"GLYCOSYLATED HEMOGLOBIN LEVELS AND WOUND HEALING IN DIABETIC FOOT ULCERS, IN TYPE 2 DIABETES – ONE YEAR PROSPECTIVE STUDY"

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Endorsement by the HOD/ Principal/ Head of the Institution

This is to certify that the dissertation entitled **"GLYCOSYLATED HEMOGLOBIN LEVELS AND WOUND HEALING IN DIABETIC FOOT ULCERS, IN TYPE 2 DIABETES – ONE YEAR PROSPECTIVE STUDY"** is a bonafide research work done by **Dr. PRIYANKA R HEGDE** under the guidance of

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LIST OF ABBREVIATIONS

DM	–	Diabetes Mellitus
DFU	–	Diabetic Foot Ulcer
HbA1c	–	Glycosylated hemoglobin
Hb	–	Hemoglobin
PVD	–	Peripheral Vascular Disease
WHO	–	World Health Organization
ADA	–	American Diabetes Association
IDF	–	International Diabetes Federation
FBG	–	Fasting blood glucose
RBG	–	Random blood glucose
PPBG	–	Post prandial blood glucose
RBC	–	Red blood cells
GDM	–	Gestational diabetes mellitus
PCOS	–	Polycystic ovarian syndrome
PDGF	–	Platelet derived growth factor
AGEs	–	Advanced glycation end products
MMPs	–	Matrix metalloproteinases
ABPI	–	Ankle brachial pressure index
TCC	–	Total contact casts
CI	–	Confidence interval
BMI	–	Body mass index
MRSA	–	Methicillin resistant staphylococcus aureus
P value	–	Probability value
HPLC	–	High performance liquid chromatography

eAG	–	Estimated average glucose
UKPDS	–	United Kingdom Prospective Diabetes Study
DCCT	–	Diabetes Control and Complications Trial
NICE	–	National Institute of Healthcare and Excellence
RCT	–	Randomized control trial

ABSTRACT

Introduction: Diabetes mellitus is a metabolic disorder that is characterized by hyperglycemia. It is associated with many chronic complications that lead to significant disability, morbidity and even mortality. Diabetic foot ulcers (DFUs) are now the most common cause of non-traumatic lower limb amputation. The main pathophysiological factors associated with DFUs are – neuropathy, vasculopathy, wound infection and poor wound healing. Diabetes is known to alter all stages of the normal wound healing process. Studies have proven that hyperglycemic state alters cellular and molecular processes which occur in wound healing. Thus, control of hyperglycemia or strict glycemic control may help to promote faster wound healing.

The long-term glycemic control is best represented by glycosylated hemoglobin or HbA1c which is the level of average plasma glucose over 2 to 3 months. HbA1c is now an indispensable laboratory test that is used to screen and diagnose diabetes mellitus. It is also used to guide the treatment regimens to attain adequate glucose control. Elevated HbA1c levels have been implicated as predictors of microvascular complications of diabetes such as neuropathy, retinopathy and nephropathy. The aim of this study is to find an association between HbA1c and wound healing and also to establish HbA1c as a predictor of wound healing in DFUs.

Methodology: This prospective study was conducted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, from January 2017 to December 2017. It included 90 type 2 diabetic patients who were admitted to the hospital with diabetic foot ulcers. The HbA1c levels of all patients was measured at admission for all the 90 patients. The 90 patients were then divided into 3 groups based on their HbA1c levels into group 1 (<7%), group 2 (7% to 8%) and group 3 (>8%). The healing of diabetic foot ulcers with conventional saline dressing was recorded as area

reduction over 15 days. The wound healing was calculated as area reduction per day or rate of wound healing (rate of wound healing = area reduction/15). The association between HbA1c levels and rate of wound healing was then analyzed.

Results: Of the 90 patients, 67 (74.4%) were males and most of them (35 of 90 or 38.9%) aged more than 61 years. The mean duration of diabetes was around 9 years and majority of them (44.4%) had diabetic foot ulcer for 1 to 4 weeks. All of these parameters and other parameters such as location of ulcer and grade of ulcer showed no significant difference in distribution among the 3 groups. Presence of neuropathy, PVD or wound infection which are implicated as risk factors for DFU did not show statistically significant association with the rate of wound healing. Only HbA1c level was found to have statistically significant association with rate of wound healing. (P value < 0.001)

Conclusion: This study concluded that HbA1c was the only independent factor to be significantly associated with wound healing and wound outcome. Few studies done previously have found a positive association between HbA1c levels and wound healing. Thus, HbA1c may be considered as a good predictor of wound healing in DFUs. More similar studies and RCTs are required to establish this.

Keywords: glycosylated hemoglobin, HbA1c, wound healing, diabetic foot ulcers, type 2 diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, which can be caused by reduced insulin secretion, decreased glucose utilization or increased glucose production.[1]

The worldwide prevalence of DM is 422 million as reported in 2016, with a global prevalence of 8.5% of total population. The disease is on a steady rise and the number is projected to double by 2030. Diabetes currently affects more than 62 million Indians, which is more than 7.1% of the adult population, making it second only to China as the country with the most number of diabetics. [2]

DM is associated with many chronic complications. These include retinopathy, nephropathy, cardiovascular diseases, neuropathy and limb complications. DM is also associated with impaired wound healing, increased rate of wound infection and wound failure. Hyperglycemia and impaired glycemic control which is characteristic of DM, is thought to interfere with normal process of wound healing.[1]

Limb and foot ulceration represent a common and often serious problem. Diabetic foot ulcer (DFU) is now the leading cause of nontraumatic lower limb amputation. [2] The lifetime risk of a diabetic developing a foot ulcer is 15% out of which 14-24% risk amputation.[3]

Multiple factors are involved in the pathogenesis of DFUs such as neuropathy, vasculopathy, infection, altered foot biomechanics and poor wound healing.[1] Thus, treatment of diabetic foot ulcer requires multidisciplinary approach.

The optimization of wound healing process in diabetic foot ulcers can be achieved by identifying modifiable factors that affect wound healing. Previous studies done to identify such factors have not yielded satisfactory results. There is a lack of a single and universally accepted predictor of wound healing in diabetic foot ulcers.

Studies have proved that uncontrolled diabetes mellitus or impaired glycemic control is associated with increased risk and faster progression of microvascular and macrovascular complications. Studies have also proved that an improvement in the glycemic control reduces risk of retinopathy by 47%, nephropathy by 54% and neuropathy by 60%. It also reduces the occurrence and progression of other complications including lower limb ulceration and amputation.[1] Considering the above, it may be postulated that an improvement in glycemic control may also improve and promote wound healing in diabetics.

The glycemic control of a patient can be measured using various tests such as – fasting blood glucose (FBG), post-prandial blood glucose (PPBG), random blood glucose (RBG) and glycosylated hemoglobin. (HbA1c).

Glycosylated hemoglobin or HbA1c is a form of hemoglobin which is formed by covalent bonding of glucose to hemoglobin. The level of HbA1c in blood indicates an average 3-month glycemic control (as the lifespan of RBCs is 120 days). HbA1c test can therefore be used to monitor the long-term glycemic control of patients with DM.[4] The advantage of HbA1c over FBG include, greater convenience of testing, since fasting is not required prior to test, and lesser day to day variations. Therefore, HbA1c is now a routine and mandatory test used in screening and diagnosing DM.

Few studies have been done previously, to find an association between HbA1c and wound healing in DFUs and the results have been inconclusive. Therefore, this study was designed to establish an association between HbA1c and healing in DFUs and to also find if it can be used as a predictor of wound healing.

OBJECTIVES

To study the association between HbA1c levels and rate of wound healing of diabetic foot ulcers in patients with type 2 diabetes mellitus.

REVIEW OF LITERATURE

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[5]

Diabetes mellitus can be classified into the following types–

- ***Type 1***- complete or near-total insulin deficiency.
- ***Type 2*** - more common and is characterized by variable degrees of insulin resistance, impaired insulin secretion, and glucose intolerance.
- ***Gestational DM*** – glucose intolerance developed during pregnancy.
- ***Other types*** – include specific genetic defects in insulin secretion or action and metabolic abnormalities that impair insulin secretion.[1]

The risk factors for developing DM include – family history of diabetes, obesity, previously identified with impaired glucose tolerance, history of GDM, hypertension, hypertriglyceridemia and polycystic ovarian syndrome (PCOS).

Table 1: Criteria for diagnosis of DM (according to ADA)[1] –

Criteria	Value
Random blood glucose (RBG)	Symptoms of diabetes with RBG $\geq$ 200mg/dl
Fasting plasma Glucose	126 mg/dl
HbA1c	$\geq$ 6.5%
2-hour Oral glucose tolerance test (OGTT)	Plasma glucose > 200 mg/dl

Complications of DM: The metabolic dysregulation associated with DM causes secondary pathophysiological changes in multiple organ systems that lead to various complications which are a major cause of morbidity and mortality associated with the disease.

The chronic complications of DM are –

1. ***Microvascular***
    - Eye disease – retinopathy, macular edema
    - Neuropathy – sensory, motor and autonomic
    - Nephropathy
2. ***Macrovascular*** - Coronary arterial disease, peripheral arterial disease, cerebrovascular disease.
3. ***Other*** – gastrointestinal (gastroparesis, diarrhoea), dermatological, diabetic foot and limb complications.[1]

Diabetic foot ulcer:

Lower extremity complications including foot ulcers form a major source of morbidity in diabetics. DM is the leading cause of nontraumatic lower extremity amputation. Limb amputation greatly affects the quality of life of individuals and also places a burden on families and health care systems. The incidence of DFU in different populations is 1 to 4% and prevalence ranges from 5 – 10%. The lifetime risk of a diabetic developing foot ulceration is around 15%.[7]

Applied anatomy of the foot:

"The human foot is a masterpiece of engineering and a work of art" – Leonardo da Vinci

The human foot symbolizes the evolution of humans to biped beings, helping in weight bearing and locomotion. It is an integrated and complex structure comprising of 26 bones, 33 joints and over 100 muscles, tendons and ligaments.[29]

The foot can be divided into –

- ***Forefoot*** – consists of phalanges (proximal, middle and distal) and metatarsal bones. It plays an important role in the gait cycle when the foot leaves the ground during toe – off. In diabetic neuropathy, plantar pressure is increased due to toe and metatarsal deformities leading to ulcerations.
- ***Midfoot*** – includes the 3 cuneiforms, navicular and cuboid. It articulates with the hindfoot through the Chopart's joint and the forefoot through the Lisfranc's joint
- ***Hindfoot*** – consists of the talus and calcaneum. It supports the weight of the body while standing and walking.

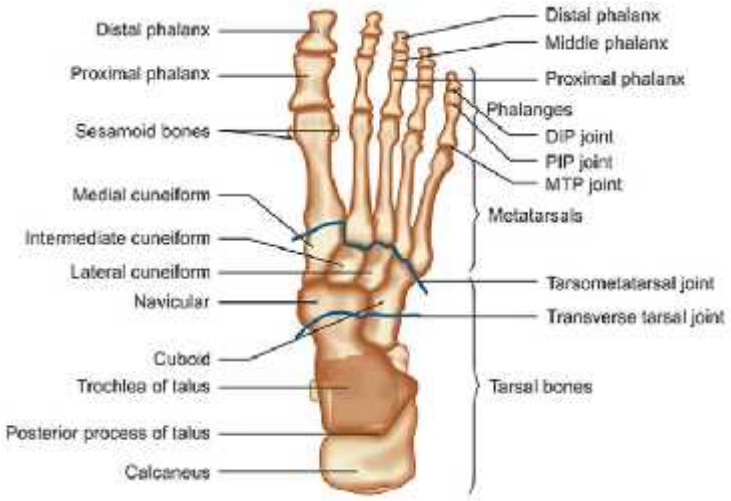


Figure 1: Bones of the foot. [29]

The muscles of the foot include -

- ***Extrinsic muscles*** – originate from the leg and insert into the foot. These are mainly involved in movement. It includes muscles of the anterior, lateral and posterior compartments of the leg.

Table 2: Extrinsic muscles of foot

Muscle group	**Muscles**	**Nerve supple**
Anterior compartment (dorsiflexors)	o Tibialis anterior o Extensor hallucis longus o Extensor digitorum longus	Deep peroneal nerve
Lateral compartment	o Peroneus longus o Peroneus brevis	Superficial peroneal nerve
Posterior compartment (plantar flexors)	o Gastrocnemius o Soleus o Tibialis posterior o Flexor digitorum longus o Flexor hallucis longus	Tibial nerve

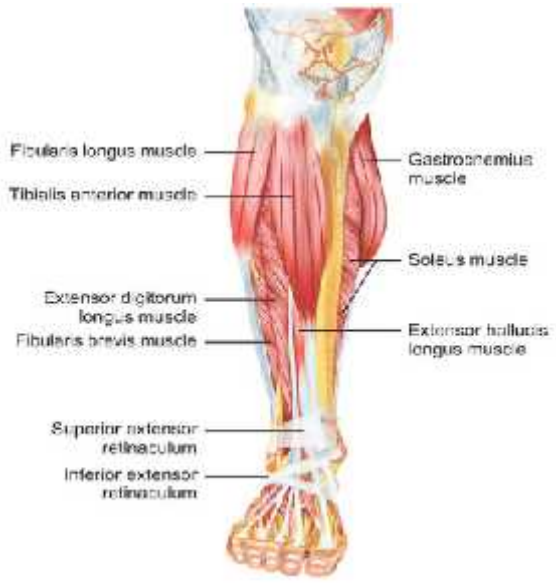


Figure 2: Extrinsic muscles of foot.[29]

- ***Intrinsic muscles*** – origin and insertion in the foot. These muscles and tendons contribute in supporting the arches of the foot. Neuropathy leads to dysfunction of these muscles which causes foot deformities. The muscles are dorsal and plantar. Plantar muscles consist of 4 layers.[29, 32]

Table 3: Intrinsic muscles of foot

Muscle group	**Muscle**	**Nerve supply**
Dorsal muscles	Extensor digitorum brevis Extensor hallucis brevis	Deep peroneal nerve
Plantar muscles		
1st layer	Abductor hallucis Flexor digitorum brevis Abductor digiti minimi	Medial and lateral plantar nerve
2nd layer	Quadratus plantae Lumbricals	Medial and lateral plantar nerves
3rd layer	Flexor hallucis brevis Flexor digiti minimi brevis Adductor hallucis	Medial and lateral plantar nerves
4th layer	Dorsal and plantar interossei	Lateral plantar nerve

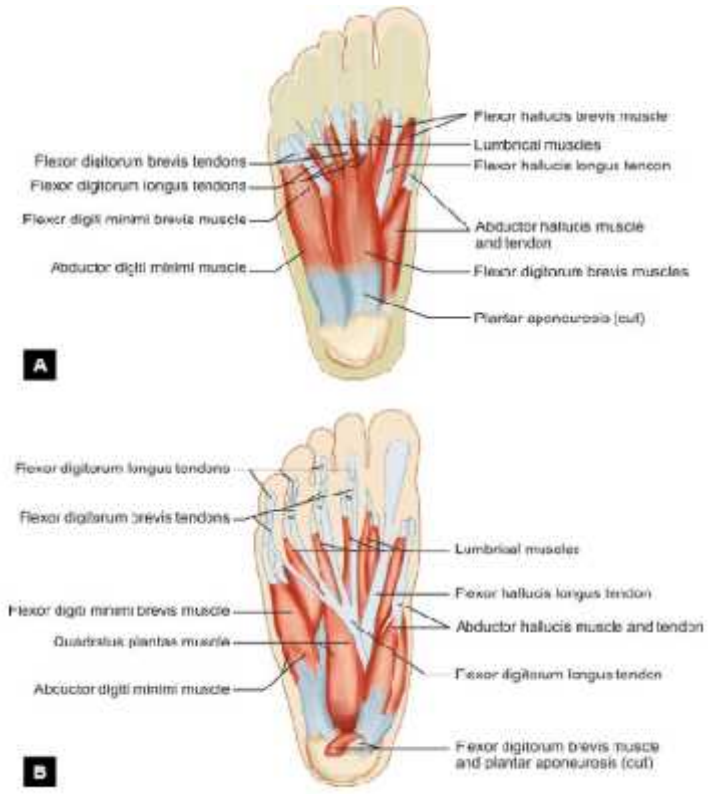


Figure 3: Intrinsic muscles of foot.

Arches of the foot –

The bones of the foot do not lie in a horizontal plane, but are arched. Arches are formed by metatarsal and tarsal bones and are strengthened by ligaments and tendons of the foot. These arches have a protective role. They absorb and distribute the downward forces from the body while standing and walking.

There are 2 main arches –

- ***Longitudinal arch***: formed between the posterior end of calcaneum and metatarsal heads. It consists of medial and lateral part.
- ***Transverse arch***: is highest in the coronal plane. It cuts through the head of the talus and ends in the metatarsal.

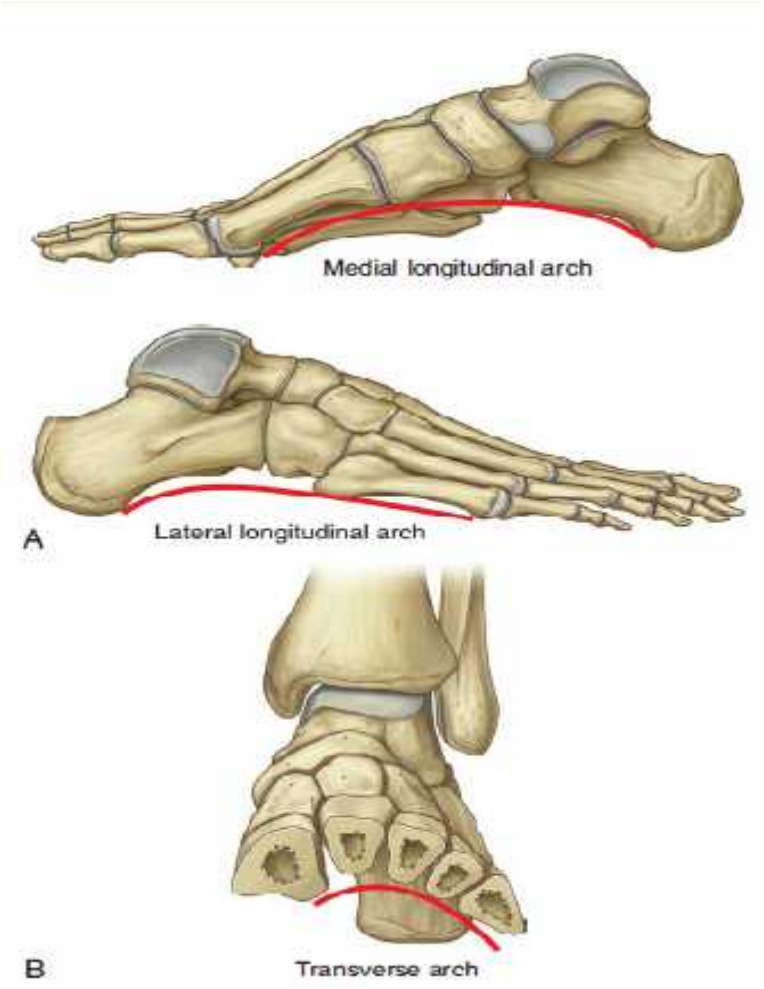


Figure 4: Arches of foot[32]

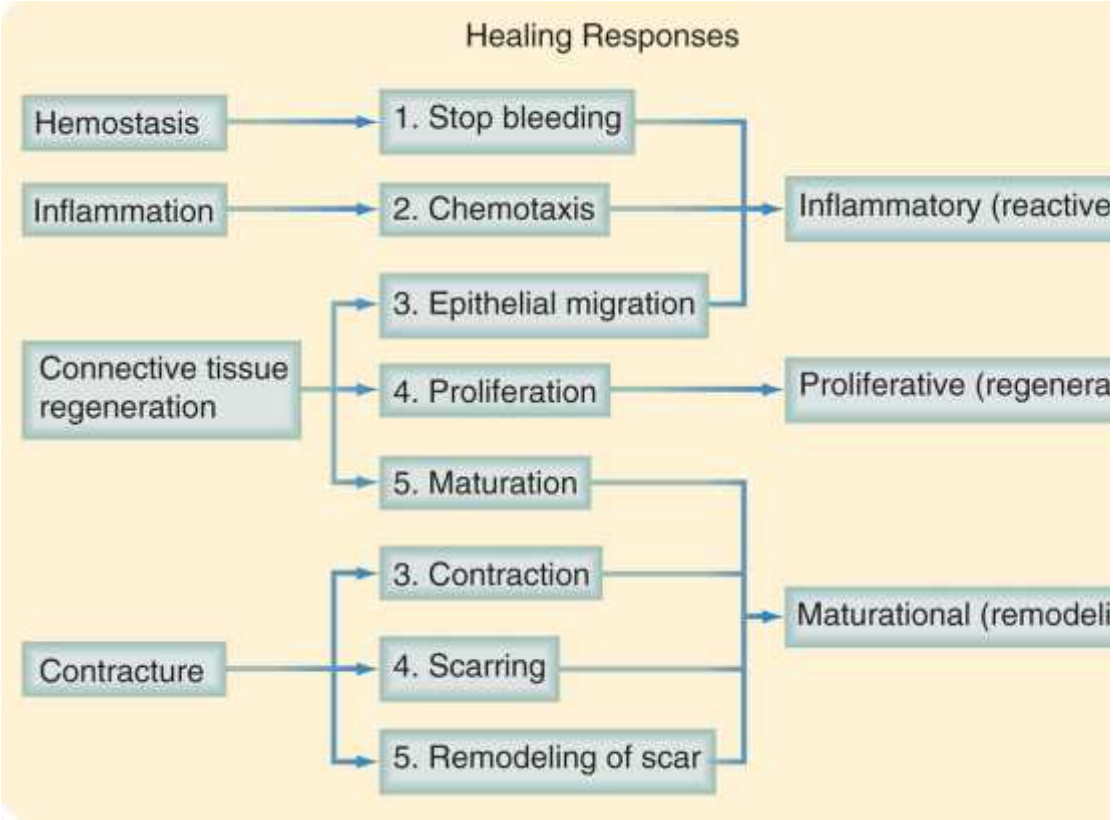
Wound healing:

"*Healing is a matter of time, but it is sometimes also a matter of opportunity" – Hippocrates*

Wound healing is the effort of injured tissues to restore their normal function and structural integrity.[13]

The process of wound healing involves a series of cellular and biochemical events which all wounds need to undergo to successfully re-establish tissue integrity. This process can be divided broadly into the following phases:

- Inflammatory phase
- Proliferative phase
- Maturation phase



Flowchart 1: Phases of wound healing

Inflammatory phase – consists of hemostasis and inflammation. Hemostasis initiates inflammation. Wounding causes exposure of subendothelial collagen to platelets which in-turn initiates platelet aggregation, degranulation and activation of coagulation cascade. Platelets also release a number of factors such as platelet derived growth factor (PDGF), fibronectin and serotonin, which are chemotactic and increase the vascular membrane permeability. Due to this there is infiltration of the wound by cells. Polymorphonuclear cells are the first infiltrating cells within 24 – 48 hrs of injury. Their primary role is phagocytosis of bacteria and tissue debris. Macrophages

infiltrate the wound next and play important role in healing. They peak in number by 48 to 96 hours and remain till healing is complete. They play a role in phagocytosis but the most important function is recruitment and activation of other cells necessary for proliferation, by releasing mediators such as cytokines and growth factors. T lymphocytes are also included in infiltrating cells but their role is undetermined.[3,13]

Proliferative phase - is characterised by formulation of granulation tissue. It roughly lasts for 4 to 12 days and includes the following processes –

- ***Angiogenesis*** – is the process of formation of new blood vessels which is necessary to support wound environment. It is stimulated by cytokines which are produced by platelets and macrophages.
- ***Fibroplasia*** – is the proliferation of fibroblasts. Fibroblasts are initially sparse then are chemoattracted to site of injury. They are activated by macrophages, platelet derived cytokines and growth factors. Their primary function is synthesis of collagen. Fibroblasts replace the fibrin matrix with collagen – rich matrix for developing granulation tissue. They also produce proteoglycans and glycosaminoglycans which form extra-cellular matrix.
- ***Epithelialization*** – is the restoration of external skin barrier. It includes the following sequence of changes that occurs in wound keratinocytes – detachment, migration, proliferation, differentiation and stratification. [3,13]

Maturational phase - is the final phase of wound healing and involves remodelling and re-organisation of collagen. This results in strengthening of the wound. Scar remodelling continues for almost 6 – 12 months post injury.

Wound contraction occurs due to centripetal movement of whole thickness of the

surrounding skin, resulting in decrease in size of scar. It is carried out by specialised fibroblasts – myofibroblasts and their interaction with extracellular matrix.[3,13]

Factors affecting wound healing:

Factors that negatively affect or impede wound healing can either be local or systemic. If these factors are not corrected, it can result in wound complications and chronic non-healing wounds.

LOCAL -

- Wound infection – leads to chronic inflammation and delay in healing process.
- Foreign body in wound
- Wound hypoperfusion or hypoxia
- Ionizing radiation
- Repeated trauma

SYSTEMIC -

- Malnutrition and deficiency of vitamins (C, A, E) and minerals (zinc, iron).
- Immunodeficiency
- Metabolic disorders - Diabetes mellitus, obesity
- Drugs – steroids, cytotoxins.
- Advanced age – altered immune response, delayed epithelialization, collagen synthesis and angiogenesis. [3,13,14]

Impaired wound healing in diabetics:

Due to increasing incidence and its epidemic nature, diabetes mellitus is now the most important systemic factor that is involved in delayed wound healing. It affects all stages of the wound healing process. Multiple factors and complex pathophysiological mechanisms are involved at the macroscopic and microscopic level in impaired wound healing in diabetics.

As discussed, DM is associated with neuropathy, atherosclerosis and infection. Neuropathy causes repetitive trauma to tissues and atherosclerosis of large and small vessels contributes to tissue hypoxia and ischemia. Diabetics are susceptible to infection due to attenuated inflammatory response, impaired chemotaxis and inefficient phagocytosis.[13,22]

Studies have shown that uncontrolled diabetes can cause specific changes at the cellular level of wound healing. It is seen to impair angiogenesis, capillary growth, granulocyte function, fibroblast proliferation and collagen synthesis. There is also increased degradation and decreased deposition of collagen. The collagen formed in diabetic ulcers is brittle as compared to normal collagen.

Hyperglycemia in diabetes results in keratinocyte dysfunction resulting in inadequate epithelialisation. Hyperglycemic environment also causes T-cell dysfunction which makes wound susceptible for infection.[15, 16, 19]

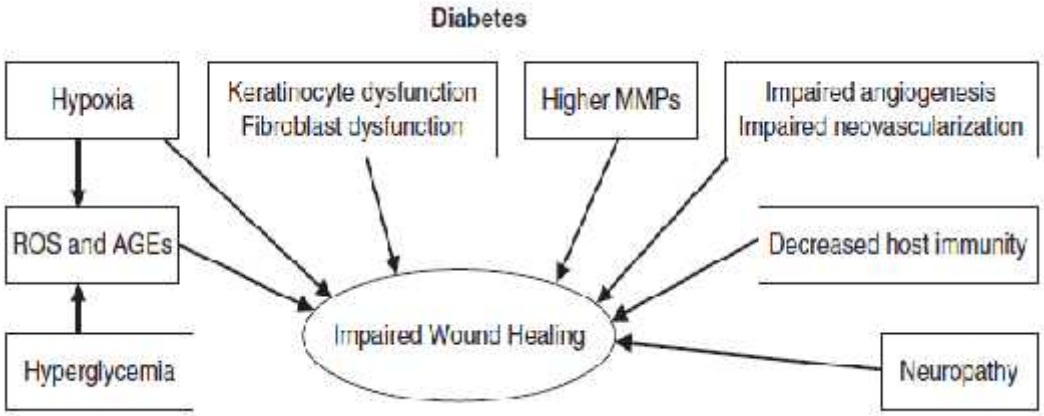
Hyperglycemia causes metabolic alterations in the cell which leads to impaired wound healing in diabetics. One hypothesis for this is that high glucose levels leads to increased activity of the polyol pathway, in which glucose is converted to sorbitol which collects in the cell. Sorbitol increases risk of oxidative stress on the

cell.[15,18]

Hyperglycemia is also seen to cause activation of protein kinase C (PKC), which alters transcription of genes for fibronectin, collagen and ECM proteins.[1]

Another study suggests that hyperglycemia and increased intracellular glucose leads to formation of pathological by-products called "advanced glycation end products" (AGEs). They are modifications of proteins and lipids that are non-enzymatically glycated and oxidised after contact with aldose sugars. They are thought to play a role in microvascular and macrovascular complications of diabetes. AGEs accumulate in the cell and may disturb cellular structure and function. They have been shown to cross- link with proteins and alter composition and structure of extracellular matrix, thus causing delayed wound healing.[15,17]

Some studies have also suggested that wounds in diabetics contain decreased growth factor levels. Growth factors are necessary for normal wound healing. Decreased levels of growth factors is due to increased levels of matrix metalloproteinases (MMPs) in the wounds. MMPs are enzymes that have proteolytic activity and thus destroy growth factors.[15,34]



Flowchart 2: Causes of impaired wound healing in diabetes

Pathophysiology of Diabetic foot ulcer:

The pathophysiological changes that occur in the foot of diabetics is now termed as 'diabetic foot syndrome' and foot ulcer forms a part of this. The following are implicated as risk factors for DFU and amputations – male sex, duration of diabetes > 10 years, abnormal foot structure, peripheral arterial disease, history of previous ulcer or amputation, smoking and poor glycemic control.

Altered biomechanics of the foot in diabetes –

The human foot is a remarkable structure which has undergone evolutionary change enabling humans to walk upright with bipedal gait. The whole weight of the body is borne on the feet making it susceptible to stress and injury. Understanding of the biomechanics can help in prevention of such injury.

Gait cycle: is the sequence of movements occurring in the foot during walking or locomotion. It consists of 2 parts – stance phase and swing phase.

- Stance phase – is the weight bearing phase, when foot is in contact with the ground. It is divided into 3 parts – contact of heel, midstance, propulsion.
- Swing phase – is when the feet is off the ground. It can be divided into – initial, mid and terminal swing.

Due to neuropathy and hyperglycemia in diabetes, there is alteration in the normal anatomy of the foot. This results in abnormal foot biomechanics, predisposing the foot to injury and ulceration. The altered biomechanics include –

- High plantar foot pressures – usually occurs at site of bony prominences. It is seen in deformed foot.

- Decreased plantar tissue thickness – loss of protective soft tissue (cushioning) in the plantar surface of the foot can occur due to atrophy of intrinsic muscles. It also leads to high foot pressures.
- Limited joint mobility – reduced range of motion in joints of the foot is thought to occur due to glycosylation causing stiffening of collagen in joints, tendons and ligaments. It also contributes to increased plantar pressure.[7,29]

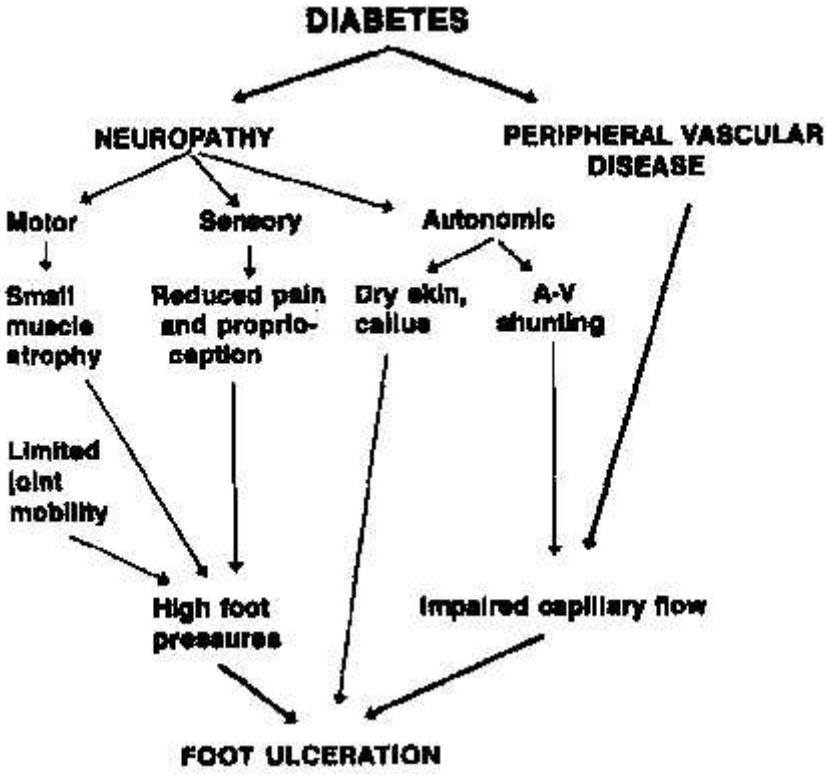
The cause for foot ulceration and lower limb complications in diabetics is due to interaction between several factors which are –

- Neuropathy – sensory, motor and autonomic
- Peripheral vascular disease or ischemia
- Infection
- Poor or abnormal wound healing [1,8]
- ***Neuropathy*** - distal lower limb neuropathy in diabetics affects all components of the nervous system – sensory, motor and autonomic and each of them contribute to development of ulceration.[9] Sensory neuropathy causes loss of sensations like pain, pressure, temperature and proprioception. These are protective to the foot and their loss makes the foot vulnerable to repeated trauma leading to ulcers.[9] Motor neuropathy causes atrophy and weakness of intrinsic muscles of the foot leading to flexion deformities of the toes, loss of plantar arches and abnormal gait. Autonomic neuropathy results in loss of sweat secretion (anhidrosis) which leads to dry, cracked skin which is susceptible to bacterial invasion. It also causes loss of sympathetic vascular tone which causes shunting of blood from arteries to veins, bypassing the

capillaries and tissues. Neuropathy thus forms a major cause for ulceration in diabetes by altering foot biomechanics.[9,10]

- ***Peripheral vascular disease*** and ischemia is the other major cause for foot ulceration. Atherosclerosis of lower limb vessels, usually distal, occurs more commonly in diabetics (2-3 times) than in normal population. PVD causes tissue ischemia which leads to tissue necrosis and ulceration.[9,10]

- ***Infection*** – is also implicated in pathogenesis of foot ulcers. Diabetics have increased susceptibility to infections due to impaired neutrophil function. Infected diabetic foot ulcers usually are polymicrobial containing both aerobic and anaerobic organisms. The most common organisms are staphylococci and streptococci.[11,12]



Flowchart 3: Pathogenesis of DFU.[11]

Classification of DFUs:

Classifying diabetic foot ulcers, aids to facilitate appropriate treatment, predict outcome and enable monitoring of healing process. There are many systems of classification that are in use.

The easiest method of classification is:

1. Neuropathic

   Ischemic

   Neuro-ischemic.

2. **Meggit – Wagner system** - most commonly used system, described by Meggit and Wagner. Foot ulcers graded based on depth of wound and extent of tissue necrosis.[8]

Table 4: Wagner's grade

GRADE	**LESION**
0	no ulcer, susceptible foot – deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer involving tendon
3	Deep ulcer with abscess or osteomyelitis
4	Local gangrene of forefoot or heel
5	Gangrene of entire foot

3. **University of Texas San Antonio (UTSA) system –**

Table: 5

Stage	**Grade**			
	0	**1**	**2**	**3**
A	Pre or post ulcerative lesions completely epithelized	Superficial wounds not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to joint
B	Infected	Infected	infected	Infected
C	Ischemic	Ischemic	Ischemic	Ischemic
D	Infected and ischemic	Infected and ischemic	Infected and ischemic	Infected and ischemic

4. **PEDIS system –**

Table: 6

Grade				
	1	**2**	**3**	**4**
Perfusion	Normal	Non- critical PAD	Critical limb ischemia	
Extent/size (cm^2)				
Depth tissue loss	Full thickness	Deep involving muscle	Bone and/ or joint	
Infection	None	Mild	Moderate/ severe	SIRS
Sensation	Intact	LOPS (loss of perceptive sensation)		

Assessment of DFUs:[7, 9]

Assessment of diabetic foot is an integral part of examination in diabetics. It is done to detect at risk foot and also to assess presence of neurological or vascular deficits. Assessment is done by the following -

- ***History*** – a comprehensive history may reveal symptoms and signs of neuropathy. History of duration of diabetes, duration of ulcer is noted. Many times, the patient is unaware of the foot ulcer as they are painless due to neuropathy.
- ***Inspection*** – to look for skin changes like cracks and fissures, callosity, ulcer and deformities of the foot.
- ***Neurological assessment*** -
    - Semmes – Weinstein monofilament test – is used to test for presence or absence of protective sensation in the foot. It exerts a linear force of 10g. The important areas assessed are uncallused regions of plantar surface of metatarsal heads.
    - Vibration sensation or threshold is tested using 128 Hz tuning fork.
    - Ankle reflex
    - Pinprick sensation
    - Temperature discrimination

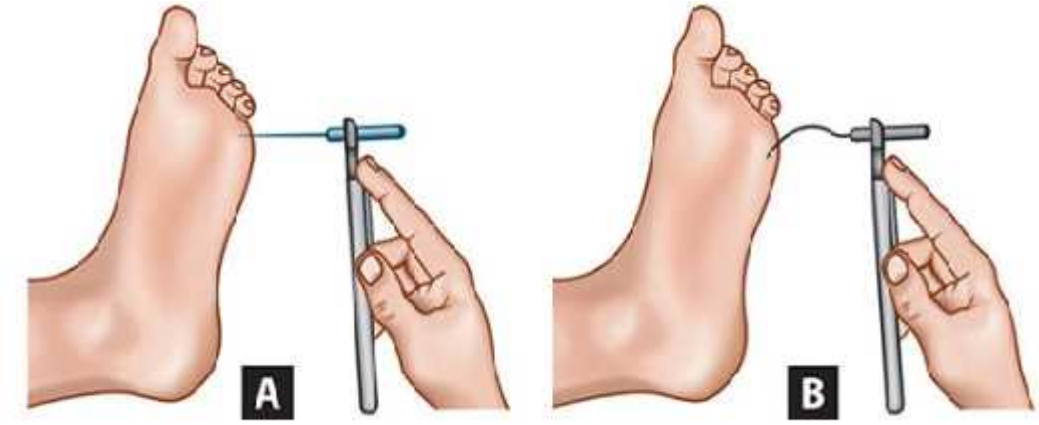


Figure 5: Monofilament test, placed perpendicular to plantar test area, force should be just enough to buckle the monofilament.

- ***Vascular assessment*** – to assess the peripheral circulation:
  - Palpation of distal arteries
  - Ankle brachial pressure index (ABPI) – is the ratio of systolic blood pressure at the ankle to the blood pressure in upper arm. It is determined by Doppler ultrasonography and is used to indicate adequacy of peripheral arterial blood flow. Normal value is 0.9 to 1.2. values less than 0.9 indicate significant ischemia.
  - Colour doppler – to look for patency of blood flow in peripheral arteries.
  - Transcutaneous oxygen tension in toes - < 40 mm of hg suggests severe ischemia.
  - ***Radiological assessment*** – baseline radiograph of the foot is advised for all patients with DFUs to evaluate the foot anatomy for changes that indicate neuroarthropathy (Charcot's joint). It may also reveal presence of osteomyelitis.

- ***Plantar pressure measurement*** – increased plantar pressure is associated with foot ulcers. Quantitative estimation of foot pressures during different activities helps in preparing appropriate footwear. It can be detected using – Harris mat and other digital methods like Podiascan and podometry.

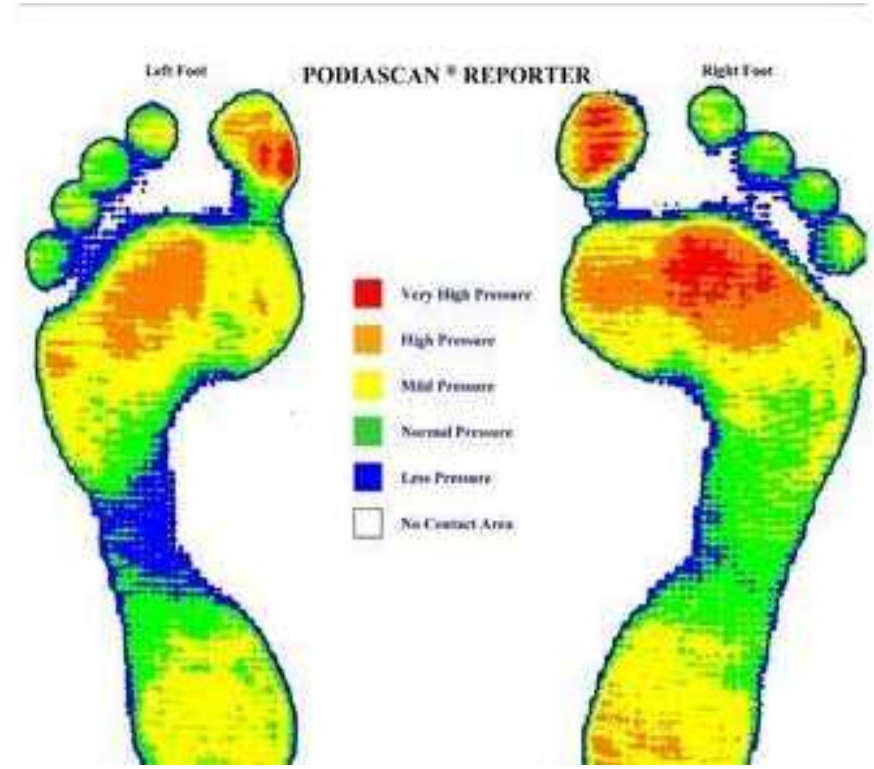


Figure 6: Podiascan

- ***Infection*** – presence of infection is confirmed by wound culture and leucocytosis in blood.

- ***Glycemic control*** – Inadequate glycemia control is associated with increased risk of neuropathy, ischemia and foot ulceration. The blood sugar control is monitored by FBG, random blood glucose and HbA1c.

Glycosylated haemoglobin (HbA1c):

Glycosylated or glycated haemoglobin is a form of haemoglobin that is derived from non-enzymatic addition of glucose to amino group of haemoglobin. HbA1c is a specific glycated haemoglobin that is formed by attachment of glucose to N – terminal valine of beta chain of haemoglobin. The levels of HbA1c in blood depends on the concentration of glucose in the blood and the lifespan of RBCs or erythrocytes. The average lifespan of RBCs is 120 days, therefore HbA1c level represents the average blood glucose levels over 8 to 12 weeks, thus making it free from fluctuations that occur daily in blood glucose levels. [4,20]

Measurement of HbA1c: HbA1c was first described in 1969 as an unusual form of haemoglobin in diabetics. The basic principle of all methods of HbA1c measurement is separation of glycated and non-glycated forms. HbA1c is reported as a percentage of total haemoglobin.

The methods include –

- Ion - exchange high performance liquid chromatography (HPLC)
- Affinity chromatography
- Immunoassays
- Capillary electrophoresis

Most laboratories use ion exchange HPLC method as there is no interference by Schiff base or carbamylated Hb.

The DCCT (Diabetes Control and Complications Trial) has found a linear correlation between HbA1c and average glucose levels.

The equation is as follows: AG (mg/dl) = (28.7*HbA1c)-46.7.[28]

Table: 7 Relation between HbA1c level and average blood glucose levels

HbA1c	Estimated average glucose (eAG)
5	97 (76-120)
6	126 (100-152)
7	154 (123-185)
8	183 (147-217)
9	212 (170-249)
10	240 (193-282)
11	269 (217-314)
12	298 (240-347)

Interpretation of HbA1c levels –

- < 5.7% - normal
- 5.7 – 6.4% – prediabetes or impaired glucose tolerance
- > 6.5% - diabetes mellitus

The target HbA1c level that is recommended by the ADA is < 7% in diabetics. This level is recommended to prevent complications of diabetes. For older patients, the recommended target may be upto 8% to avoid the risk of hypoglycaemia.[28]

HbA1c is now a recommended standard laboratory test that is used for screening and diagnosing diabetes mellitus. It is also used to monitor the long term

glycemic control, adjust therapy, assess the quality of diabetes care and also predict the risk of development of complications. NICE (National Institute of Healthcare and Excellence) guidelines recommend measurement of HBA1c every 2 to 6 months in diabetics till the blood glucose concentration is stable.[4] The advantage of HbA1c is that there is no requirement of fasting prior to testing. Also, there is less variation as compared to FBG.

Limitations of HbA1c – HbA1c cannot be used to diagnose diabetes in children or diagnose type 1 diabetes and gestational DM. HbA1c levels are also affected by factors which alter erythrocyte life span like hemolytic anemia, severe iron deficiency anemia, hemoglobinopathies and recent RBC transfusions. HbA1c cannot be used to diagnose diabetes in children and HbA1c levels may also be altered in pregnancy, uremia, hyperbilirubinemia and hypertriglyceridemia[20,28]

HbA1c and complications of DM - Studies have found that raised HbA1c is associated with increased risk of both microvascular and macrovascular complications of DM. Studies have also shown that a higher HbA1c level (indicates poor glycemic control) is associated with earlier onset and faster progression of diabetic complications like retinopathy, nephropathy, cardiovascular and peripheral vascular disease. Studies and trials conducted over the years such as the DCCT and UKPDS (United Kingdom Prospective Diabetes Study) have also proved that improvement in the glycemic control results in fewer diabetic complications.

The UKPDS also demonstrated that each percentage decrease in HbA1c was associated with 35% reduction in microvascular complications. [20,21,1]

Therefore, HbA1c can be used as a predictor and prognostic indicator of diabetic complications.

HbA1c as a predictor of wound healing in diabetics:

As discussed above, multiple factors play a role in impaired wound healing in diabetes mellitus and hyperglycemia or poor glycemic control seems to be the main cause. HbA1c is a quantifiable test and indicates the long-term glycemic control. Thus, a decrease in HbA1c levels may be associated with better wound healing.

A prospective study by Apelqvist et al involving patients with diabetic foot ulcers showed significant association between various clinical risk factors and healing process but little evidence of association with Hba1c levels.[26]

But some recent studies contradict this observation and show positive association of HbA1c with wound healing. Results of a study done by Christman et al, in John Hopkins University showed a positive association and concluded that the HbA1c levels and wound healing rate were inversely related, i.e higher HbA1c levels were associated with lower wound healing rates.[23]

Another study done by Markuson et al concluded that 'healing does occur regardless of HbA1c levels, but ulcers with higher HbA1c levels take a significantly longer period to heal'.[24] A prospective study conducted by Kumar et al on Indian patients found that the healing was earlier in patients whose HbA1c was less than or equal to 6.5.[25]

A recent study by Shashanka, suggested that 'slower wound healing is associated with increased HbA1c levels and can be considered as an independent biomarker in assessing wound healing of diabetic foot ulcer'[27]Most studies done previously to find the association between HbA1c and wound healing in DFU, are inconclusive. Therefore in this study we sought to find a definitive relationship between the two.

Prevention of DFUs: [9,36]

- "prevention is better than cure" – Desiderius Erasmus.

Prevention of ulceration and recurrence of ulcers in diabetics should be the goal of any diabetic foot therapy. A diabetic patient must be educated appropriately regarding the following strategies.

The preventive measures consist of the following –

- Lifestyle modification – involves leading healthy lifestyle, regular physical activity to keep weight in check and prevent comorbidities.
- Nail and skin care – include trimming of toe nails frequently and preventing cracks and fissures on plantar aspect of the feet.
- Annual comprehensive foot examination – yearly testing and examination of the feet by health experts to look for neuropathy, vasculopathy or foot deformities.
- Appropriate foot wear – wearing footwear which is well fitting and provides adequate protection.
- Blood pressure control
- Glycemic control – maintaining blood sugar levels with appropriate medications.
- Daily self-examination of feet is recommended for diabetic patients. The patients inspect their feet on a daily basis and look for any skin changes, cracks and calluses. This is especially recommended in patients with established neuropathy as they have loss of sensations.

Management of DFU:[33]

Multiple etiological factors play a role in DFU pathogenesis. Hence the treatment of diabetic foot ulcers is a multidisciplinary approach which involves both local and systemic approaches.

1. ***Wound control*** – can be achieved by the following:

- Debridement – is the removal of devitalised tissue. It reduces bacterial load of ulcer, restores chronic wounds to acute wounds and aids in formation of granulation tissue. It can be achieved by various methods.

  - Surgical debridement is also known as 'sharp method' is performed using a scalpel or scissors.

  - Chemical debridement includes use of specific chemicals such as acetic acid, hydrogen peroxide, sodium hypochlorite and eusol to remove necrotic tissue. Enzymatic debridement makes use of various enzymes such as collagenase, papain and streptokinase which remove necrotic tissue without damaging normal tissues.

  - Autolytic debridement involves the use of dressings that create a moist wound environment so that host defence mechanisms (neutrophils and macrophages) can clear the necrotic tissue. Autolytic agents include normal saline, hydrocolloid and hydrogels.

  - Biological debridement has been used recently. It is the application of sterile maggots which have the ability to digest surface debris, bacteria and necrotic tissues only, leaving healthy tissues intact.

- Dressing – ideal dressings should be sterile and non – adherent. They help to protect ulcers from trauma, absorb exudate, reduce infection and promote healing. Dressings can be done by conventional methods which is made of fabric material such as gauze and tulle grass which contains paraffin. Dressings containing silicon polymer are also used as they are less adherent and cause minimal trauma. Recently studies have shown that use of biological dressing that contains collagen and elastin such as Dermagraft are superior to conventional dressing.

2. ***Pressure relief or mechanical control*** – aims to redistribute plantar pressures and protect the vulnerable parts of the foot. This is achieved by usage of various off-loading methods.

   - Total contact casts (TCC) are well moulded minimally padded casts that maintain contact with entire aspect of foot. It completely offloads the foot, protects from infection and promotes ambulation. But these casts are not suitable for infected or ischemic ulcers.

   - Alternative to TCC is removable plastic walkers. They are popular because of their ease of use and comfort. They can be used for infected wounds and superficial ulcers.

3. ***Peripheral vascular disease control*** – improved blood flow in foot ulcers lead to faster healing. This can be achieved by revascularization methods such as angioplasty or bypass. Antiplatelet drugs are used to delay progression of vascular disease. Their main role is to maintain the flow that is already present and prevent further thrombotic occlusion.

4. ***Infection control*** – culture from infected diabetic foot ulcers usually yield multiple bacteria which can be Gram positive, Gram negative aerobes and anaerobes. Therefore, combination of broad spectrum systemic antibiotics which target all these groups are administered to reduce the infection and promote healing.

5. ***Metabolic control*** – involves control of blood glucose levels, blood pressure and serum lipid levels. Most foot ulcers in diabetics is caused by inadequate control of blood glucose. Chronic hyperglycemia is associated with neuropathy which is a major cause of DFU.

6. ***Other therapies (newer and adjuvant therapies) -***

   - Hyperbaric oxygen – is used as an adjunct therapy for DFUs. It involves the administration of 100% oxygen at high pressures to the wound which promotes wound healing.

   - Growth factors – are produced by recombinant DNA technology. They include platelet derived growth factors (PDGF) and Becaplermin. Local application of these is found to promote wound healing as diabetic wounds are found to be deficit in growth factors.

   - Low intensity laser therapy – acts by photobiomodualtion. It stimulates inactivated tissue components and promotes wound healing.

   - Vacuum assisted closure – involves the application of negative pressure to wounds to promote faster healing.

METHODOLOGY

The present study was conducted on diabetic foot ulcer patients admitted in Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Study design: Prospective observational study

Study period:1 year (from January 2017 to December 2017)

Source of data: Patients with diabetic foot ulcers admitted in KLES Dr. Prabhakar Kore Hospital and MRC, from January 2017 to December 2017.

Sample procedure: Convenience sampling

Sample size calculation – using Cohen's convention method.[30,31]

Considering - Type 1 error (α) = 0.05

Power ($1 - \beta$) = 80%

Medium effect size = 0.25 (Cohen's f – effect size for ANOVA).

Number of patients needed per group = 30

To compare rate of wound healing in 3 groups of 30 each,

Total sample size is = 30+30+20 = **90.**

Selection Criteria:

Inclusion criteria –

- Type 2 diabetic patients with foot ulcer
- Hospital stay for minimum 15 days
- Age > 18 years
- Diabetic foot ulcer of Wagner grade 1 and 2

Exclusion criteria –

- Diabetic foot ulcer of Wagner grade 3 or more
- Foot ulcers with gangrene
- Osteomyelitis of foot
- Diabetic ketoacidosis
- Immunodeficiency states
- Hemoglobinopathies
- Autoimmune diseases and malignancy.
- Patients receiving unconventional treatment for DFUs.

Procedure:

The study was approved by the Ethical Research Committee of JNMC, Belagavi. All patients that satisfied the selection criteria were included in the study. They were briefed about the nature of the study. Written and informed consent was obtained. Descriptive data of the patients like age, sex and detailed history of ulcer, diabetes mellitus and comorbidities were entered in pre-designed proforma by interviewing each patient.

The HbA1c levels of all patients were obtained at admission. It was measured in the biochemistry laboratory by High performance liquid chromatography (HPLC) method. The 90 patients were divided into 3 groups according to the HBA1c levels as

- Group 1 - < 7%
- Group 2 - 7 – 8 %
- Group 3 - >8 %.

All ulcers were treated by conventional saline dressing which was done on a daily basis. Antibiotics were administered according to wound culture and sensitivity.

All patients were put on insulin therapy for diabetes during course of hospital stay. Ulcer characteristics such as shape, location, edge, margins, floor of ulcer were noted on – Day 0 (beginning of study) and Day 14 (end of study).

Measurement of ulcer area:

- Digital photograph of the ulcer was taken using the software application – **Tissue Analytics.**

The photographs were taken using the Tissue Analytics software interface which was installed on android smartphone. The photograph was taken after placing a green circle sticker of $1cm^2$ area next to the wound (used as a scale) on day 0 and day 14. The software then calculated and displayed the length, width and area of the ulcer.

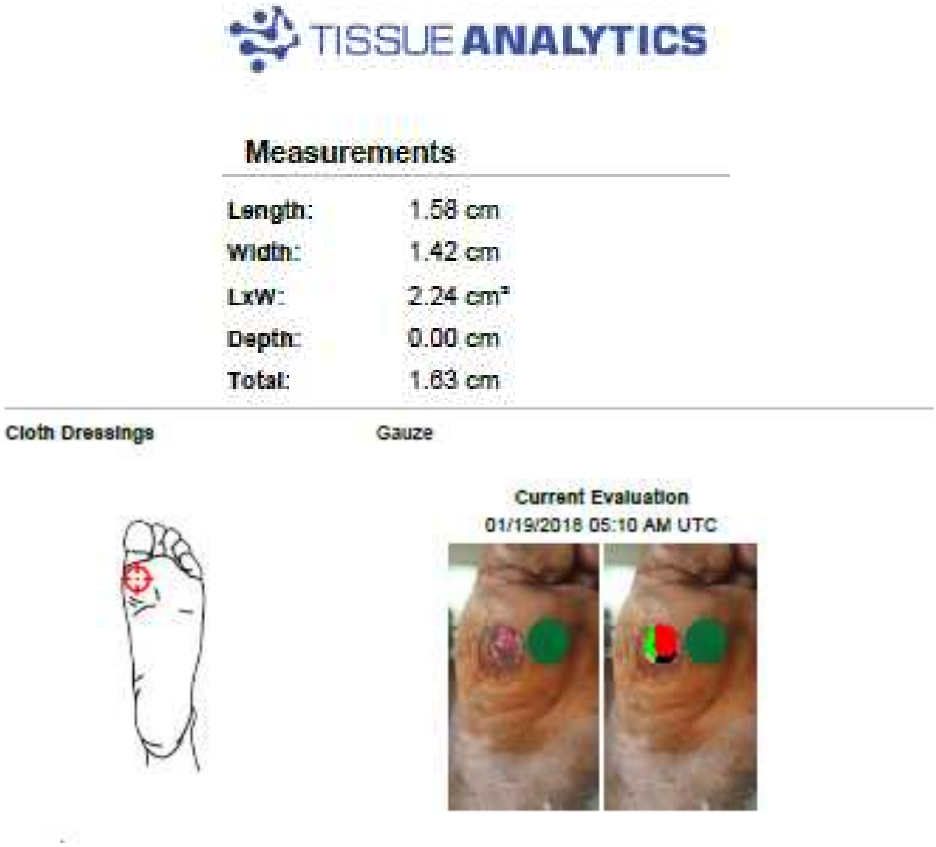


Figure 7: Tissue analytics software analysis of wound

Calculation of rate of wound healing:

The initial wound area on day 0 (x) and the final wound area on day 14 (y) were noted. From this data the wound area reduction and rate of wound healing was calculated as follows:

- Wound area on D0 = x
- Wound area on D14 = y
- Reduction in wound area = x-y
- Rate of wound healing or area reduction per day = **x-y/15**

All the data collected from the patients was then tabulated in Microsoft Excel sheets. The data was statistically analyzed.

Statistical analysis –

The following statistical methods were made use of in the study:

Descriptive analysis was carried out by mean and standard deviation for quantitative variables. Categorical variables were represented as frequency and proportion. The data was also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

HbA1C and rate of healing were considered as primary outcome variables. The correlation was analysed using ANOVA and student's unpaired t – test.

P value < 0.05 was considered statistically significant.

IBM SPSS version 22 and MedCal version 17 software were used for statistical analysis and calculations.

DISCUSSION

According to the latest WHO statistics, diabetic foot ulcers (DFUs) are now the most common cause of non-traumatic lower limb amputations. Therefore, given the large burden of the disease it is important to identify factors that can increase the risk of DFUs and also identify factors that affect the healing of these ulcers, thereby helping to decide the treatment plan and prevent limb loss.

A study done by Margolis et al demonstrated that the 'risk factors that are most dramatically associated with wound healing are – wound size, wound duration and grade of the wound.[36] Another study done by Fife et al which aimed to create a predictive model for diabetic foot ulcer outcome, found that wound duration, wound size, wound grade presence of infection, and patient age to be factors that predicted wound healing.

A study by Shahbazian et al evaluated the risk factors for DFUs and found that age, duration of diabetes, retinopathy and elevated HbA1c increased the risk of ulceration significantly.

Another study by AlGoblan et al done to predict diabetic foot ulcer healing using routine clinical and laboratory parameters found elevated BMI (body mass index) and HbA1c to be factors that were associated with poor wound healing.[39] HbA1c reflects the long-term glycemic control and helps in prediction of complications as well as response to treatment of diabetes.

Another study by Hasan et al found that higher HbA1c levels were seen in patients with diabetic foot ulcers. (86% of patients with DFU had high HbA1c).[35]

Hence HbA1c levels may be considered as a risk factor and predictor of wound healing in diabetic foot ulcers.

This study was undertaken to find an association between HbA1c levels and wound healing in DFUs and was conducted in KLES Dr. Prabhakar Kore Hospital and medical research Centre, Belgaum.

A total of 90 diabetic patients with foot ulcers were included in the study. HbA1c levels were measured for all the patients at admission. The range of HbA1c in the study population was 5.4% to 15.6% with a mean of 8.76%.

The patients included in the study were divided into 3 groups of 30 each based on their HbA1c levels, as –

- Group 1 – < 7%
- Group 2 – 7% to 8%
- Group 3 - > 8%

The demographic data such as age, sex, duration of diabetes, duration and location of ulcer was analyzed among the study population as a whole and among the 3 groups.

The incidence of diabetic foot ulcers, was found to be more common in males (74.4%) than females (25.6%). DFU was also found to be more common in older patients more than 61 years (38.9%). The incidence was seen to increase as the age progressed.

The mean duration of DM of the study population was around 9 years (ranging between 1month to 30 years). Also, in most of the patients in the study the duration of ulcer at time of presentation was 1 to 4 weeks (44.4%). The duration of diabetic foot

ulcers was calculated from onset till presentation to the hospital. Of the 90 subjects, most patients had an ulcer of duration between 1 to 4 weeks (44.4%). 31.1% had ulcer of less than 1 week and 24.4% had ulcer duration of more than 4 weeks.

In this study, Wagner grade 1 and grade 2 ulcers were included. 37 of 90 patients (41.1%) had grade 1 ulcer and 53 patients (58.9%) had grade 2 ulcer. The grade of DFUs has been established as an important indicator for outcome in diabetic foot ulcers. Higher grades are associated with longer healing time and resulted in amputations. In our study, the rate of wound healing was described as area reduction per day and therefore the grade of ulcer was not significantly associated with wound healing.

The location of diabetic foot ulcers in the study population was classified as dorsal or plantar. 47 (52.2%) of them had plantar ulcers and 43 (47.8%) had dorsal ulcers.

The differences in means of the above data in the 3 groups was found to be statistically non-significant, (P value > 0.05) which meant that there was homogenous distribution among the 3 groups.

In this study, healing of ulcer was represented as the rate of wound healing or area reduction per day. It indicates decrease in the size of ulcer per day.

Our study results showed a statistically significant ($p < 0.05$) difference in wound healing rates among the groups 1and 3 and 2 and 3. Therefore elevated HbA1c levels were associated with decreased rate of wound healing. Also, a moderate negative correlation was found between wound healing rates and HbA1c levels.

(Pearson coefficient: -0.638). This suggests that with increasing HbA1c values the rate of wound healing decreases and vice versa.

Important risk factors which may have affected the outcome of diabetic foot ulcers were present in the study population. These included neuropathy, PVD and wound infection.

In this study, neuropathy was seen in 40 (44.4%) patients and peripheral vascular disease was seen in 28 patients (31.1%). These patients had sensory neuropathy which was detected using monofilament test. None of them had Charcot's foot. All of these patients were offloaded with appropriate footwear during the hospital stay. In this study, the presence of neuropathy was not significantly associated with rate of wound healing (P value <0.05). This could be because the patients were offloaded during the observation period of the study.

PVD was seen in 28 (31.1%) of 90 patients. It was detected clinically or by doppler study of lower limb vessels. Ulcers associated with gangrenous changes of foot were excluded. In this study, presence of PVD was not significantly associated with rate of wound healing. This could be due to presence of good collaterals in the patients.

The incidence of wound infection in the study population was 53.1%. These included ulcers that showed growth in culture after 48 hours of incubation. The most common microorganism isolated was staphylococcus and MRSA. Others included gram negative bacteria like E. coli, pseudomonas and proteus species. A study done on Indian patients by Kateel et al on 120 DFU patients, found similar results with Staphylococcus aureus being the most common microorganism followed by E. coli and pseudomonas.[40] The presence of wound infection did not significantly affect the

rate of wound healing because the patients were put on appropriate antibiotic therapy according to sensitivity during the hospital stay.

In our study of type 2 diabetic individuals with foot ulcer, only elevated HbA1c was found to be significantly associated with wound healing. Few studies done previously have shown such results, but other studies have found no association.

Two meta-analytical studies by Margolis et al to identify risk factors for delayed healing of neuropathic DFUs, found 'the patient's age, sex, serum HbA1c level at the start of the study were unassociated with the probability of wound healing.'[41, 42]

Another study by Pecoraro et al which evaluated independent variables, found that healing of DFU was not significantly affected by age, type of diabetes, wound duration, HbA1c, wound infection, and neuropathy.[43]

Studies which have found association between HbA1c and wound healing have used different parameters to quantify wound healing. A study by Markuson et al correlated HbA1c levels with the time taken for ulcer to heal (healing time). The results showed that the healing time was shorter when admission HbA1c values were lower. For HbA1c < 7%, 66.7% of ulcers healed in less than 12 weeks, for HbA1c between 7.1% to 10%, 50% percent of ulcers healed within 12 weeks and for HbA1c > 10.1%, only 25% of them healed within 12 weeks.[24]

Another study by Kumar et al, also quantified wound healing by time taken for wound to heal. The study found that healing was earlier in patients whose HbA1c was < 6.5% (39 days) as compared to > 6.5% (46.5 days). [25]

In this study we used the rate of wound healing or area reduction per day to quantify the wound healing in DFUs. This quantitative endpoint might have contributed positively to demonstrating a correlation between HbA1c and wound healing. Similar results were shown in study by Christman et al, in which wound healing was measured as a rate and lower HbA1c levels were associated with better healing rates. The study also reported that for each 1% increase in HbA1c, the rate of wound healing decreased by $0.028cm^2$.[23]

A study by Shashanka et al, also showed that the rate of wound healing or mean ulcer area change per day was significantly (P value <0.001) associated with HbA1c levels and concluded that HbA1c levels can be considered as an independent biomarker to assess the wound healing in DFUs.[27]

This study therefore, can be considered as one of the few studies which establishes a correlation between HbA1c and wound healing. This study also compared different levels of HbA1c (as per each group) and its association with wound healing, thereby establishing a numerical cut-off value of HbA1c to predict wound outcome (HbA1c > 8%).

LIMITATIONS

The study design was prospective observational study with no intervention being done. A randomized control trial (RCT) in which there is intervention and control groups can therefore strongly establish HbA1c as a predictor of wound healing and outcome.

The follow up period in this study was limited to the hospital stay of the patient taking into consideration only 15 days. A longer follow up period would have established if the ulcer healed fully or the patient had complications such as callous ulcer or amputation.

SCOPE FOR FURTHER STUDIES

Further studies with design of RCT must be carried out to evaluate the efficacy of HbA1c as a predictor for wound healing in DFUs. One such study by Taher et al compared the HbA1c levels and wound healing following stricter glycemic control which was achieved by oral hypoglycemic agents and found that wound healing was faster when HbA1c levels decreased.[45]

Such studies are necessary to establish a definitive association of HbA1c and wound healing which can help in making treatment protocols and also prevent limb loss and morbidity.

CONCLUSIONS

The conclusions drawn from this study which aimed to find the association between HbA1c levels and wound healing in DFUs are -

1. HbA1c was the only factor that was significantly associated with the rate of wound healing. Elevated HbA1c levels were associated with poor wound healing.

2. Other factors which may have affected wound healing such as neuropathy, vasculopathy and wound infection even though present, did not significantly affect the rate of wound healing.

HbA1c is now a mandatory laboratory test which is used to screen and diagnose diabetes mellitus. It indicates the average plasma glucose levels over 2-3 months. Elevated HbA1c has been established as risk factor and predictor of some complications of DM.

From the results of this study we can conclude that HbA1c may be considered as a predictor for wound healing in DFUs.

SUMMARY

This prospective study was conducted to find an association between HBA1c levels and rate of wound healing in diabetic foot ulcers in patients with type 2 DM. 90 inpatients were included in the study as per the selection criteria. HbA1c levels were noted on presentation and subjects divided into 3 groups of 30 each based on the HBA1c levels (<7%, 7% to 8% and > 8%). The healing of the DFUs was represented as rate of wound healing or area reduction per day.

Most of the participants in the study were males and most of them were aged more than 60 years. The mean duration of diabetes was 9 years and duration of ulcer was 1 to 4 weeks. Only ulcers with Wagner grade 1 and 2 were included in the study. The rate of wound healing was calculated by dividing the difference in wound area on day 0 and day 14 by 15 (total no. of days). All the data collected was then analyzed using relevant statistical methods.

The distribution of variables like age, sex, duration of diabetes, duration and location of ulcer, Wagner grade of ulcer was equal among the groups. In this study, factors like neuropathy, PVD or wound infection did not show statistically significant association with the rate of wound healing. HbA1c level was the only independent parameter that showed statistical significance with rate of wound healing. The Pearson correlation coefficient was - 0.638. A moderate negative correlation between HbA1c and wound healing rate which meant that as the levels of HbA1c increased the rate of wound healing decreased.

Thus, based on these results it was concluded that HbA1c levels are associated with wound healing in DFUs and may be considered as a predictor of wound healing. Further larger studies and randomized control studies are required to establish this.

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ANNEXURE I – CONSENT FORM

Study title:

Glycosylated hemoglobin levels and wound healing in diabetic foot ulcers, in type 2 diabetes – 1 year prospective study at KLES Dr Prabhakar Kore Hospital, and Medical Research Centre, Belagavi.

Mr/ Ms/ Dr. _____ , you are hereby invited to take part in a clinical research study. To help you decide, you should understand the study and what it will involve for you. To make an informed decision to take part, you should know the purpose of the study and the risks and benefits involved.

This process is called 'informed consent'. Please take your time to read the following information carefully.

It cannot be promised that the study will help you but in the future, the information we get from this study may help improve the treatment of patients with the same condition.

You have been requested to participate in the above mentioned study as you fit into the laid out criteria for or as a study subject/participant.

Objective and purpose of study:

To study the association between HbA1c levels and wound healing rate in diabetic foot ulcers in patients with type 2 diabetes mellitus. Establishing a correlation between blood glucose levels (as indicated by HbA1c levels) and healing of diabetic foot ulcers, will help in predicting the outcome of disease and thus helping in making better treatment options.

Expenses and payment:

The test is provided at no cost to you. You will not receive any payment for taking part in this study.

Procedure:

Once you have signed the informed consent, necessary personal information and detailed medical history will be taken by the investigator. After this 5ml of blood will be sent for HbA1c level estimation, along with other necessary routine blood investigations. Values will be noted down.

You will be subjected to examination of the foot ulcer along with measurement of the ulcer dimensions and follow up will be done till 15 days of your hospital stay.

Risk and Benefits:

There are no observable risks associated with the study.

The benefits of this study is: by establishing an association between HbA1c levels and wound healing of diabetic foot ulcers, optimization of blood glucose levels can be achieved to promote faster healing and hence prevention of complications of diabetic foot ulcers.

Alternatives:

our participation in this study is entirely voluntary. You are free to refuse to participate or withdraw from the study at any time. You will still receive standard medical care from the hospital. The investigator holds the right to terminate the study at any time, if for example participant recruitment is inadequate.

Privacy and Confidentiality:

All information collected during the study will remain confidential. Your medical files will be reviewed only at the hospital or study doctor's office, in order to check the information and verify the result without breaking your confidentiality. By signing this consent form, you are giving permission for processing of your personal information in a database and transferring of this information or any part of it to people involved in the study. The results of the study will be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Institution / Sponsor's policy:

Does not apply to this research

Questions or queries regarding the study:

In case you have any questions related to the study or in case of study related injury or illness, you can contact:

i. **Dr _____Department of General Surgery, J.N. Medical College, KAHER**
ii. **Dr _____, Professor Department of General Surgery J.N. Medical College, KAHER**

If you have any queries regarding your rights as a study subject, you may call:

Dr Ganga Pilli, Professor and Head of Department of Pathology,

Chairman of J.N. Medical College Institutional Ethics Committee on Human Subjects Research, Ph no – 9480275601 or 0831 2473777 extension – 1527 at J.N. Medical College Belgaum.

Thank you for reading this and considering if you will take part in the study.

CONSENT FORM

Study title: Role of glycosylated hemoglobin in wound healing of diabetic foot ulcers in type 2 diabetes – 1 year prospective study at KLEs Dr Prabhakar Kore Hospital, and Medical Research Centre Belgaum.

Please initial box

i. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐

ii. I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

iii. I understood that sponsor of the clinical trial, others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understood that my identity will not be revealed in any information released to third parties or published. ☐

iv. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes. ☐

v. I agree to take part in the above study. ☐

Subject's name:

Signature / left thumb impression of subject:

Date:

Name of person obtaining informed consent:

Signature of person obtaining informed consent:

(If a patient has limited ability to read and write, an impartial witness should be present during the entire informed consent discussion and patient's legally acceptable representative should sign on the patient's behalf.) In these instances the patient his/her thumb impression taken in place of signature.

Patient's legally acceptable representative's statement: **NA**

I, as the patient's legally acceptable representative was present during the consenting procedure and understand the preceding information describing this study. All of the questions regarding the study and the patient's participation in it have been answered to my satisfaction. I state that all aspects of the study were clearly presented during the consent procedure. The patient is willing to participate in this study and I sign below on his/her behalf testifying to this effect.

Name of the patient:

Name of representative:

Relationship to the patient:

Signature of representative:

Date:

Impartial witness declaration:

By signing the consent form I attest that the information was accurately explained to and apparently understood by the patient and the representative (if applicable) and that the informed consent was freely given by the patient.

Name of impartial witness:

Signature:

Date -

ANNEXURE-II PROFORMA
PRO FORMA

1. Name of patient: _____

2. Age: 1 - ≤18 2 - > 18 ☐

3. Sex: 1 - Male 2 - Female ☐

4. DOA: ☐☐☐☐☐☐☐☐

5. DOD: ☐☐☐☐☐☐☐☐

6. Date of Interview: ☐☐☐☐☐☐☐☐

7. OP no: ☐☐☐☐☐☐☐

8. IP no: ☐☐☐☐☐☐

9. Address: 1 - Belgaum 2 - Outside Belgaum ☐

10. Phone no: | | | | | | | | | | |

11. Occupation: 1 - Unemployed

2 - Unskilled

3 - Semi – skilled

4 - Skilled

5 – Professional

12. Education: 1 –Illiterate

2 – Primary (1st-7th std)

3 – High school (8^{th} – 10^{th} std)

4 – Intermediate

5 – Degree and above

13. Socio-economic status:

1 – Low 2 – Middle 3 – High

Screening -

14. H/O diabetes: 1 – yes 2 – no

15. If yes, type of diabetes:

Type 1	
Type 2	

16. H/O other illness: 1 – yes 2 – no

17. If yes:

1 – Malignancy 2 – Asthma/COPD 3- HIV/AIDS

4 – Autoimmune disorders 5 – Hemoglobinopathy

18. Urine for Ketone bodies:

1 – Positive 2 – Negative

19. ABPI: 1- <0.9 2 – 09-1.2 3 - >1.3 ☐

20. Applicant is willing to give consent: 1 – Yes 2 – No ☐

21. Final result: ☐

1 – Ineligible 2 – Eligible but refused

3 – Eligible and participating

Data Collection instrument:

1. Duration of ulcer – ☐

1 - < 1 week 2 – 1 – 4 weeks 3 - > 4 weeks

2. Location of ulcer – ☐

1 – Left foot 2 – Right foot

☐

3. Mode of onset: 1 – Traumatic

2 – Spontaneous

3 – Pressure

4 – Other

4. Associated symptoms:

1 – Fever 2 – Pain 3 – Discharge

5. Duration of diabetes:

6. On medication for diabetes: 1 – Yes 2 – No

7. If Yes, type of medication: 1 – Oral hypoglycemic agents

2 – Insulin

H/O hypertension: 1 – Yes 2 – No

Examination:

1.

Height	Weight	BMI

2.

Pulse rate	Blood pressure	Temperature	Respiratory Rate

3. Peripheral pulsations of lower limb:

	Right lower limb	Left lower limb
1. Dorsalis pedis		
2. Anterior tibial		
3. Posterior tibial		
4. Popliteal		
5. Femoral		

6. ABPI:

Ankle Systolic Pressure **=**

Brachial Systolic pressure

4. Foot Deformity:

1- Toe deformity 2 – Charcot's foot

5. Neuropathy -

6. Wound Observations:

	Day 0	Day 7	Day 14
1. Site of ulcer			
2. Shape 1 – oval 2 – circular 3 – irregular			
3. Margin 1- Regular 2- Irregular			
4. Edge 1- Indistinct, diffuse 2- Attached to base 3- Not attached, hanging 4- Rolled in 5- Hyperkeratotic/ callous like 6- Fibrotic/ scarred			
5. Floor 1- Red granulation tissue 2- Pale granulation tissue 3- Slough/necrotic tissue			
6. Base 1- Fascia, tendons 2- Soft tissue 3- Bone			

7. Discharge 1- None 2- Serous 3- Purulent 4- Serosanguinous 5- Sero-purulent			
8. Surrounding skin 1- Edema 2- Eczema 3- Pigmented 4- Normal			

7. Wagner Grading:

1	
2	
3	
4	
5	

8. Ulcer dimensions:

	Day 0	Day 7	Day 14
Length (mm)			
Width(mm)			
Area (mm^2)			

9. Inference:

i. Wound area on D0 =

ii. Wound area on D14 =

iii. Wound area reduction = (Area on D0 –area on D14)

iv. Rate of wound healing per day = (Wound area reduction)

15

Investigations:

1. HbA1c:

2. Diabetic profile:

   i. FBS -
   ii. PPBS -
   iii. UKB -

3. CBC:

   i. Hemoglobin –
   ii. Total count –
   iii. Differential count – N - ; L- ; M- ; B- ; E-
   iv. Platelets -

4. Blood urea:

5. Serum Creatinine:

6. Lipid profile:

   i. Total cholesterol -
   ii. HDL -
   iii. LDL -
   iv. Triglyceride –

7. Wound culture and sensitivity: ☐

   1- No growth 2 – Growth present

   If 2 –
   Organism –

   Sensitivity –

8. Radiograph of affected foot:

   AP view –

   Lateral view –

9. Colour Doppler of lower limb (if indicated) -

ANNEXURE - III - PHOTOGRAPHS

Photo 1: HPLC machine used to measure serum HbA1c levels

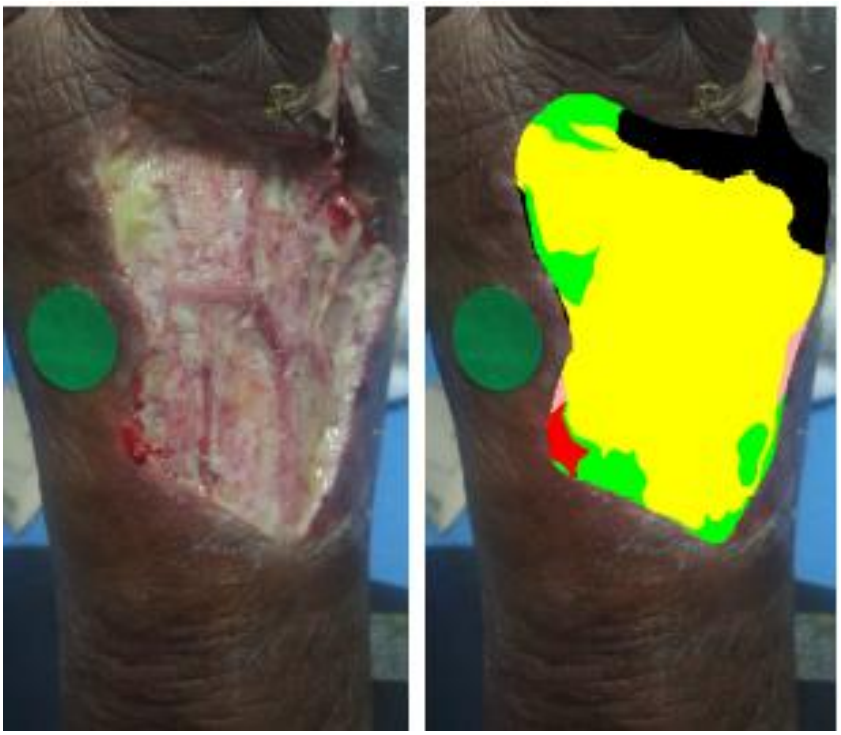
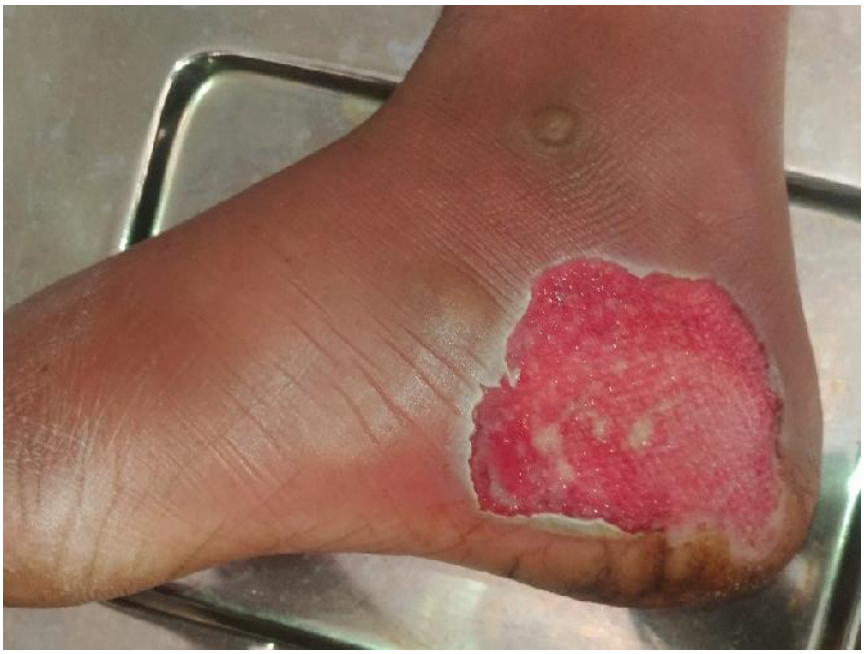


Photo 2: Photograph analysis of the ulcer by software – tissue analytics.



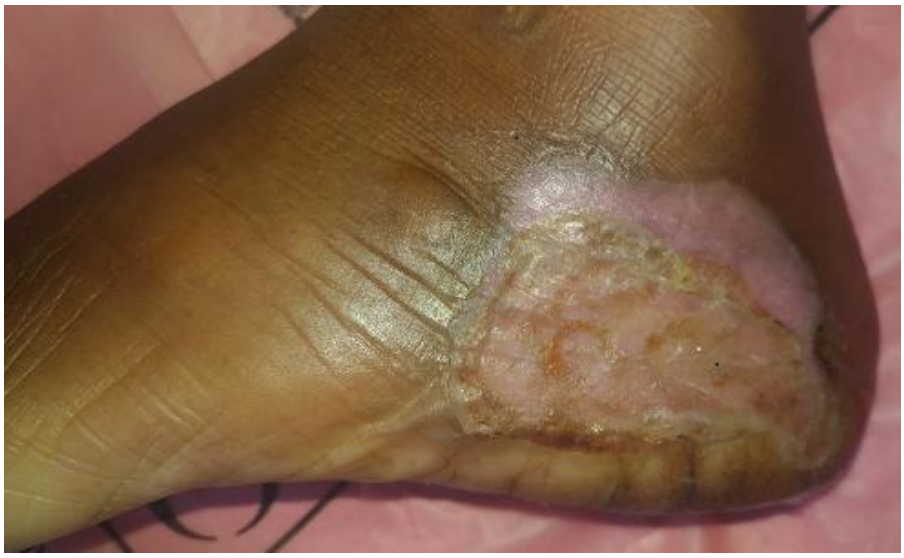


Photo 3: Photographs of ulcer on day 0 and day 14 in group 1

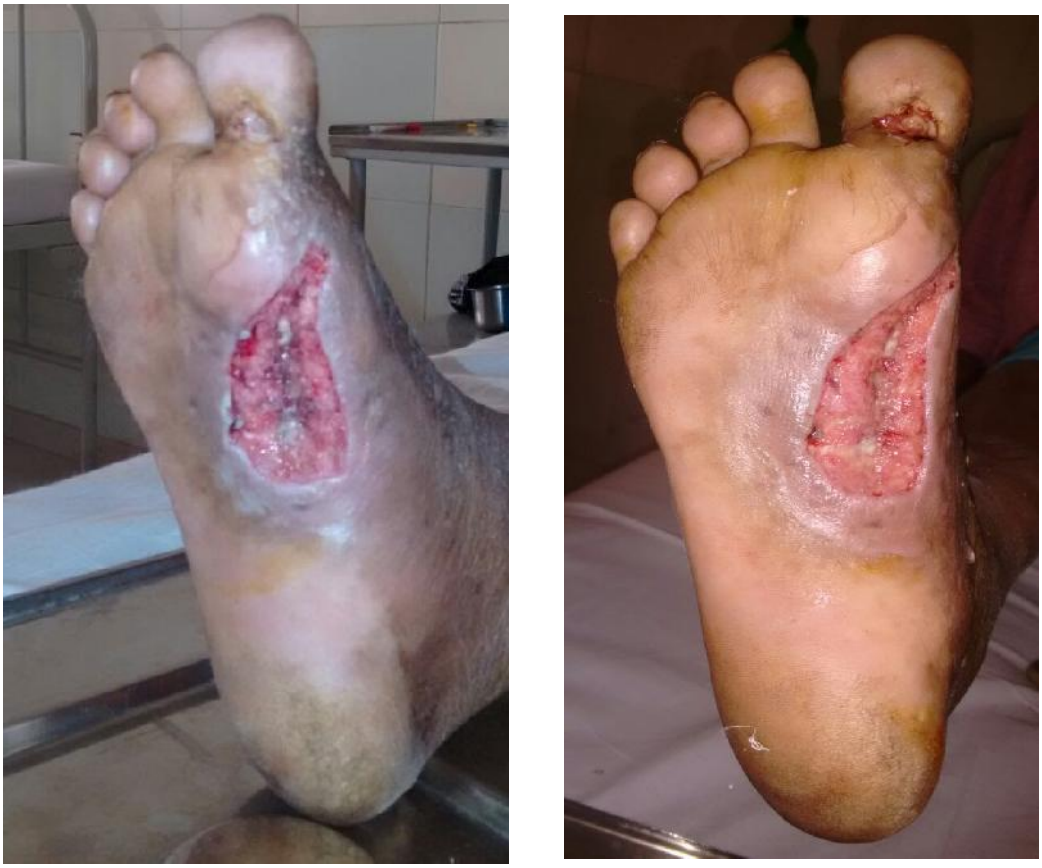


Photo 4: Photographs of ulcer on day 0 and day 14 in group 2

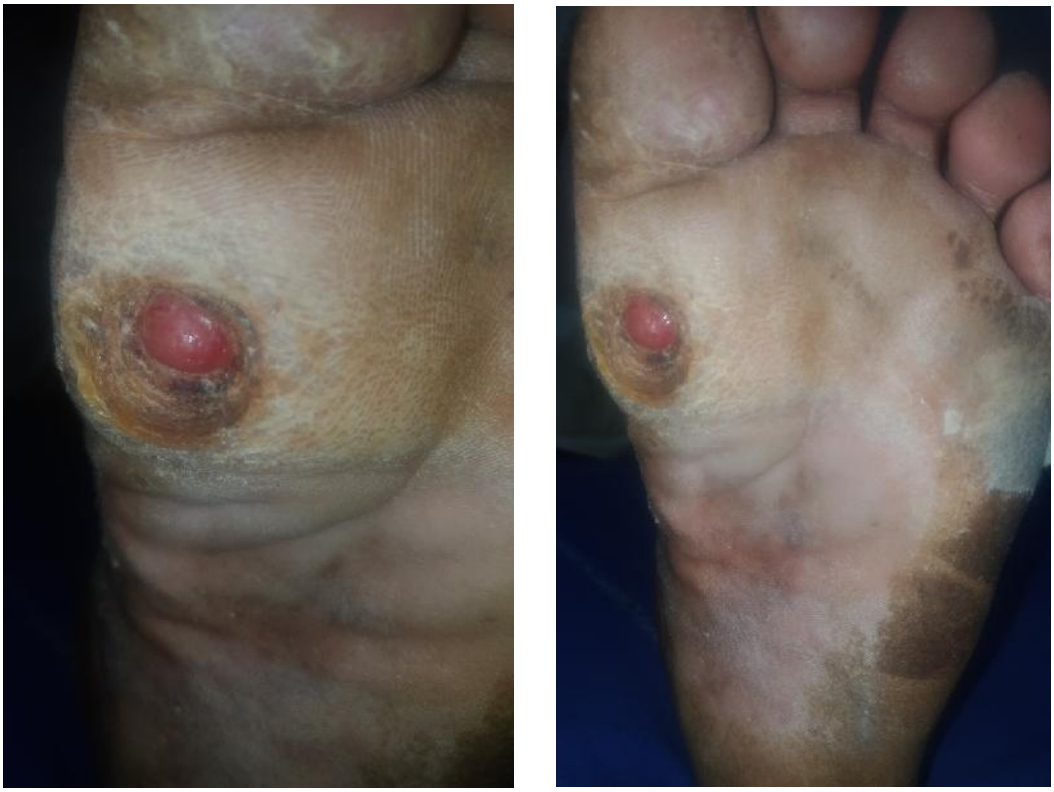


Photo 5: Photographs of ulcer on day 0 and 14 in group 3

ANNEXURE-V

KEY TO MASTERCHART

SL no	–	serial number
IP no	–	inpatient number
M	–	male
F	–	female
DOU	–	duration of ulcer
DODM	–	duration of diabetes mellitus
HTN	–	hypertension
PVD	–	peripheral vascular disease
BMI	–	body mass index
FBS	–	fasting blood sugar
HbA1c	–	glycosylated hemoglobin
Hb	–	Hemoglobin
TLC	–	total leucocyte count

SL NO	IP NO	SEX	AGE	ONSET	DODM	DOU	SITE	HTN	NEUROPATHY	PVD	WAGNER STAGE	BMI	FBS	HbA1c	Hb	TLC	CULTURE	CREATININE	AREA D0	AREA D14	AREA REDUCTION	RATE OF HEALING /DAY
1	814748	M	68	spon	20 years	1-4 wks	DORSUM	YES	YES	YES	1	32	127	7.9	13.1	18300	NO	1.2	318	310	8	0.53
2	832468	M	65	trauma	20 years	1-4 w	PLANTAR	NO	YES	YES	2	21	253	14.8	12.2	13090	NO	1.8	134	123	11	0.7
3	832219	M	51	pressure	7 years	>4 w	PLANTAR	NO	NO	NO	2	31	201	12.2	14.2	8800	yes (staph)	0.9	334	326	8	0.53
4	831645	M	50	spon	7 years	<1 w	PLANTAR	NO	NO	NO	1	27	124	6.7	11.3	18500	yes (staph)	0.7	642	628	14	0.93
5	801274	M	46	spon	8 years	1 - 4 w	DORSUM	NO	YES	YES	1	27	188	7.4	14.2	10800	yes (staph)	0.8	61	51	10	0.67
6	847606	M	75	trauma	15 years	1-4 w	PLANTAR	NO	YES	NO	1	23	120	6.8	9.8	22500	yes (strep)	3.8	556	544	12	0.8
7	824874	M	55	spon	10 years	1 - 4 w	DORSUM	YES	NO	NO	1	23	148	7.8	13	15,900	yes (mrsa)	1.6	21	5.5	15.5	1
8	852271	M	65	spon	5 months	1 - 4 w	PLANTAR	YES	NO	NO	1	31	129	6.4	12	8800	NO	2	163	146	17	1.13
9	834818	F	50	trauma	10 years	> 4 w	PLANTAR	YES	NO	NO	2	21	244	13.2	10.4	14860	yes(proteus)	1.1	420	409	11	0.7
10	827816	M	47	spon	7 years	1 - 4 w	PLANTAR	YES	NO	YES	2	25	156	11.7	13.4	20000	yes (e.coli)	1.1	300.4	288	12.4	0.82
11	854899	M	62	spon	10 years	1 - 4 w	DORSUM	YES	NO	NO	2	25	263	9.9	14.7	27000	yes (CONS)	1.2	301.5	290.5	11	0.7
12	843255	M	42	spon	6 years	< 1 wk	DORSUM	NO	NO	NO	2	27	178	7.8	13.3	10800	NO	1	118.4	104.2	14.2	0.93
13	852836	M	58	trauma	18 years	> 4 w	DORSUM	NO	YES	YES	2	24	122	7.6	10.9	12900	NO	1.3	116.3	109.2	9.1	0.6
14	824752	F	56	pressure	10 years	1 - 4 w	PLANTAR	YES	NO	NO	1	27	268	11.4	10.4	12700	yes (mrsa)	1.7	324	313	11	0.7
15	831007	F	56	spon	20 years	1-4 w	DORSUM	YES	YES	NO	2	37	127	6.6	13.6	5110	yes (mrsa)	0.8	269	258	11	0.7
16	843985	M	60	trauma	10 years	< 1 wk	DORSUM	NO	YES	NO	2	25	210	14.4	10.8	14.7	yes(commensal)	1	331	327	4	0.2
17	849212	M	85	trauma	10 years	1 - 4 wks	DORSUM	NO	YES	YES	2	19	206	6.7	12	26300	yes(pseudomonas)	0.9	372	367	5	0.33
18	831241	M	63	spon	14 years	1 - 4 wks	PLANTAR	YES	YES	NO	2	26	157	10.7	11.1	12400	NO	1.7	152	144	8	0.53
19	835953	F	36	trauma	1 m	1-4 wks	PLANTAR	NO	NO	YES	2	25	159	14.2	7.3	8560	yes(citrobacter)	1.2	378	369	9	0.6
20	826700	M	45	spon	18 years	> 4 wk	DORSUM	YES	YES	NO	1	22	166	6.9	10.9	11160	NO	1.2	136.6	120.8	15.8	1.05
21	827765	M	46	trauma	8 years	1 - 4 wks	PLANTAR	NO	NO	NO	2	21	125	6.9	14.4	25160	NO	1.4	227	212	15	1
22	832944	M	70	spon	5 years	< 1 wk	PLANTAR	YES	NO	NO	2	21	118	6.6	9.8	9090	NO	1.4	168	155	13	0.86
23	852998	M	62	trauma	1 year	< 1 wk	DORSUM	NO	NO	NO	1	26	134	6.8	14.4	8750	NO	0.8	336.2	322.8	13.4	0.89
24	834704	M	54	trauma	2 years	1- 4 wks	DORSUM	NO	NO	NO	1	24	119	7.5	11.4	8040	NO	1.2	217	205	12	0.8
25	832731	F	57	trauma	8 years	1-4wks	DORSUM	YES	YES	NO	2	25	262	14	12.4	20700	yes(candida)	1.1	143.9	142.9	1	0.06
26	830251	F	55	spon	2 months	1-4 wks	DORSUM	NO	NO	NO	1	22	198	7.1	9.6	11240	NO	0.9	147.9	136.9	11	0.73
27	814443	M	50	pressure	8 years	> 4 wks	PLANTAR	YES	YES	NO	2	26	127	10.8	10.4	8000	NO	0.7	376	370	6	0.4
28	848332	M	71	trauma	3 months	< 1 wk	PLANTAR	YES	NO	NO	2	23	168	7.9	14.5	15220	YES(e.coli)	1	941	938	3	0.2
29	854969	F	46	pressure	5 years	>4 wk	PLANTAR	NO	NO	YES	2	28	220	15.6	10.7	8260	NO	1.4	264	262	2	0.13
30	860795	M	45	trauma	1 year	< 1 wk	DORSUM	NO	NO	NO	1	24	96	7.1	12.5	6720	NO	0.9	878	864	14	0.93
31	834480	M	66	trauma	30 years	< 1 wk	PLANTAR	NO	YES	NO	1	19	157	15.2	10.9	13650	yes(proteus)	1	844.6	844.2	0.4	0.02
32	829243	M	55	spon	8 years	<1wk	DORSUM	YES	NO	NO	1	30	134	6.1	12.2	6700	NO	1.1	2844	2840	4	0.26

SL NO	IP NO	SEX	AGE	ONSET	DODM	DOU	SITE	HTN	NEUROPATHY	PVD	WAGNER STAGE	BMI	FBS	HbA1c	Hb	TLC	CULTURE	CREATININE	AREA D0	AREA D14	AREA REDUCTION	RATE OF HEALING /DAY
33	859231	M	64	trauma	6 years	< 1 wk	PLANTAR	NO	NO	YES	2	26	115	7.9	11.2	25900	yes(staph)	1.6	101.3	90.1	11.2	0.74
34	869293	M	66	spon	18 years	< 1 wk	DORSUM	NO	YES	YES	1	21	122	6.9	12.7	12700	NO	1.5	117	102.8	14.2	0.94
35	870146	M	70	spon	16 years	1 - 4 wks	PLANTAR	NO	YES	NO	2	20	242	10.2	12.3	11170	NO	1	233	226	7	0.46
36	870594	M	30	other	3 years	>4 wk	PLANTAR	NO	NO	NO	1	29	156	7.9	9.6	14390	YES(e.coli)	0.8	1076	1064	12	0.8
37	870286	M	54	spon	4 years	> 4wk	DORSUM	NO	NO	NO	2	26	203	6.5	16.9	4250	yes(staph)	0.9	631	623	8	0.53
38	861234	F	52	spon	21 years	1-4wks	DORSUM	YES	YES	YES	2	18	176	7.9	11.1	7280	yes(commensal)	1	897.4	883.6	13.8	0.92
39	833408	M	49	spon	10 years	<1wk	PLANTAR	NO	YES	YES	2	22	278	13.2	10.5	15840	yes(klebsiella)	1.2	1145	1144	1	0.06
40	869570	M	65	spon	10 years	> 4wks	PLANTAR	NO	YES	NO	2	25	240	12	10.7	11760	yes(pseudomonas)	0.6	754	749	5	0.33
41	870425	M	42	trauma	5 years	1-4 wks	DORSUM	YES	NO	NO	1	28	135	7.2	12	12370	NO	0.9	968	961	7	0.46
42	869117	F	38	trauma	6 years	1 - 4 wks	PLANTAR	NO	NO	NO	2	22	123	10.4	10.1	7780	NO	0.9	562	554	8	0.53
43	864698	M	60	spon	15 years	> 4 wks	PLANTAR	YES	YES	NO	2	29	188	6.7	12.2	10700	yes(mrsa)	1.5	185	175	10	0.66
44	867535	F	65	spon	3 years	> 4 wks	PLANTAR	NO	NO	NO	1	22	156	7.2	9.6	14390	YES(e.coli)	0.8	366	354	12	0.8
45	870936	F	75	trauma	20 years	> 4 wks	PLANTAR	YES	YES	YES	2	24	250	9.2	10.6	10260	NO	1.4	149	140	9	0.6
46	797358	M	70	spon	25 years	1-4 wks	PLANTAR	YES	YES	YES	2	25	139	6.6	8.8	6900	NO	1.6	256	243	13	0.86
47	809182	F	59	pressure	16 years	<1 wk	DORSUM	NO	YES	YES	1	18	154	6.3	9.5	9500	NO	1.4	895.1	880.3	14.8	0.98
48	823746	F	65	pressure	12 years	1 - 4 wks	DORSUM	YES	NO	YES	1	25	198	7.6	9.5	7300	yes(commensal)	1.3	657	643	14	0.93
49	808935	M	68	trauma	18 years	<1 wk	DORSUM	YES	YES	NO	2	21	175	10.8	10.8	9000	yes(proteus)	0.8	256.4	248.2	8.2	0.54
50	810246	M	63	pressure	12 years	1 - 4 wks	DORSUM	NO	YES	NO	1	30	185	10.7	14.3	8120	NO	0.6	179	168.2	10.8	0.72
51	812902	M	45	trauma	3 years	< 1 wk	DORSUM	NO	NO	NO	2	26	132	6.4	14.2	6270	NO	1.2	213	203	15	1
52	816933	M	56	trauma	9 years	1- 4 wks	DORSUM	YES	NO	NO	1	23	156	6.2	11.3	10,600	YES(e.coli)	1.8	610	596	14	0.93
53	816945	M	62	pressure	15 years	> 4wks	PLANTAR	YES	YES	NO	1	20	144	7.9	10.6	8200	NO	1.4	215	203	12	0.8
54	818239	M	45	trauma	6 years	< 1 wk	PLANTAR	NO	NO	NO	2	19	135	6.9	13.9	8630	NO	1.5	188.6	185.9	2.7	0.18
55	820837	M	68	spon	20 years	1- 4 wks	DORSUM	YES	NO	YES	2	29	188	6	9.5	7500	NO	1	965.2	952.9	12.3	0.82
56	827765	M	46	trauma	6 years	<1 wk	PLANTAR	NO	NO	NO	2	21	256	7.9	14.4	25160	yes(citrobacter)	1.4	356	350	6	0.4
57	843985	M	60	spon	13 years	1 - 4 wks	PLANTAR	YES	YES	NO	1	25	245	14.4	10.3	11700	yes(staph)	1.6	412	410.2	1.8	0.12
58	793920	F	56	trauma	14 years	< 1 wk	DORSUM	YES	NO	YES	2	34	210	7	8.3	8200	NO	1.5	1056	1044	12	0.8
59	808629	M	70	spon	15 years	1 - 4 wks	PLANTAR	YES	YES	NO	1	19	198	11	10	11800	yes(e.coli)	2	645	638	7	0.46
60	810627	M	66	trauma	12 years	1- 4 wks	DORSUM	NO	YES	YES	2	24	223	7.6	11.3	15400	yes(strep. P)	1.6	764.5	756.1	8.4	0.56
61	813183	M	54	pressure	16 years	> 4 wks	PLANTAR	NO	YES	NO	2	22	148	7.5	11.5	20900	yes(pseudomonas)	1.1	288.2	276.5	11.7	0.78
62	823490	M	58	spon	7 years	< 1 wk	PLANTAR	YES	NO	NO	1	20	288	12.1	13.8	11600	yes(pseudomonas)	1.5	1124	1120	4	0.26
63	829559	F	55	trauma	5 years	< 1 wk	DORSUM	NO	NO	NO	2	27	163	7.5	10.1	6000	yes(pseudomonas)	0.7	975	967	8	0.53
64	838266	M	63	pressure	20 years	> 4 wks	PLANTAR	YES	YES	NO	2	21	154	7.6	13	16000	yes(klebsiella)	1.3	156	144	12	0.8

SL NO	IP NO	SEX	AGE	ONSET	DODM	DOU	SITE	HTN	NEUROPATHY	PVD	WAGNER STAGE	BMI	FBS	HbA1c	Hb	TLC	CULTURE	CREATININE	AREA D0	AREA D14	AREA REDUCTION	RATE OF HEALING /DAY
65	841307	M	63	spon	11 years	1 - 4 wks	PLANTAR	YES	NO	YES	1	26	123	5.4	9.2	5890	NO	1.8	359	348	11	0.73
66	842517	M	52	trauma	10 years	1 - 4 wks	DORSUM	NO	YES	NO	2	32	195	9.1	11.9	19900	yes(klebsiella)	1.9	705	699	6	0.4
67	847606	M	75	pressure	25 years	> 4 wks	PLANTAR	YES	YES	YES	1	24	265	8	9.8	22500	yes(strep bovis)	1	256.4	247.2	9.2	0.61
68	843617	M	35	spon	1 year	< `1 wk	DORSUM	NO	NO	NO	2	21	343	15.4	12	18300	yes(mrsa)	0.8	593	593	0	0
69	783730	F	48	trauma	6 years	1 - 4 wks	DORSUM	YES	YES	NO	2	28	210	6.9	11.5	13600	NO	0.6	897	888	9	0.6
70	795381	M	58	trauma	5 years	1 -4 wks	PLANTAR	NO	NO	NO	1	31	125	6.8	11.8	10000	NO	0.7	401	395	6	0.4
71	810071	M	64	pressure	16 years	> 4 wks	PLANTAR	YES	NO	YES	2	25	168	8.5	9.9	22000	yes(mrsa)	1.3	265	257	8	0.53
72	842393	F	35	trauma	2 years	< 1 wk	DORSUM	NO	NO	NO	1	22	235	12.7	11.1	13100	yes(pseudomonas)	0.8	472	470	2	0.13
73	802858	F	75	spon	15 years	> 4 wk	PLANTAR	YES	YES	NO	1	29	265	6.5	14.1	15000	yes(mrsa)	0.7	245	233	12	0.8
74	801232	M	49	trauma	3 years	<1 wk	DORSUM	NO	NO	NO	2	19	98	7.4	11.3	11000	NO	0.5	157	149	8	0.53
75	803469	F	70	pressure	10 years	1 - 4 wks	PLANTAR	YES	YES	YES	2	24	189	7.8	10.6	9500	NO	1.6	268.4	257.1	11.3	0.78
76	829040	M	44	trauma	1 year	< 1 wk	PLANTAR	NO	NO	NO	1	21	166	5.7	13.4	13340	yes(strep pyogenes	1.2	684.5	672.9	11.6	0.77
77	826499	M	51	spon	6 years	1 - 4 wks	DORSUM	YES	NO	NO	2	30	263	6.8	9.7	10000	NO	1.7	521	514	7	0.46
78	765652	M	66	other	25 years	>4 wks	DORSUM	YES	YES	YES	2	23	126	7.9	11.1	9200	NO	1.1	391.5	384.6	6.9	0.46
79	775437	M	71	pressure	20 years	> 4 wks	PLANTAR	NO	NO	NO	2	29	262	11.1	11.6	9900	yes(e.coli)	0.9	952	946	6	0.4
80	777940	F	50	trauma	4 years	< 1 wk	PLANTAR	YES	NO	NO	2	22	140	7.8	10.2	11000	yes(staph)	1.2	741	728	13	0.86
81	784041	F	45	trauma	11 years	1 - 4 wks	DORSUM	NO	YES	YES	1	18	133	7.5	9.3	11000	NO	2	565.7	560	5.7	0.38
82	802858	F	56	pressure	8 years	> 4 wks	DORSUM	YES	YES	YES	2	26	198	14.1	10.2	24660	yes(pseudomonas)	0.7	452	450	2	0.13
83	806151	M	24	spon	1 month	< 1 wk	DORSUM	NO	NO	NO	1	20	98	6.5	10.1	8990	NO	0.5	862	849	13	0.86
84	818080	M	65	pressure	6 months	1 - 4 wks	PLANTAR	NO	NO	NO	1	27	213	13	11.5	13700	yes(CONS)	0.8	187.5	185	2.5	0.16
85	824433	M	57	trauma	8 years	< 1 wk	PLANTAR	YES	YES	NO	2	25	158	7.6	13	9100	NO	0.9	308	300	8	0.53
86	824200	M	49	pressure	5 years	1- 4 wk	DORSUM	NO	NO	YES	2	31	96	6.1	11.2	6880	NO	1.1	1054.2	1043.9	10.3	0.68
87	826977	M	69	spon	15 years	> 4 wk	DORSUM	NO	YES	YES	2	25	151	7.3	13.5	15100	yes(CONS)	0.9	625	616	9	0.6
88	873771	F	42	trauma	2 years	1 - 4 wks	PLANTAR	YES	NO	NO	1	21	120	5.9	11.9	11400	NO	0.5	876.2	865.1	11.1	0.74
89	824697	M	54	trauma	1 year	< 1 wk	DORSUM	NO	NO	NO	1	25	102	6.2	9	11500	yes(staph)	0.7	432	419	13	0.86
90	820160	M	38	spon	3 years	1 - 4 wks	PLANTAR	YES	NO	NO	2	21	204	6.8	14.5	9000	NO	0.6	586.5	571.3	15.2	1.01

SL NO	HBA1C	SEX	AGE	DODM	DOU	HTN	WAGNER STAGE	SITE	NEUROPATHY	PVD	CULTURE	RATE OF HEALING/DAY
GROUP 1												
1	5.4	M	63	11 years	1 - 4 wks	YES	1	PLANTAR	NO	YES	NO	0.73
2	5.7	M	44	1 year	< 1 wk	NO	1	PLANTAR	NO	NO	yes(strep pyogenes)	0.77
3	5.9	F	42	2 years	1 - 4 wks	YES	1	PLANTAR	NO	NO	NO	0.74
4	6	M	68	20 years	1- 4 wks	YES	2	DORSUM	NO	YES	NO	0.82
5	6.1	M	55	8 years	<1wk	YES	1	DORSUM	NO	NO	NO	0.26
6	6.1	M	49	5 years	1- 4 wk	NO	2	DORSUM	NO	YES	NO	0.68
7	6.2	M	56	9 years	1- 4 wks	YES	1	DORSUM	NO	NO	YES(e.coli)	0.93
8	6.2	M	54	1 year	< 1 wk	NO	1	DORSUM	NO	NO	yes(staph)	0.86
9	6.3	F	59	16 years	<1 wk	NO	1	DORSUM	YES	YES	NO	0.98
10	6.4	M	65	5 months	1 - 4 w	YES	1	PLANTAR	NO	NO	NO	1.13
11	6.4	M	45	3 years	< 1 wk	NO	2	DORSUM	NO	NO	NO	1
12	6.5	M	54	4 years	> 4wk	NO	2	DORSUM	NO	NO	yes(staph)	0.53
13	6.5	F	75	15 years	> 4 wk	YES	1	PLANTAR	YES	NO	yes(mrsa)	0.8
14	6.5	M	24	1 month	< 1 wk	NO	1	DORSUM	NO	NO	NO	0.86
15	6.6	F	56	20 years	1-4 w	YES	2	DORSUM	YES	NO	yes (mrsa)	0.7
16	6.6	M	70	5 years	< 1 wk	YES	2	PLANTAR	NO	NO	NO	0.86
17	6.6	M	70	25 years	1-4 wks	YES	2	PLANTAR	YES	YES	NO	0.86
18	6.7	M	50	7 years	<1 w	NO	1	PLANTAR	NO	NO	yes (staph)	0.93
19	6.7	M	85	10 years	1 - 4 wks	NO	2	DORSUM	YES	YES	yes(pseudomonas)	0.33
20	6.7	M	60	15 years	> 4 wks	YES	2	PLANTAR	YES	NO	yes(mrsa)	0.66
21	6.8	M	75	15 years	1-4 w	NO	1	PLANTAR	YES	NO	yes (strep)	0.8
22	6.8	M	62	1 year	< 1 wk	NO	1	DORSUM	NO	NO	NO	0.89
23	6.8	M	58	5 years	1 -4 wks	NO	1	PLANTAR	NO	NO	NO	0.4
24	6.8	M	51	6 years	1 - 4 wks	YES	2	DORSUM	NO	NO	NO	0.46
25	6.8	M	38	3 years	1 - 4 wks	YES	2	PLANTAR	NO	NO	NO	1.01
26	6.9	M	45	18 years	> 4 wk	YES	1	DORSUM	YES	NO	NO	1.05
27	6.9	M	46	8 years	1 - 4 wks	NO	2	PLANTAR	NO	NO	NO	1
28	6.9	M	66	18 years	< 1 wk	NO	1	DORSUM	YES	YES	NO	0.94
29	6.9	M	45	6 years	< 1 wk	NO	2	PLANTAR	NO	NO	NO	0.18
30	6.9	F	48	6 years	1 - 4 wks	YES	2	DORSUM	YES	NO	NO	0.6

SL NO	HBA1C	SEX	AGE	DODM	DOU	HTN	WAGNER STAGE	SITE	NEUROPATHY	PVD	CULTURE	RATE OF HEALING/DAY
GROUP2												
1	7	F	56	14 years	< 1 wk	YES	2	DORSUM	NO	YES	NO	0.8
2	7.1	F	55	2 months	1-4 wks	NO	1	DORSUM	NO	NO	NO	0.73
3	7.1	M	45	1 year	< 1 wk	NO	1	DORSUM	NO	NO	NO	0.93
4	7.2	M	42	5 years	1-4 wks	YES	1	DORSUM	NO	NO	NO	0.46
5	7.2	F	65	3 years	> 4 wks	NO	1	PLANTAR	NO	NO	YES(e.coli)	0.8
6	7.3	M	69	15 years	> 4 wk	NO	2	DORSUM	YES	YES	yes(CONS)	0.6
7	7.4	M	46	8 years	1 - 4 w	NO	1	DORSUM	YES	YES	yes (staph)	0.67
8	7.4	M	49	3 years	<1 wk	NO	2	DORSUM	NO	NO	NO	0.53
9	7.5	M	54	2 years	1- 4 wks	NO	1	DORSUM	NO	NO	NO	0.8
10	7.5	M	54	16 years	> 4 wks	NO	2	PLANTAR	YES	NO	yes(pseudomonas)	0.78
11	7.5	F	55	5 years	< 1 wk	NO	2	DORSUM	NO	NO	yes(pseudomonas)	0.53
12	7.5	F	45	11 years	1 - 4 wks	NO	1	DORSUM	YES	YES	NO	0.38
13	7.6	M	58	18 years	> 4 w	NO	2	DORSUM	YES	YES	NO	0.6
14	7.6	F	65	12 years	1 - 4 wks	YES	1	DORSUM	NO	YES	yes(commensal)	0.93
15	7.6	M	66	12 years	1- 4 wks	NO	2	DORSUM	YES	YES	yes(strep. P)	0.56
16	7.6	M	63	20 years	> 4 wks	YES	2	PLANTAR	YES	NO	yes(klebsiella)	0.8
17	7.6	M	57	8 years	< 1 wk	YES	2	PLANTAR	YES	NO	NO	0.53
18	7.8	M	55	10 years	1 - 4 w	YES	1	DORSUM	NO	NO	yes (mrsa)	1
19	7.8	M	42	6 years	< 1 wk	NO	2	DORSUM	NO	NO	NO	0.93
20	7.8	F	70	10 years	1 - 4 wks	YES	2	PLANTAR	YES	YES	NO	0.78
21	7.8	F	50	4 years	< 1 wk	YES	2	PLANTAR	NO	NO	yes(staph)	0.86
22	7.9	M	68	20 years	1-4 wks	YES	1	DORSUM	YES	YES	NO	0.53
23	7.9	M	71	3 months	< 1 wk	YES	2	PLANTAR	NO	NO	YES(e.coli)	0.2
24	7.9	M	64	6 years	< 1 wk	NO	2	PLANTAR	NO	YES	yes(staph)	0.74
25	7.9	M	30	3 years	>4 wk	NO	1	PLANTAR	NO	NO	YES(e.coli)	0.8
26	7.9	F	52	21 years	1-4wks	YES	2	DORSUM	YES	YES	yes(commensal)	0.92
27	7.9	M	62	15 years	> 4wks	YES	1	PLANTAR	YES	NO	NO	0.8
28	7.9	M	46	6 years	<1 wk	NO	2	PLANTAR	NO	NO	yes(citrobacter)	0.4
29	7.9	M	66	25 years	>4 wks	YES	2	DORSUM	YES	YES	NO	0.46
30	8	M	75	25 years	> 4 wks	YES	1	PLANTAR	YES	YES	yes(strep bovis)	0.61

SL NO	HBA1C	SEX	AGE	DODM	DOU	HTN	WAGNER STAGE	SITE	NEUROPATHY	PVD	CULTURE	RATE OF HEALING/DAY
GROUP 3												
1	8.5	M	64	16 years	> 4 wks	YES	2	PLANTAR	NO	YES	yes(mrsa)	0.53
2	9.1	M	52	10 years	1 - 4 wks	NO	2	DORSUM	YES	NO	yes(klebsiella)	0.4
3	9.2	F	75	20 years	> 4 wks	YES	2	PLANTAR	YES	YES	NO	0.6
4	9.9	M	62	10 years	1 - 4 w	YES	2	DORSUM	NO	NO	yes (CONS)	0.7
5	10.2	M	70	16 years	1 - 4 wks	NO	2	PLANTAR	YES	NO	NO	0.46
6	10.4	F	38	6 years	1 - 4 wks	NO	2	PLANTAR	NO	NO	NO	0.53
7	10.7	M	63	14 years	1 - 4 wks	YES	2	PLANTAR	YES	NO	NO	0.53
8	10.7	M	63	12 years	1 - 4 wks	NO	1	DORSUM	YES	NO	NO	0.72
9	10.8	M	50	8 years	> 4 wks	YES	2	PLANTAR	YES	NO	NO	0.4
10	10.8	M	68	18 years	<1 wk	YES	2	DORSUM	YES	NO	yes(proteus)	0.54
11	11	M	70	15 years	1 - 4 wks	YES	1	PLANTAR	YES	NO	yes(e.coli)	0.46
12	11.1	M	71	20 years	> 4 wks	NO	2	PLANTAR	NO	NO	yes(e.coli)	0.4
13	11.4	F	56	10 years	1 - 4 w	YES	1	PLANTAR	NO	NO	yes (mrsa)	0.7
14	11.7	M	47	7 years	1 - 4 w	YES	2	PLANTAR	NO	YES	yes (e.coli)	0.82
15	12	M	65	10 years	> 4wks	NO	2	PLANTAR	YES	NO	yes(pseudomonas)	0.33
16	12.1	M	58	7 years	< 1 wk	YES	1	PLANTAR	NO	NO	yes(pseudomonas)	0.26
17	12.2	M	51	7 years	>4 w	NO	2	PLANTAR	NO	NO	yes (staph)	0.53
18	12.7	F	35	2 years	< 1 wk	NO	1	DORSUM	NO	NO	yes(pseudomonas)	0.13
19	13	M	65	6 months	1 - 4 wks	NO	1	PLANTAR	NO	NO	yes(CONS)	0.16
20	13.2	F	50	10 years	> 4 w	YES	2	PLANTAR	NO	NO	yes(proteus)	0.7
21	13.2	M	49	10 years	<1wk	NO	2	PLANTAR	YES	YES	yes(klebsiella)	0.06
22	14	F	57	8 years	1-4wks	YES	2	DORSUM	YES	NO	yes(candida)	0.06
23	14.1	F	56	8 years	> 4 wks	YES	2	DORSUM	YES	YES	yes(pseudomonas)	0.13
24	14.2	F	36	1 m	1-4 wks	NO	2	PLANTAR	NO	YES	yes(citrobacter)	0.6
25	14.4	M	60	10 years	< 1 wk	NO	2	DORSUM	YES	NO	yes(commensal)	0.2
26	14.4	M	60	13 years	1 - 4 wks	YES	1	PLANTAR	YES	NO	yes(staph)	0.12
27	14.8	M	65	20 years	1-4 w	NO	2	PLANTAR	YES	YES	NO	0.7
28	15.2	M	66	30 years	< 1 wk	NO	1	PLANTAR	YES	NO	yes(proteus)	0.02
29	15.4	M	35	1 year	< `1 wk	NO	2	DORSUM	NO	NO	yes(mrsa)	0
30	15.6	F	46	5 years	>4 wk	NO	2	PLANTAR	NO	YES	NO	0.13