dressings play a crucial role in creating a conducive environment for wound healing, managing exudate, and preventing infection. Key considerations in dressing selection include:

- **Moisture Balance**: Maintaining an optimal moisture balance in the wound bed to promote granulation tissue formation and epithelialization, while preventing maceration or desiccation of the surrounding tissues [100].

- **Absorption Capacity**: Selecting dressings with appropriate absorbent properties to manage exudate levels, minimize bacterial contamination, and prevent leakage or maceration of periwound skin [101].

- **Antimicrobial Properties**: Antimicrobial compounds like silver, iodine, or honey can be added to dressings to help lower the bacterial load, stop infections, and speed up wound healing—especially in the case of infected ulcers [102].

- **Protection and Offloading**: Utilizing dressings with protective properties to cushion and protect vulnerable areas of the foot, offload pressure points, and prevent friction and trauma that may exacerbate ulceration [103-104].

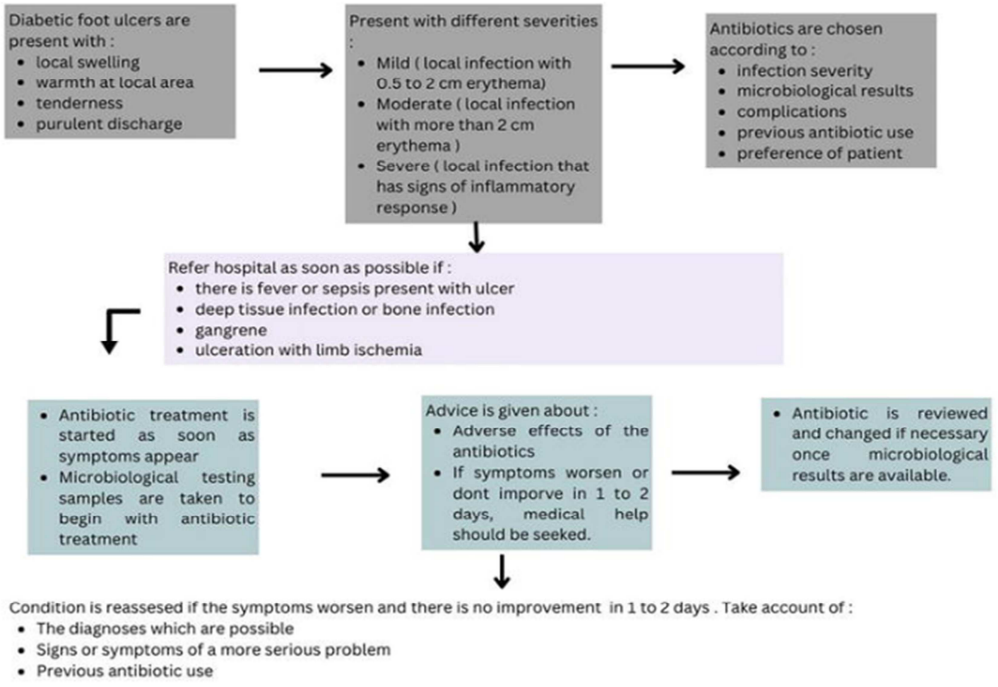

Image 9 – Management of diabetic ulcers

Offloading and Pressure Redistribution

Offloading is essential in reducing mechanical stress and pressure on diabetic foot ulcers, promoting tissue perfusion, and facilitating wound healing. Offloading techniques may include:

- **Total Contact Casting (TCC):** Application of a fiberglass or plaster cast to the entire foot and lower leg, distributing weight-bearing forces evenly and offloading pressure from the ulcer site, while maintaining mobility and functionality [105].

- **Removable Cast Boots**: Prefabricated or custom-made removable cast boots that provide offloading of the affected foot while allowing for regular wound assessment, dressing changes, and patient comfort [106].

- **Pressure-Relieving Devices**: Utilization of specialized footwear, orthotic devices, or customized insoles with pressure-relieving properties to redistribute weight, reduce shear forces, and prevent recurrence of ulcers [107].

7.3 Adjunctive Therapies

In addition to standard wound care and offloading measures, adjunctive therapies may be employed to enhance wound healing and address specific aspects of ulcer management, including:

- **Topical Growth Factors**: Application of Platelet-Derived Growth Factor (PDGF) or Recombinant Human Epidermal Growth Factor (rhEGF), to promote angiogenesis, collagen synthesis, and epithelialization in chronic or non-healing ulcers [108].

- **Negative Pressure Wound Therapy (NPWT):** Application of negative pressure to the wound bed using specialized dressings and vacuum-assisted devices, promoting wound contraction, reducing edema, and enhancing granulation tissue formation [109].

- **Hyperbaric Oxygen Therapy (HBOT)**: 100 percent oxygen is administered in a hyperbaric chamber at high pressures, enhancing oxygen delivery to hypoxic tissues, stimulating angiogenesis, and promoting tissue repair in ischemic or infected ulcers [110].

7.4 Surgical Interventions for Diabetic Ulcers

In cases where conservative management fails to promote healing or when complications such as infection, ischemia, or necrosis are present, surgical interventions may be necessary to address diabetic ulcers effectively. This chapter discusses various surgical options available for managing diabetic ulcers and their respective indications, techniques, and outcomes.

Debridement and Wound Excision

Surgical debridement involves the selective removal of necrotic tissue, foreign material, and non-viable structures from the ulcer bed to promote wound healing and prevent infection. Techniques may include sharp debridement using scalpels or scissors, mechanical debridement with curettes or scrubbing devices, or enzymatic debridement with topical agents. Surgical wound excision may be indicated for deep or extensive ulcers involving underlying structures, such as tendons, bones, or joints, to achieve complete wound closure and prevent complications [111].

Skin Grafts and Flaps

Skin grafting and flap procedures may be employed to provide durable coverage and promote wound healing in diabetic ulcers refractory to conservative measures. Options include:

- **Split-Thickness Skin Grafts**: Harvesting of epidermal and dermal layers from a donor site and grafting onto the ulcer bed to provide temporary coverage and facilitate re-epithelialization [112].

- **Full-Thickness Skin Grafts**: Harvesting of full-thickness skin from a donor site, including epidermis and dermis, for grafting onto deep or large ulcers, offering better cosmetic and functional outcomes [113].

- **Local Flaps**: Transfer of adjacent healthy tissue with intact blood supply to cover defects and promote wound healing, utilizing various flap designs, such as advancement, rotation, or transposition flaps [114].

- **Free Flaps**: Microsurgical transfer of tissue from distant donor sites, such as the abdomen or thigh, to reconstruct complex defects and provide vascularized tissue for optimal wound healing, particularly in cases of extensive tissue loss or vascular compromise [105].

Amputation and Limb Salvage

In severe or advanced cases of diabetic ulcers complicated by infection, ischemia, or necrosis, partial or complete limb amputation may be necessary to prevent further tissue damage, systemic spread of infection, or mortality. Options include:

- **Toe or Ray Amputation**: Removal of affected digits or metatarsal heads to eliminate infection, relieve pressure, and preserve functional integrity of the foot [106].

- **Transmetatarsal Amputation (TMA)**: Removal of the forefoot and metatarsal bones to achieve a stable plantigrade foot for weight-bearing and ambulation, while preserving as much limb length as possible [107].

- **Below-Knee Amputation (BKA)**: Removal of the foot and distal tibia and fibula to achieve a functional residual limb for prosthetic fitting and mobility, while preserving knee function and ambulatory capacity [108].

- **Above-Knee Amputation (AKA)**: Removal of the entire lower limb above the knee joint, typically reserved for extensive tissue loss, gangrene, or failed attempts at limb salvage, with consideration for rehabilitation and prosthetic use [109].

7.5 Revascularization Procedures

In cases of diabetic ulcers complicated by critical limb ischemia and impaired perfusion, revascularization procedures may be indicated to restore blood flow and promote wound healing. Options include:

- **Endovascular Interventions**: Percutaneous angioplasty and stenting of arterial stenoses or occlusions to improve blood flow and limb perfusion, often performed under fluoroscopic guidance with minimal incisions and short recovery times [110].

- **Surgical Bypass Grafting**: Creation of new blood flow pathways using autologous or synthetic grafts to bypass diseased or occluded arteries and restore distal perfusion to the affected limb, typically performed using open surgical techniques [111].

Complications and Preventive Measures for Diabetic Ulcers

The therapy of diabetic ulcers has advanced, but complications related to the condition still exist. These consequences can have a major negative influence on the quality of life and outcomes for patients.. Additionally, preventive measures are essential to mitigate the risk of ulcer development and recurrence. This chapter examines common complications of diabetic ulcers and outlines preventive measures aimed at reducing morbidity and improving long-term outcomes.

8.1 **Complications of Diabetic Ulcers**

Diabetic ulcers are prone to several complications, including:

- Diabetic ulcers are prone to several complications, including:

- **Infection**: Persistent or untreated ulcers can become infected, leading to cellulitis, abscess formation, osteomyelitis, and systemic spread of infection, with the potential for limb loss and mortality [112].

- **Delayed Healing**: Factors like hyperglycaemia, malnutrition, peripheral neuropathy, and peripheral vascular disease can impede the wound healing process, prolonging ulcer chronicity and increasing the risk of complications [113].

- **Tissue Necrosis and Gangrene**: Severe ulcers may progress to tissue necrosis and gangrene, particularly in the setting of ischemia, infection, or delayed treatment, necessitating aggressive interventions to prevent limb loss [114].

- **Amputation**: Non-healing or advanced ulcers may require partial or complete limb amputation to prevent further tissue damage, sepsis, or mortality, with significant physical and psychological consequences for affected individuals [105].

8.2 **Preventive Measures**

Preventing diabetic ulcers and minimizing the risk of recurrence are paramount goals of diabetic foot care. Key preventive measures include:

- **Glycaemic Control**: Maintaining optimal blood glucose levels through diet, exercise, medication adherence, and regular monitoring reduces the risk of neuropathy, vascular disease, and impaired wound healing associated with diabetes mellitus [106].

- **Foot Care Education:** Educating patients about proper foot hygiene, nail care, footwear selection, and daily foot inspections empowers individuals to recognize early signs of ulceration, prevent trauma, and seek timely medical attention [107].

- **Pressure Offloading**: Offloading high-pressure areas of the foot using orthotic devices, specialized footwear, or total contact casting redistributes weight and reduces the risk of pressure ulcers, particularly in individuals with neuropathy or deformities [108].

TYPE	KEY POINTS
REMOVABLE CAST WALKERS	Similar pressure decrease to TCCs More acceptable, easy to remove Can be used on infected and ischemic wounds Reduced healing rate compared with TCCs
SCOTCHCAST BOOTS	Lighter, padded cast covering foot to ankle Can be made non-removable
HEALING SANDALS	-Designed to limit dorsiflexion of metatarsophalangeal joints -Reusable, Light weight, stable. Increases falls in patients with impaired balance
CRUTCHES, WALKERS, WHEELCHAIRS	-off loads foot in entirety -Patients need good upper body strength

Table 3 -Types of pressure off loading devices

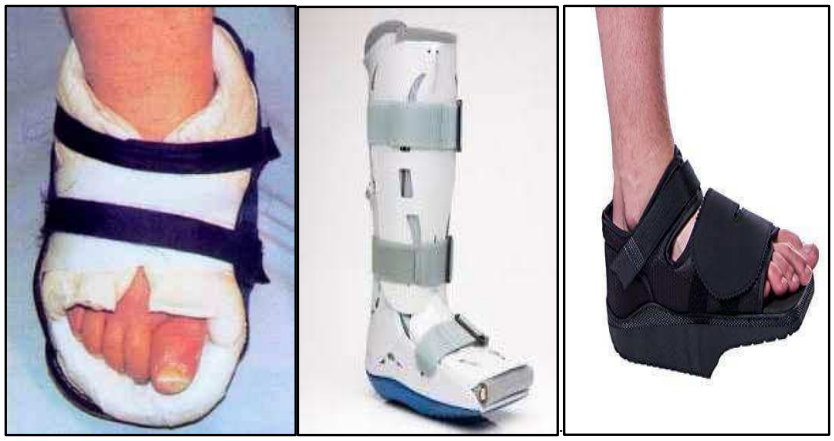

Image 11- Types of Pressure Off loading Devices

- **Regular Foot Examinations**: Performing comprehensive foot examinations during routine healthcare visits enables early detection of foot problems, ulceration, or changes in sensation, facilitating prompt intervention and preventive measures [109].

- **Vascular Assessment**: Screening for peripheral arterial disease using ankle-brachial index (ABI) measurements, Doppler ultrasound, or arterial imaging helps identify vascular insufficiency and guide interventions to improve limb perfusion and wound healing [110].

- **Multidisciplinary Foot Care**: Collaborative care involving podiatrists, wound care specialists, vascular surgeons, endocrinologists, and other healthcare providers optimizes ulcer management, addresses comorbidities, and promotes holistic approaches to foot care [111].

The Science Behind Topical Insulin

Diabetic ulcers present a multifaceted challenge in wound management, often characterized by impaired healing processes due to underlying metabolic dysregulation and microvascular complications. In recent years, the application of topical insulin has garnered attention as a potential therapeutic intervention to facilitate wound healing. This chapter delves into the intricate mechanisms by which insulin influences the healing cascade and elucidates the scientific rationale behind its efficacy in diabetic ulcer management.

9.1 Insulin Signalling Pathways in Wound Healing:

Insulin, beyond its well-known role in glucose metabolism, exerts profound effects on various cellular processes crucial for wound repair and regeneration. Key signalling pathways implicated in insulin-mediated wound healing include:

- **PI3K/Akt Pathway: Phosphoinositide 3-kinase (PI3K)** is activated by insulin attaching to its receptor, which causes PKA to be phosphorylated and PKA to be activated (Akt). In order for tissue to regenerate in the wound bed, Akt signalling supports cell migration, proliferation, and survival [115].

- **MAPK/ERK Pathway**: Insulin stimulation triggers the cascade of Mitogen-Activated Protein Kinase (MAPK), ultimately causing Extracellular Signal-Regulated Kinase (ERK) to become activated. ERK signalling regulates gene expression, cell proliferation, and matrix remodelling, contributing to wound closure and scar formation [116].

- **mTOR Pathway**: Insulin activates the mammalian Target Of Rapamycin (mTOR) complex, promoting protein synthesis, angiogenesis, and epithelialization during the proliferative phase of wound healing [117].

- **Wnt/β-Catenin Pathway**: Insulin modulates Wnt signalling, promoting β-catenin stabilization and nuclear translocation. β-catenin activation regulates cell fate determination, stem cell proliferation, and tissue regeneration in response to injury [118].

9.2 Angiogenic and Anti-inflammatory Effects of Insulin:

In addition to its direct actions on wound cells, insulin exerts angiogenic and anti-inflammatory effects that contribute to an optimal microenvironment for tissue repair:

- **Angiogenesis**: Insulin enhances endothelial cell proliferation, migration, and tube formation, promoting neovascularization and improving tissue perfusion in ischemic wounds [119].

- **Anti-inflammatory Effects**: Insulin increases the release of anti-inflammatory cytokines like Interleukin-10 (IL-10), while it suppresses the synthesis of pro-inflammatory cytokines like Tumor Necrosis Factor - alpha (TNF-α) and Interleukin - 1 beta (IL-1β). This anti-inflammatory environment minimizes tissue damage, reduces inflammation, and speeds up the resolution stage of wound healing [120].

9.3 Modulation of Extracellular Matrix Remodelling

Insulin plays a crucial role in regulating extracellular matrix (ECM) remodelling, a dynamic process essential for wound closure and scar maturation:

- **Collagen Synthesis**: Insulin stimulates collagen production by fibroblasts and myofibroblasts, promoting the deposition of new ECM components and enhancing wound tensile strength [121].

- **Matrix Metalloproteinases (MMPs) Regulation**: Insulin modulates MMP activity, balancing ECM degradation and synthesis. This controlled proteolytic

activity is crucial for ECM remodelling and scar maturation during the late stages of wound healing [122].

9.4 Formulation and Delivery of Topical Insulin

The successful application of topical insulin in diabetic ulcer management relies on the development of suitable formulations and effective delivery systems.

Formulation Considerations

Formulating insulin for topical application requires careful consideration of several factors, including stability, permeability, bioavailability, and patient acceptability. Common formulation approaches include:

- **Creams and Ointments**: Insulin can be incorporated into topical creams or ointments for easy application to the wound site. These formulations provide a protective barrier, enhance moisture retention, and facilitate absorption of insulin into the skin [123].

- **Hydrogels**: Hydrogel-based formulations offer a versatile platform for delivering insulin to diabetic ulcers. Hydrogels provide a moist environment conducive to wound healing, allow sustained release of insulin, and can be tailored to control drug release kinetics [124]

- **Sprays and Aerosols**: Insulin solutions can be aerosolized or sprayed onto the wound surface using specialized devices. Sprays offer convenience, uniform coverage, and rapid absorption, making them suitable for large or irregularly shaped wounds [125].

- **Nanoparticle Systems**: Nanotechnology-based delivery systems, such as liposomes, nanoparticles, and nanoemulsions, enable targeted and controlled release of insulin to the wound site. Nanoparticles protect insulin from enzymatic degradation, enhance penetration through the skin barrier, and improve therapeutic efficacy [126].

9.5 Delivery Systems

Optimal delivery of topical insulin depends on the selection of appropriate administration techniques and devices. Key considerations include:

- **Application Techniques**: Healthcare providers must ensure thorough cleansing and debridement of the wound before applying topical insulin. Uniform distribution of the formulation over the ulcer surface is essential to maximize contact with wound tissue [127].

- **Dressings and Bandages**: In order to keep the topical insulin formulation in contact with the wound, dressings are essential. Non-adherent dressings, hydrocolloids, or foam dressings are preferred to prevent adherence and promote wound healing [128].

- **Frequency and Duration**: The frequency and duration of topical insulin application vary depending on the formulation, wound severity, and individual patient factors. Healthcare providers should establish clear dosing regimens and monitor response to treatment to optimize outcomes [129].

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9.6 Practical Considerations

Successful implementation of topical insulin therapy requires attention to practical considerations, including storage, stability, patient education, and adherence:

- **Storage Conditions**: Insulin formulations should be stored according to manufacturer recommendations to maintain stability and potency. Refrigeration may be required for certain formulations, while others can be stored at room temperature [130].

- **Patient Education**: Patients should receive thorough instructions on the proper application technique, frequency of administration, and expected outcomes of topical insulin therapy. Clear communication and ongoing support are essential to ensure patient adherence and engagement [131].

- **Monitoring and Evaluation**: Healthcare providers should closely monitor wound progress, glycemic control, and potential adverse effects associated with topical insulin therapy. Regular wound assessments and adjustments to treatment regimens may be necessary to optimize outcomes [132].

9.7 Clinical Applications of Topical Insulin

In clinical practice, the use of topical insulin has shown promise as an adjunctive therapy for diabetic ulcers. Patient selection criteria, integration into wound care protocols, and clinical outcomes are key considerations:

Patient Selection Criteria

Effective utilization of topical insulin requires careful consideration of patient characteristics, wound characteristics, and therapeutic goals. Patient selection criteria may include:

- **Ulcer Characteristics**: Topical insulin may be most beneficial for chronic, non-healing ulcers with evidence of impaired wound healing despite standard care. Factors such as ulcer size, depth, location, and presence of infection should be evaluated [133].

- **Glycaemic Control**: Adequate glycaemic control is essential for optimizing wound healing outcomes. Patients with poorly controlled diabetes may benefit from topical insulin therapy to mitigate the adverse effects of hyperglycaemia on wound healing [134].

- **Comorbidities**: Concurrent medical conditions such as peripheral vascular disease, neuropathy, and renal insufficiency ought to be considered when evaluating the applicability of insulin therapy applied topically. Close monitoring and multidisciplinary collaboration may be necessary for optimal management [135].

Integration into Wound Care Protocols

Topical insulin can be integrated into comprehensive wound care protocols as either an adjunctive therapy or a primary treatment modality. Key considerations include:

- **Multimodal Approach**: When combined with other wound care techniques like debridement, unloading, infection management, and vascular optimization, topical insulin is most successful. A multimodal approach addresses the multifactorial nature of diabetic ulcers and maximizes therapeutic efficacy [136].

- **Individualized Treatment Plans**: Tailoring treatment plans to individual patient needs is crucial for optimizing outcomes. Healthcare providers should assess response to therapy regularly and adjust treatment regimens accordingly based on wound progress, glycaemic control, and patient preferences [137].

- **Wound Assessment and Documentation**: Accurate and thorough documentation of wound characteristics, treatment interventions, and clinical outcomes is essential for monitoring progress, evaluating response to therapy, and facilitating communication among healthcare team members [138].

Bhettani et al. aimed to assess how well topical insulin heals diabetic foot ulcers in comparison to traditional povidone iodine dressings. This experimental study involved 110 patients divided into two groups, treated either with a solution of insulin or normal saline. Assessments of the wounds were made on days 7, 14, and 21. In contrast to the control group, results demonstrated a significant reduction in wound size with topical insulin. The study found that applying topical insulin considerably hastens the healing of diabetic foot ulcers [139].

Edek et al. aimed to assess topical insulin's efficacy as a supplemental treatment for a leg ulcer that is resistant to previous treatments. The case study involved a 64-year-old male with a chronic leg ulcer due to venous stasis. Topical

insulin was applied daily, resulting in a significant reduction in ulcer size over four weeks. The study concluded that topical insulin may be a promising treatment for non-healing ulcers by accelerating the wound healing process [140].

Meena et al. intended to evaluate how well topical insulin dressings worked to treat diabetic foot ulcers. The quasi-experimental study included 30 diabetic patients who received insulin dressings. Wound measurements were taken before and after one week of treatment. Results indicated significant improvement in wound healing with insulin dressing, evidenced by a decrease in wound size and depth. According to the study's findings, insulin dressings help diabetic patients' wounds heal more quickly [141].

Thakur et al. aimed to investigate at a tertiary medical facility how well topical insulin heals diabetic ulcers. The cross-sectional study included 60 patients, divided into groups receiving either topical insulin or saline applications. Statistical analysis showed significantly faster granulation tissue formation and reduced wound size and depth in the insulin group. The study found that applying topical insulin to diabetic ulcers greatly accelerates wound healing [142].

Gautam et al. aimed to evaluate if topical insulin is effective in curing diabetic foot ulcers. This prospective observational study involved 100 patients divided into two groups: one receiving topical insulin and the other receiving conventional treatment. When compared to the control group, the insulin group's wound size and length of stay were significantly smaller. The study concluded insulin positively impacts wound healing and can be beneficial for managing diabetic foot ulcers [143].

Rao et al. sought to compare the effects of local insulin against topical phenytoin in the management of diabetic foot ulcers. In this prospective, randomized, open-label trial, ninety patients were enrolled and divided into three groups: insulin, phenytoin, and traditional wound care. In comparison to the other groups, the insulin group's wound size and depth were significantly reduced, according to the results. The study found that when treating diabetic foot ulcers, local insulin application works better than phenytoin and traditional wound dressings [144].

Patel et al. aimed to assess if topical insulin is beneficial in treating diabetic foot ulcers. Fifty diabetic foot ulcer patients were divided into two groups for this study; one group received normal care, while the other group received insulin dressings. The insulin group outperformed the control group in terms of wound healing rate and ulcer size reduction. According to the study's findings, applying topical insulin helps diabetic foot ulcers heal more quickly [145].

Singh et al. aimed to determine the benefits of using topical insulin's effect on diabetic foot ulcer wound healing. The study was conducted with 40 patients, half of whom received insulin dressings while the other half received conventional treatment. The insulin-treated group showed a faster rate of wound closure and improved healing in contrast to the controls. According to the study's findings, topical insulin helps diabetic patients' wounds heal more quickly [146].

MATERIALS AND METHODS:

Source of Data:

The source of data will be patients with diabetic ulcers admitted in general surgery wards at KAHER'S Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi and KLES Dr. Prabhakar Kore Hospital and Medical Research Centre

Study Design:

Study design: Randomized control trial

Using SPSS program

Study Period:

1 year, from September 2022 to August 2023

Sample Size:

formula:

The two-proportion formula for the minimal sample size is

$N= Z\alpha/2^2\ PQ/L^2$

$N= (1.96)^2 \times 4.54 \times 95.46 \div 5 \times 5$

N= 67

Zα/2= 1.96 AT 5% LEVEL OF SIGNIFICANCE

P = 4.54

L = 5

Q = 100-p

where p_1 and p_2 -proportions of the two groups.

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

The test's power and significance level are related to zβ and zβ, respectively.

At the 5% significance level, zα = 1.96 and zβ = 0.84 correspond to 85% test power.

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

There would be two groups with a size of 70.

Sampling technique:

Computer generated random numbers by SPSS program are used to assign the type of intervention chosen for the patient that is, group A (Insulin dressing) and group B (Normal saline dressing)

Inclusion Criteria:

- Patient in the age group of 18-75 years (both sexes)
- Patient with a diabetic ulcer of > 2 weeks duration
- Ulcer size should be less than 100cm2

Exclusion Criteria:

- Patients suffering from cardiovascular disease or on anticoagulant therapy.
- Patients having wounds with exposure of tendon or bone.
- Patient with any immunosuppressive disease or on immunosuppressant therapy.

- Patient with history of hypersensitivity to insulin.
- Pregnancy
- Uncontrolled diabetes HBA1C >9 %
- Renal failure serum creatinine > 3 mg/dl

Study protocol

A thorough clinical assessment was performed. Individuals who met the eligibility requirements were prospectively allotted into 2 groups, Group A and Group B.

70 patients with diabetic ulcers can be taken. The testing group of 35 will be given Insulin Dressings (GROUP A) and the control group of 35 will continue treatment with conventional moist dressings (GROUP B). Insulin dressing will be administered to Group A, while normal saline dressing without insulin will be administered to Group B. With the right antidiabetic medication, all diabetic patients will achieve glycemic control. All ulcers will have a culture and sensitivity swab taken before patients are enrolled in the study, and the ulcers will be cleaned with regular saline. Anaesthesia will be used during the surgical debridement of unclean wounds. The ulcers will then be incorporated into the research. The duration required for ulcer preparation from the time of admission until study enrollment is known as the wound preparation time. When determining how long patients would stay in hospitals, this wound preparation period was not taken into consideration. After cleaning the ulcers with normal saline, Group A will irrigate each 10 cm2 of wound with 4 units (0.1 ml) of human soluble insulin (Actrapid) in 1 ml of normal saline (0.9%). Twice a day, an insulin syringe will be used to spray the prepared solution onto the ulcer's surface. After that, the ulcer will be given time to dry before sterile

cotton gauze is applied.

In Group B, sterile gauze will be used to cover ulcers after they have been cleaned with regular saline without insulin.

Calculation of wound area:

The dimensions of the ulcer - length, width and area will be 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

day 42 (y) - final wound area.

To calculate the area reduction and percentage of area reduction, apply the formula below:

wound area reduction = x-y

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

Data collection procedure:

One-year randomized control trial

An informed consent will be obtained from the patients.

In patient individuals with diabetic foot ulcer will be identified

Detailed history and examination would be done.

History including age, sex, history of smoking, history of diabetes, history of hypertension treatment, on treatment with drugs like statin or aspirin?

Examination including = SBP / DBP, local examination, culture and sensitivity, fbs, Hba1c, viral markers, doppler for arterial and venous flow of limb

DATA ANALYSIS

Microsoft excel and the statistical program R 4.4.0 are used for data analysis. Frequency tables are used to present categorical variables.

Presenting continuous variables as Mean ± Standard Deviation (SD)/ Median (Minimum, Maximum). chi square test is used to examine if groups and categorical variables are related. The QQ plot and the Shapiro Wilk test are used to determine whether a variable is normal. Parametric tests will be applied if the data has a normal distribution. If not, tests that are not parametric will be employed.

The means of the variables across groups are compared using the two sample t test. Mann -Whitney Use the U test to compare the variable distributions between groups. P-value - 0.05 or less indicates statistical significance.

RESULTS:

70 subjects total, split into two groups of 35 each, are measured in the data.

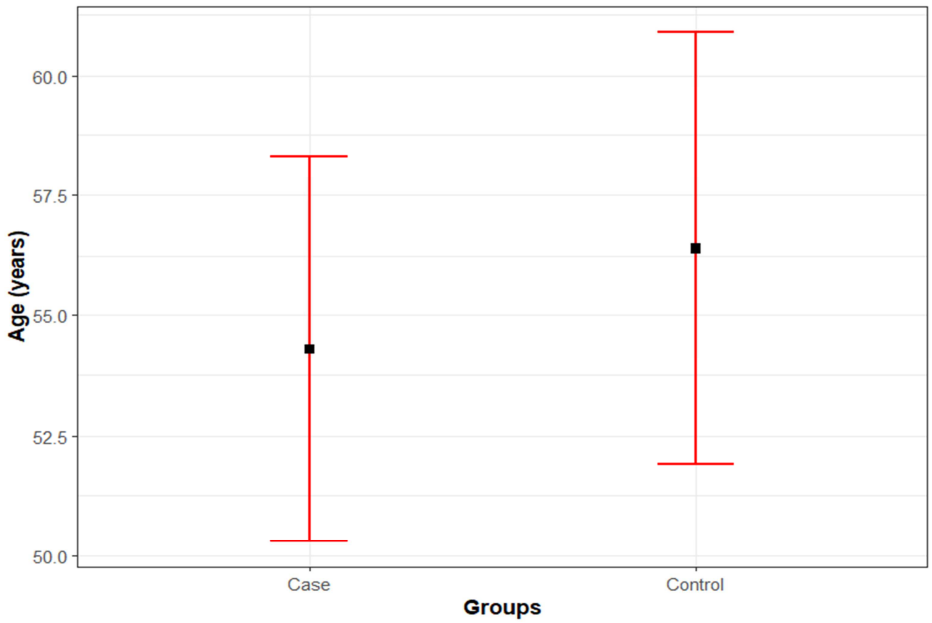
The comparison of demographic information across groups is shown in the following table.

Variables	Sub Category	Case	Control	Total	p-value
Age (years)	Mean ± SD Median (Minimum, Maximum)	54.31 ± 11.71 52 (29, 75)	56.4 ± 13.1 55 (22, 87)	55.36 ± 12.38 54 (22, 87)	0.4849[t]
Sex	Female	10 (28.57%)	10 (28.57%)	20 (28.57%)	1[C]
	Male	25 (71.43%)	25 (71.43%)	50 (71.43%)	

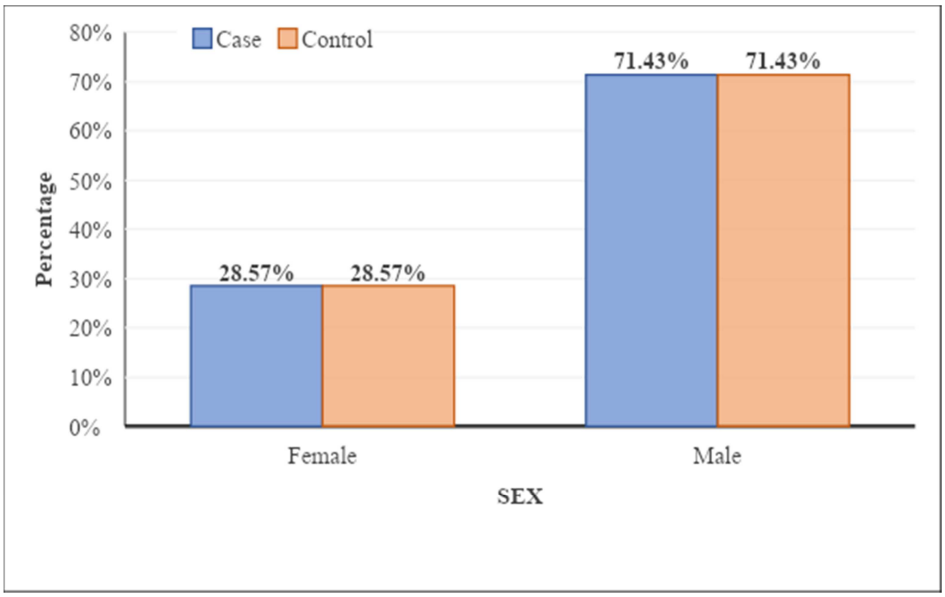
Table 4: demographic information across groups is compared.

The case group's mean age is 54.31 ± 11.71 years, and its median age is 52 years (range: 29 to 75).The age range of the control group is 22–87 years, with a mean age of 56.4 ± 13.1 years and a median age of 55.. The results of the two sample t test show that the mean age across groups does not differ significantly.

In terms of sex distribution, both groups have an identical composition: 10 (28.57%) females and 25 (71.43%) males. The Chi square test results show that there is no discernible variation in the distribution of sex among the groups.



Graph 1: Mean plot of age between groups.



Graph 2 : Sex distribution among the groups.

The comparison of medical information across groups is shown in the following table.

Table 5: A comparison of medical information between groups.

Variables	Sub Category	Case	Control	Total	p-value
Duration of DM	Mean ± SD Median (Minimum, Maximum)	7.89 ± 7.19 5 (0.08, 30)	12.77 ± 7.84 13 (0.08, 32)	10.29 ± 7.85 10 (0.08, 32)	**0.0030^{MW} ***
Smoking status	Nonsmoker	34 (97.14%)	32 (91.43%)	66 (94.29%)	0.6157^{MC}
	Smoker	1 (2.86%)	3 (8.57%)	4 (5.71%)	
HbA1c	Mean ± SD Median (Minimum, Maximum)	6.93 ± 1.23 6.8 (5.5, 10.4)	6.93 ± 1.13 6.8 (5.4, 12.1)	6.93 ± 1.17 6.8 (5.4, 12.1)	0.4614^{MW}
Culture& Sensitivity	E. coli	0	1 (2.86%)	1 (1.43%)	0.1704^{MC}
	Klebsiella	0	1 (2.86%)	1 (1.43%)	
	Pseudomonas	0	2 (5.71%)	2 (2.86%)	
	Staphylococcus aureus	2 (5.71%)	0	2 (2.86%)	
	No organisms	33 (94.29%)	31 (88.57%)	64 (91.43%)	
Viral Markers	Hbsag+	1 (2.86%)	0	1 (1.43%)	0.9999^{MC}
	Negative	34 (97.14%)	35 (100%)	69 (98.57%)	
Colour doppler	Normal study	35 (100%)	35 (100%)	70 (100%)	1^{C}

The duration of the case group is 7.89 ± 7.19 years, with a 5 year median (range: 0.08 to 30 years). In contrast, the duration of the control group is greater, with a mean of 12.77 ± 7.84 years and a median of 13 years, ranging from 0.08 to 32 years.The distribution of the duration of DM across groups differs significantly, according to the M W test (p-value - 0.0030).

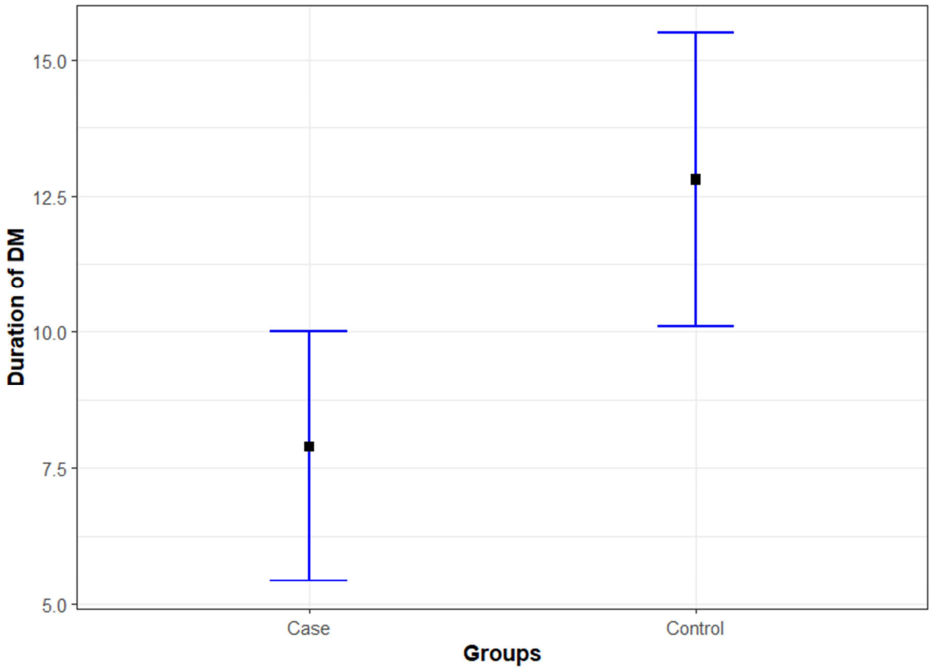
Regarding smoking status, the majority of both groups are nonsmokers, with 97.14% in the group under case study and 91.43% in the group under control. The distribution of smoking status across groups differs significantly, depending on the Chi square test results (p-value = 0.6157).

The HbA1c levels are identical in both groups, with a mean of 6.93 ± 1.23 in cases and 6.93 ± 1.13 in controls. There is no discernible variation in the distribution of HbA1c levels across group's, according to the MW test (p-value = 0.4614

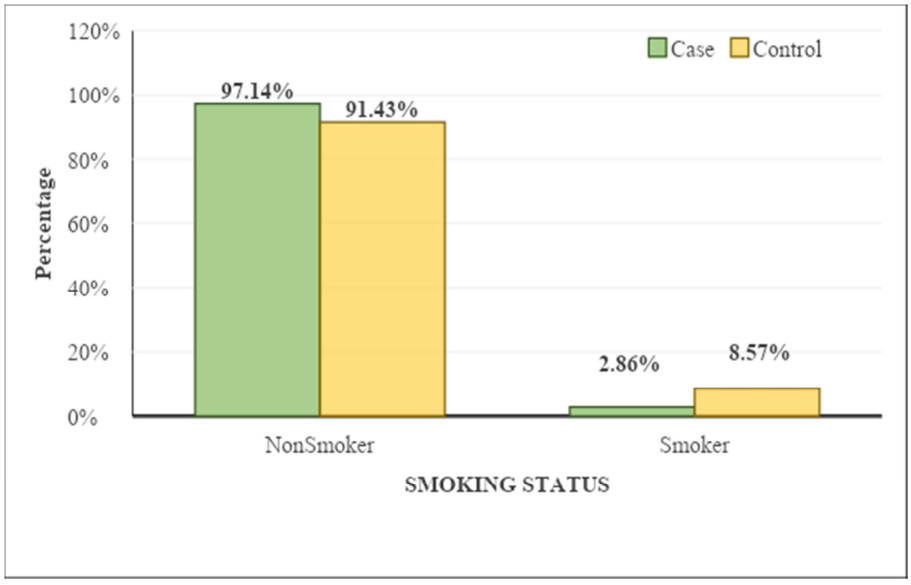
For culture and sensitivity, the majority of both groups show no organisms (In the group A, 94.29%, while in the group B, 88.57%). A few cases of bacterial growth are observed, including Staphylococcus aureus in the case group and E. coli, Klebsiella, and Pseudomonas in the group B. There is no statistically significant difference between the group A and group B culture scores, according to the Chi square test results (p value = 0.1704).

Regarding viral markers, all participants in the control group tested negative for Hbsag, whereas one member of the case group tested positive (2.86%). According to the Chi square test, there is no substantial difference between the groupA and group B viral indicators (p-value = 0.1704).

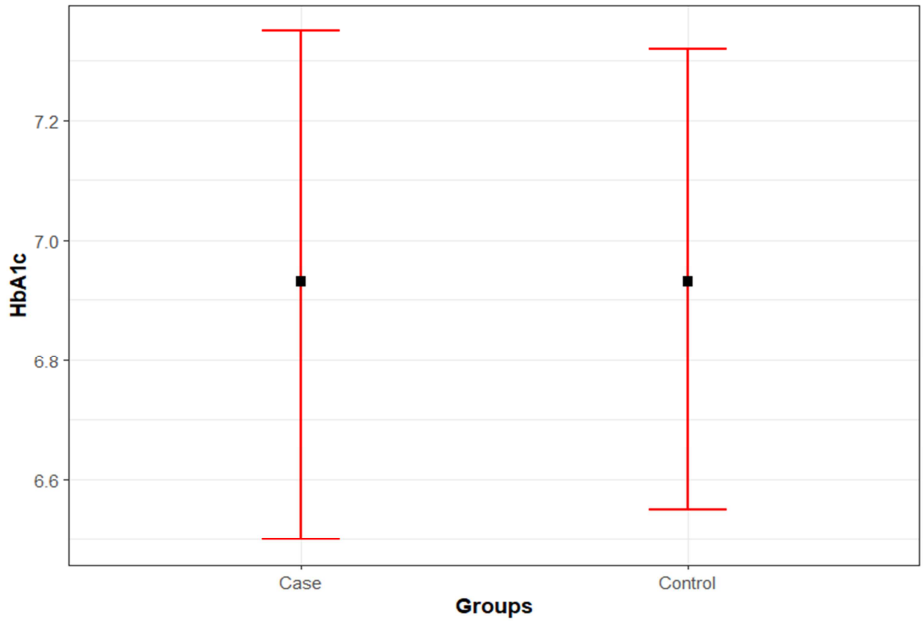
Finally, all participants in both groups showed normal results in colour Doppler studies, with no significant difference (p-value = 1).



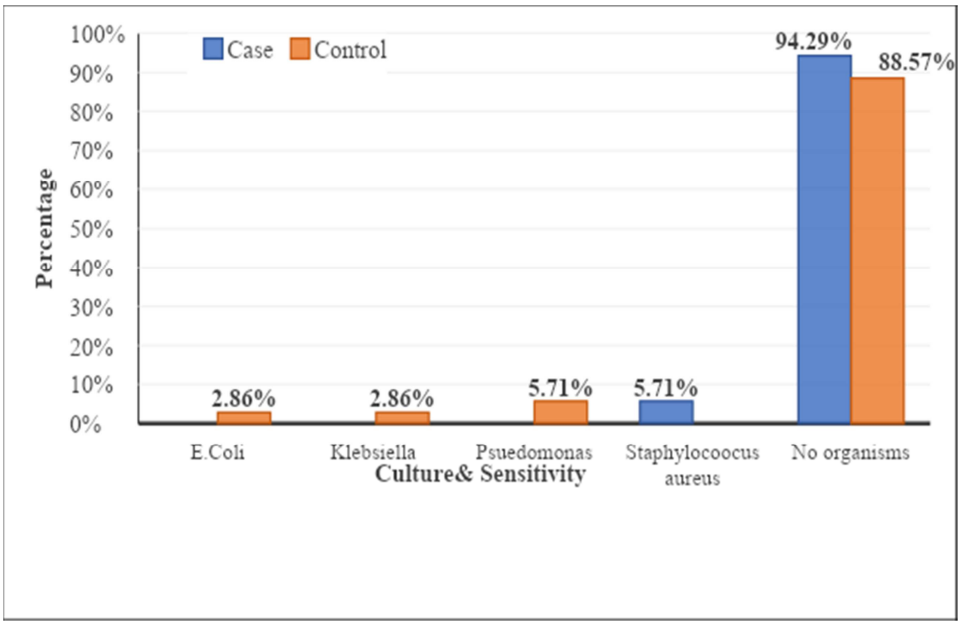
Graph 3: Mean DM duration plotted across groups.



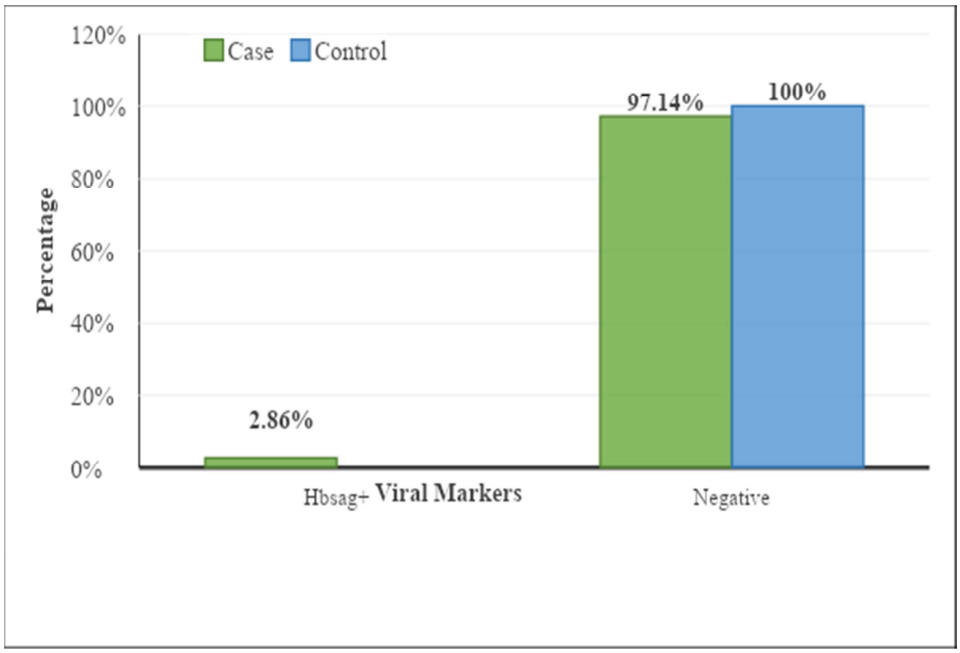
Graph 4 : Smoking status distribution among the groups.



Graph 5 : Mean plot of HbA1c over case and controls.



Graph 6: Distribution of culture and sensitivity over cases and controls



Graph 7 : Distribution of viral markers between cases and controls.

The comparison of wound details across groups is shown in the following table.

Table 6: Comparison of wound details between groups.

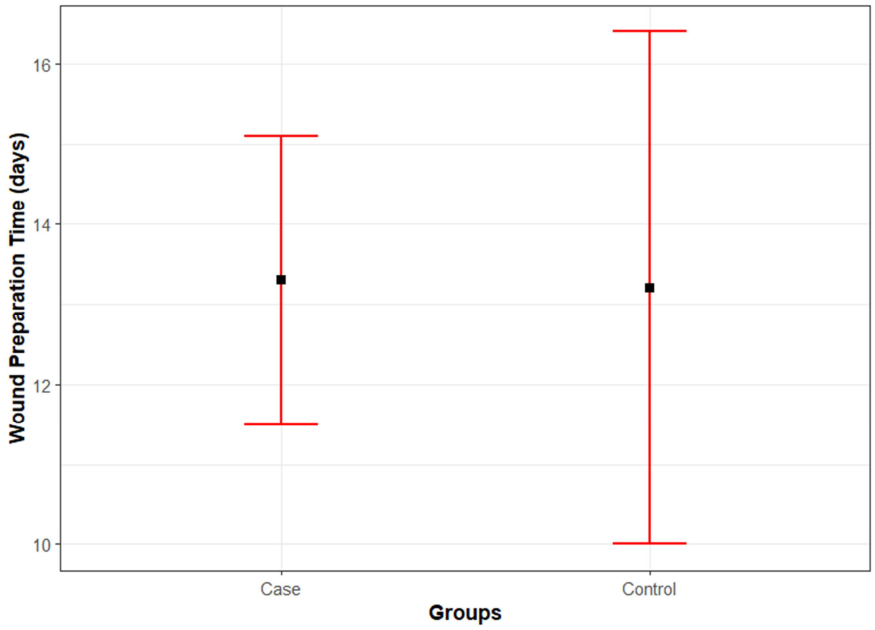
Variables	Sub Category	Case	Control	Total	p-value
Wound preparation time (days)	Mean ± SD Median (Min, Max)	13.29 ± 5.14 12 (7, 30)	13.23 ± 9.26 11 (5, 60)	13.26 ± 7.43 12 (5, 60)	0.3893^{MW}
Reduction in wound size (%)	Mean ± SD Median (Min, Max)	50.1 ± 26.77 52 (8, 92)	16.99 ± 14.52 13.3 (1.3, 70)	33.55 ± 27.12 23.3 (1.3, 92)	$<$ **0.001^{MW}***
Granulation tissue	Present	35 (100%)	35 (100%)	70 (100%)	1^{C}

** indicates statistical significance.*

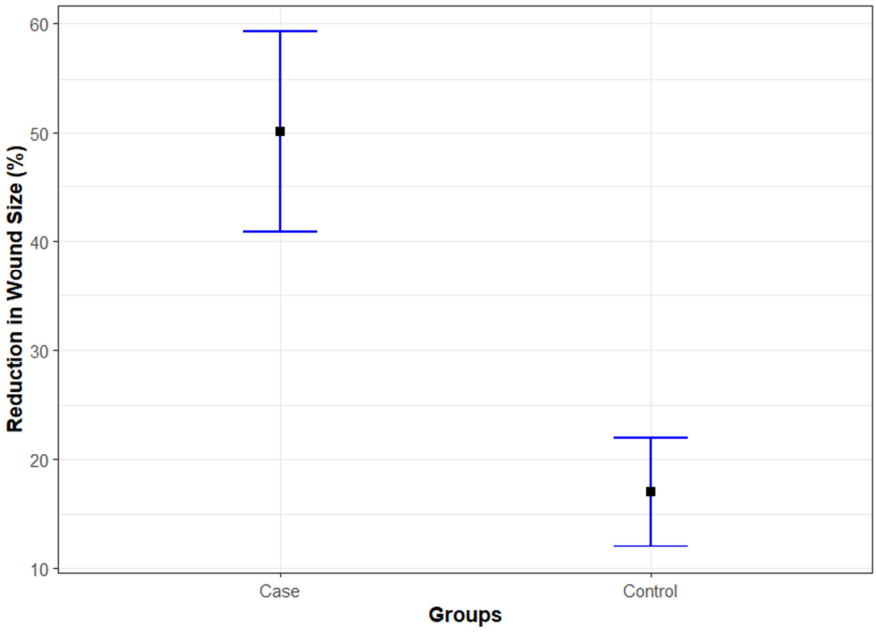
The preparation time for the case group varies from 7 to 30 days, with a mean of 13.29 ± 5.14 days and a median of 12 days.For the control group, the preparation time ranges from 5 to 60 days, with a median of 11 days and an average of 13.23 ± 9.26 days. According to the M W U test, there isn't statistically significant difference in the groupA and group B wound preparation times (p-value = 0.3893).

The case group exhibits a mean reduction of 50.1 ± 26.77% with a median of 52% (range: 8% to 92%). The control group, however, shows a much lower mean reduction of 16.99 ± 14.52% with a median of 13.3% (range: 1.3% to 70%). The case group experienced a much larger reduction in wound size than the control group, according to the M W U test results, which also indicate a significant difference (p-value < 0.001) in the degree of wound size reduction between the groups.

In terms of granulation tissue, all participants in both groups had granulation tissue present (100% in both groups), resulting in no significant difference (p-value = 1).



Graph 8 : Mean plot of wound preparation time over groups.



Graph 9 : Mean plot of Reduction in Wound Size over groups.

In summary, the study indicates that the case group (insulin dressing group) experienced significantly more effective wound healing in comparison to the diabetic ulcer control group (standard saline dressing).

DISCUSSION

One of the most common non-communicable diseases, diabetes is becoming more and more common in India as well as throughout the world. Diabetic foot ulcers are one of the most serious side effects of diabetes, affecting 15 to 25 percent of the population.

Diabetes mellitus-related foot ulcers present a significant challenge to the treating surgeon due to their intricate pathophysiology and the existence of numerous interrelated variables that impede the healing process. Achieving a balance between the local wound environment and the patient's glycemic condition is crucial for optimal wound healing outcomes.

Numerous more recent developments have been made in the local wound treatment of diabetic foot ulcers over the years. There has always been a search for an all-around modality that could be therapeutically effective, affordable, accessible, and have little to no side effects because of the rise in antibiotic resistance and the potential for negative effects with existing treatment alternatives.

Numerous elements, both internal and external to the patient, interact intricately to facilitate the healing of diabetic foot ulcers.The best chance of an ulcer healing is only possible if all of these factors—neuropathy, vasculopathy, local infection, and immunity—are properly addressed. Since the outset, managing diabetic wounds has involved local dressing, antibacterial therapy, and appropriate glucose control in addition to anti-diabetes medicine.

Many studies have shown how insulin helps the wound-healing process, and it is generally acknowledged that insulin plays a crucial role in accelerating this healing process.It was discovered through in vivo experiments that Insulin Like Growth Factor- (IGF), which genetically resembles insulin, promotes the growth and migration of keratinocytes,fibroblasts and endothelial cells.Additionally, it promotes the production of extracellular matrix and helps granulation tissue advance. In addition to promoting wound healing, granulation tissue formation, re-epithelialization, and collagen synthesis, insulin affects the activity of human growth hormone receptors in the skin. Furthermore, insulin promotes human keratinocyte migration and multiplication, which promotes cell growth and improves wound healing. Attempts were made in the 20th century to use topical insulin formulations to treat localized peripheral tissue hyperglycemia. Subsequent studies, however, have turned their attention to topical insulin administration in connection to IGF.

The goal of the study was to find out how well topical insulin worked at a tertiary healthcare facility to heal diabetic ulcers. The 70 participants were split into two groups for the analysis: the Case group, which received a Topical Insulin Dressing(Group A) and the Control group(Group B), which received a standard Saline Dressing. The analysis included information about the subjects' demographics, health, and wounds.

Demographic characteristics such as age and sex distribution were comparable between the case (54.31 ± 11.71 years and 10 females) and control groups (56.4 ± 13.1 years and 10 females), indicating no significant differences that could confound the results.

Similarly, medical details such as smoking status (p=0.6157), HbA1c levels (p = 0.4614), culture results (p = 0.1704), viral markers (p = 0.9999), and colour Doppler studies (p = 1) showed no significant variations between the groups, ensuring a relatively homogeneous sample.

However, notable differences were observed Between the cases group (median - 5) and the controls group (median -13), the case group's diabetes mellitus (DM) duration was noticeably shorter, suggesting that patients with a shorter duration of DM might respond more favorably to topical insulin therapy. Additionally, while most participants were nonsmokers in both groups, Moreover, there was no discernible variation in the distribution.of smokers, which could potentially influence wound healing outcomes.

It's interesting to note that the case group's mean +/- SD = 50.1 ± 26.77 wound size reduction was considerably higher (p = <0.001) than the control’s group mean +/- SD = 16.99 ± 14.52 wound size reduction, suggesting that topical insulin dressings are more effective at accelerating wound healing. This finding suggests that topical insulin may have a substantial impact on accelerating wound closure in diabetic ulcers compared to conventional saline dressing.

Dr. Pandey Sanjay et al., conducted a hospital based study on assessing effectiveness of normal saline dressing versus topical insulin dressings for diabetic ulcers. In this research, they excluded cases of those patients who had wagner grade 5 ulcers and patients on immunosuppressive agents similar to our study.

In this study, Topical insulin dressing was administered to patients in group A, while regular saline dressing was given to patients in group B.The patients were then

followed up to 12 days. On the 12th day, it was noted that the ulcer surface area mean difference in group A was 3.2 =/- 0.7 cm2, whereas in group B it was 2.9 +/- 0.8 cm2. Thus, it was determined that group A's wound reduction is noticeably superior to group B's. These outcomes were consistent with the study[147]

In a clinical study by Soujanya et al.,In order to determine which is more effective for healing chronic diabetic ulcers, topical insulin or topical phenytoin application was compared. In this study, ulcer size in group A showed a reduction of 42 % from day 0 to day 30 and 31 % in group B from day 0 to day 30. Twenty-six patients in group A had a good ulcer bed with good granulation tissue and negative culture growth, while twenty-three patients in group B had a good ulcer bed with negative culture growth[148].

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. Moreover, comorbidities and nutritional status are two other potential factors impacting wound healing that were not investigated in this study.

CONCLUSION

The results of our investigation demonstrate that, in diabetic foot ulcers, topical insulin treatment differed significantly from saline dressing in terms of the percentage of ulcer size reduction and the rate at which granulation tissue formed.

In conclusion, the study provides evidence supporting the topical insulin application helps in promoting the healing of diabetic ulcers.

To confirm these results and clarify the underlying mechanisms of action, more investigation including bigger sample sizes and multicentre investigations is necessary. Additionally, investigating long-term outcomes and cost-effectiveness of topical insulin therapy would be valuable for clinical practice

SUMMARY

The study titled "**STUDY OF EFFECTIVENESS OF TOPICAL INSULIN ON HEALING OF DIABETIC ULCERS AT TERTIARY HEALTH CARE CENTER"** is a randomized controlled trial study conducted at KAHER'S Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi conducted from

- The study conducted a Randomized Controlled Trial (RCT) over one year to evaluate the efficacy of topical insulin dressing compared to normal saline dressing in treating diabetic ulcers.

- 70 patients with diabetic ulcers, evenly distributed into two groups , participated in the trial. Group A received insulin dressing while Group B received normal saline dressing. Key outcome measures included wound size reduction, presence of granulation tissue, and wound preparation time.

- Data analysis was performed using SPSS, employing chi-square tests and Mann-Whitney U tests to assess statistical significance.

- Demographic analysis revealed no significant differences in age or sex distribution between Group A and Group B, ensuring baseline comparability. However, Group A exhibited a significantly shorter duration of diabetes mellitus compared to Group B, which could potentially influence wound healing outcomes.

- In terms of wound details, Group A demonstrated a substantial 50.1% reduction in wound size over the study period, whereas Group B showed a

modest reduction of 16.99%. This difference in wound size reduction between the groups strongly suggests the superior efficacy of insulin dressing in promoting diabetic ulcer healing.

- The discussion focused on elucidating the biological mechanisms through which insulin enhances wound healing, referencing previous literature to support the findings. Insulin is known to stimulate cell proliferation and collagen synthesis, crucial processes in wound repair.

- The study acknowledged limitations such as the relatively small sample size and single-center design, which may affect the generalizability of the results. Future research recommendations included larger sample sizes, multicenter trials, and longer follow-up periods to further validate the efficacy of insulin dressing and explore its broader clinical implications.

- In conclusion, the study demonstrated that topical insulin dressing significantly improves diabetic ulcer healing compared to normal saline dressing, primarily evidenced by substantial reductions in wound size.

- These findings underscore the potential of insulin as a therapeutic intervention in diabetic wound care. The study advocates for expanding research efforts to include larger and more diverse patient populations across multiple centers, with extended follow-up to corroborate and expand upon these initial findings

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ANNEXURE – I –

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

INFORMED CONSENT FORM "**STUDY OF EFFECTIVENESS OF TOPICAL INSULIN ON HEALING OF DIABETIC ULCERS AT TERTIARY HEALTH CARE CENTER"**

Name of Student/Principal Investigator:

Name of Guide/Co Investigators:

Objective:

- To assess the effectiveness of the topical insulin application in diabetic patients
- To Compare the effectiveness of topical insulin application versus normal Saline dressings in diabetic patients

Introduction: Chronic wounds or ulcers are the wounds that have failed to progress through the orderly process that produces satisfactory anatomic and functional integrity or that have proceeded through the repair process without producing an adequate anatomic and functional result. The majority of wounds that usually don't heal in 3 months are considered as chronic.1,2 The unique feature of a chronic wound is their inability to heal despite the best management which would be undertaken, especially the diabetic ulcer, pressure ulcers or bed sores. Current estimates indicate that nearly 6 million people suffer from chronic wounds worldwide. The prevalence of chronic wounds in India has been reported as 4.5 per 1000 population, whereas that of acute

wounds is nearly double, at 10.5 per 1000 population. The poor hygienic condition in some third world countries has been attributed as the main cause OUR STUDY AIMS TO FIND OUT IF TOPICAL APPLICATION OF INSULIN AS A COST-EFFECTIVE MEANS OF DRESSING TO INCREASE EFFICACY OF WOUND HEALING.

Explanation of procedure: Surgical debridement of dirty wounds will be done under anaesthesia. Then the ulcers will be included in the study. Time required for preparing the ulcers from the time of admission till enrolment in the study is considered as wound preparation time. While considering the hospital stay of patients this wound preparation time was not taken into account. In Group A, ulcers will be cleaned with normal saline and then irrigated with 4 units (0.1 ml) of human soluble insulin (Actrapid) in 1 ml normal saline (0.9%) for each 10 cm2 of wound. The solution prepared will be sprayed on the ulcer surface with an insulin syringe twice daily and ulcer left to dry and then covered with sterile cotton gauzes. In Group B, ulcers will be cleaned with normal saline without insulin and covered with sterile gauzes. 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: I 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.

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 "STUDY OF EFFECTIVENESS OF TOPICAL INSULIN ON HEALING OF DIABETIC ULCERS AT TERTIARY HEALTH CARE CENTER". 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

PROFORMA / QUESTIONNAIRE TO BE USED FOR DATA COLLECTION The proposed proforma / questionnaire to be used for data collection for the study titled **"STUDY OF EFFECTIVENESS OF TOPICAL INSULIN ON HEALING OF DIABETIC ULCERS AT TERTIARY HEALTH CARE CENTER"** is as:

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

PAST HISTORY:

FAMILY HISTORY:

PAST HISTORY: H/0 DIABETES, HTN, SMOKER

TREATMENT HISTORY:

ON GENERAL EXAMINATION: SYSTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

C.N.S.:

P.A.:

INVESTIGATIONS:

CULTURE AND SENSITIVITY

FBS

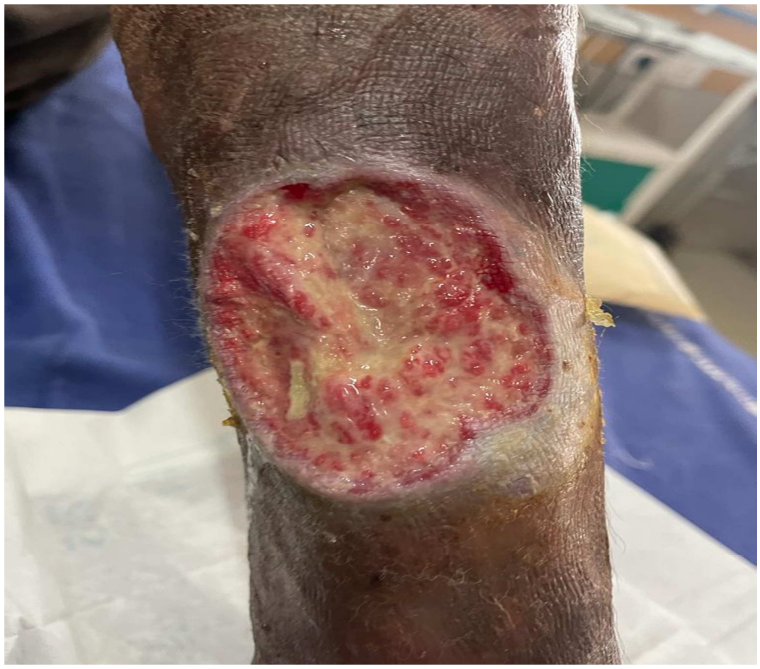
HBA1C

VIRAL MARKERS

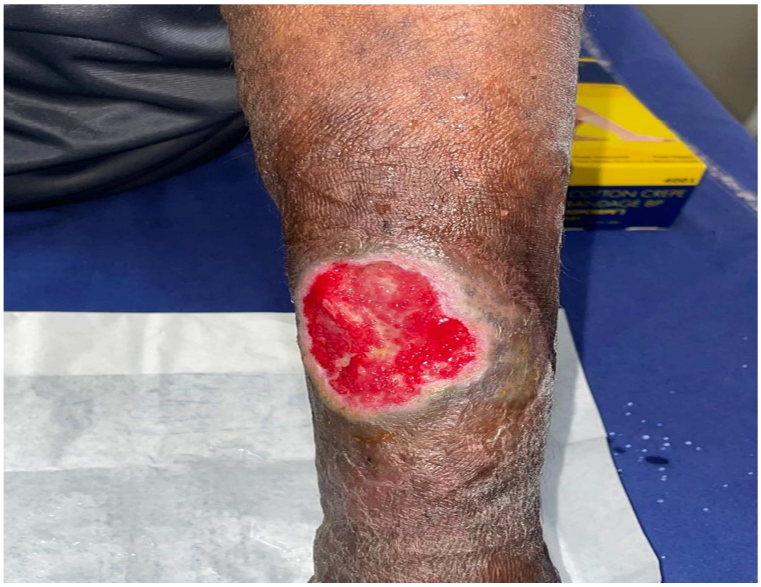
ANNEXURE – III PHOTOGRAPHS

Insulin dressing

Day 0

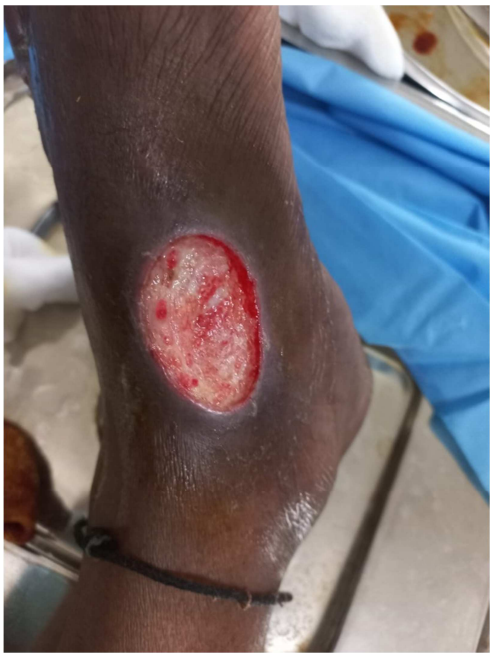


Day 42

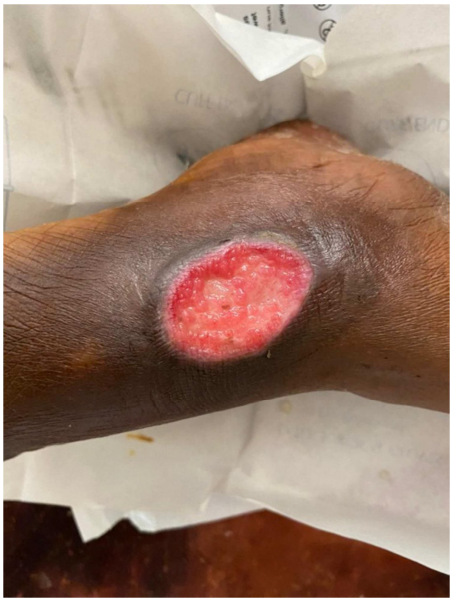


Saline dressing

Day 0



Day 42



ANNEXURE IV MASTER CHART