"A COMPARATIVE STUDY OF AMORPHOUS HYDROGEL DRESSINGS WITH SILVER NANO PARTICLES VERSUS CONVENTIONAL DRESSING FOR TREATING DIABETIC FOOT ULCERS – A RANDOMISED CONTROLLED TRIAL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"A COMPARATIVE STUDY OF AMORPHOUS HYDROGEL DRESSINGS WITH SILVER NANO PARTICLES VERSUS CONVENTIONAL DRESSING FOR TREATING DIABETIC FOOT ULCERS – A RANDOMISED CONTROLLED TRIAL"** is a bonafide research work done by **CANDIDATE REG NO. BH0113010**.

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LIST OF ABBREVIATIONS USED

Ag NPs	-	Silver nano particles
Ag or Ag0	-	Silver atoms
Ag+	-	Silver ions
AP	-	Anteroposterior
ATPase	-	Adenine triphosphatase
BC	-	Before Christ
BMI	-	Body mass index
CI	-	Confidence interval
cms	-	Centimeters
CO_2	-	Carbon dioxide
DFU	-	Diabetic foot ulcer
DM	-	Diabetes mellitus
e.g.	-	For example
ECM	-	Extra cellular matrix
EGF	-	Endothelial growth factor
g	-	Grams
GDM	-	Gestational diabetes mellitus
gm	-	Gram
HbA_1C	-	Glycated hemoglobin level
HDL	-	High-density lipoprotein
HDL-C	-	High-density lipoprotein-cholesterol
i.e.	-	That is
IDDM	-	Insulin Dependent Diabetes Mellitus
IDF	-	International Diabetes Federation

IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
iTCC	-	Instant total contact casts
kg/m^2	-	Kilograms per square meter
LDL	-	Low-density lipoprotein
MDT	-	Maggot debridement therapy
mg/dL	-	Milligrams per deciliter
mmHg	-	Millimeters of mercury
mmol/L	-	Millimole per litre
MMP	-	Matrix metalloproteinases
MMPs	-	Matrix metalloproteinases
MRI	-	Magnetic resonance imaging
MRSA	-	Methicillin resistant Staphylococcus aureus
n	-	Total number
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
NOGC	-	No growth of culture
NPs	-	Nanoparticles
p	-	Probability
PAI	-	Plasminogen activator inhibitor
PDGF	-	Platelet derived growth factor
PMN	-	Polymorphonuclear
PTV	-	Proteus vulgaris
PVA	-	Polyvinyl alcohol
PVD	-	Peripheral vascular disease
RCT	-	Randomized controlled trial

RCW	-	Removable cast walker
SD	-	Standard deviation
SSD	-	Silver sulfadiazine
TCC	-	Total contact casts
Urgo	-	Urgotul
viz.	-	Namely
VRE	-	Vancomycin resistant enterococci
vs	-	Versus
WHO	-	World Health Organization

ABSTRACT

Background and objectives

The silver-containing preparations have bactericidal properties and it has been tried in the treatment of chronic ulcers. The present study was aimed to find the effect of amorphous hydrogel dressings with silver nano particles versus conventional dressing on wound culture and slough in patients with diabetic foot ulcers.

Methodology

This one year randomized controlled trial was done in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients with chronic diabetic foot ulcers from January 2014 to December 2014were enrolled. Patients were divided into two groups of 30 each as group A (dressing and topical management using hydrogel with silver nano particles) and group B (dressing and topical management with povidone iodine).

Results

Most of the patients in group A (86.67%) and B (66.67%) were males ($p=0.067$). The mean age in group A was 60.23±9.27 years compared to 55.13±12.06 years in group B ($p=0.072$). The diabetic history, wound characteristics and culture in group A and B were comparable ($p>0.050$). On day five, maximum number of patients had negative wound culture in group A (43.33% vs 16.67%) compared to group B ($p=0.024$). The mean slough was comparable at all the intervals ($p>0.050$) in group A and B. Among the patients

with group A, the mean reduction of slough on day five (6.93±6.14% vs. 4.37±2.96%; p=0.045), day ten (15.22±7.40% vs. 9.10±7.00%; p=0.002) and day fifteen (21.57±8.71% vs. 15.90±8.11%; p=0.012) was significantly high compared to group B.

Conclusion and interpretation

From the findings of this study it may be concluded that, diabetic foot ulcers treated with amorphous hydrogel dressings with silver nano particles are efficacious in terms of reduction in slough compared to conventional dressing and reduce the micro-organisms during first five days.

Keywords

Amorphous hydrogel dressings; Diabetic foot ulcer; Silver nano particles;

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INTRODUCTION

Diabetes mellitus (DM), a metabolic disease which is characterized by hyperglycemia results from derangement in either insulin secretion and insulin action or both.[1] Most of the patients come into two broad categories that is, patients with little or no endogenous insulin secretory capacity called as Insulin Dependent Diabetes Mellitus (IDDM or type 1) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response known as Non Insulin Dependent Diabetes Mellitus (NIDDM, or type 2).[1,2]

Worldwide, the frequency of type 2 diabetes is increasing in every country. In 2014, diabetes caused 4.9 million deaths and death is noted in a person every seven seconds. Based on the estimates from International Diabetes Association, worldwide 387 million people have diabetes. This number is expected to rise to 582 million by 2035. A vast majority of these (77%) people live in low and middle income countries.[3]

Diabetes is potential epidemic in India with more than 62 million diabetic individuals.[4,5] It is predicted that, by 2030, it may afflict upto 79.4 million individuals. Other countries like China (42.3 million) and the United States (30.3 million) are also expected to see increase in the number of patients affected by DM.[6,7] India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country.[8]

Diabetes mellitus is a chronic and disabling disease which has reached an epidemic proportion in many parts of the world. It is a major and growing concern to global public health. Diabetes results in long term damage, dysfunction of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[1]

The metabolic deregulation due to DM causes secondary pathophysiological changes in various organ systems which impose tremendous burden on the individual and on the health care system. Many complications are associated with DM. These complications arise mainly due to the disruption of the vascular system resulting in inadequate circulation to the peripheral body placing the foot at higher risk of ulceration and infection. Every chronic disease brings with it fears, concerns, and people with Diabetes are no exception with daunting possibility for infections that never heal, potentially ending in the loss of the affected part of limb.[9] One-third of all diabetic patients have significant peripheral neuropathy and/or peripheral vascular disease (PVD).[10,11]

Diabetic foot problems are the common causes for hospitalization of diabetic patients (nearly 30% of admissions) with 20% of the total health-care costs which is more than all other diabetic complication.[10,11] In India prevalence of foot ulcers in diabetic patients in clinic population is 3%. The prevalence of PVD increases with advancing age to as high as 55% in those above 80 years of age compared to as low as 3.2% below 50 years of age.[12] Also it increases with duration of diabetes that is, 15% at duration of 10 years and 45% after the duration of 20 years.[13]

The management of diabetic foot ulcers needs a multidisciplinary approach. One of the major causes of non-healing of ulcer in diabetes is infection resulting in

often hospitalization. The infections are caused by a variety of micro-organism they invade the wound by multiplying. Furthermore they produce harmful toxic substances which destruct the tissue and disturb wound healing.[14]

The successful management of diabetic foot ulcers prompts offloading the wound by using appropriate therapeutic footwear,[15] daily saline or similar dressings so as to provide a moist wound environment, debridement (if necessary), antibiotic therapy (if osteomyelitis or cellulitis is present),[16] optimal diabetic control, and evaluation and correction of peripheral arterial insufficiency.

Various topical medication and gels are available for ulcer care and healing. An ideal wound care product has to control the infection and protect the normal tissues without interfering with normal wound healing. Presently diabetic foot ulcers are being managed by local dressing with agents like Povidine Iodine, EUSOL and Hydrogen Peroxide. Silver-based dressings are now available as fibers or polymeric scaffolds impregnated or coated with a Ag salt or metallic Ag in nanoparticulate form.[17]

Silver is a broad-spectrum antimicrobial agent that controls yeast, mold, and bacteria, including methicillin resistant Staphylococcus aureus (MRSA) and vancomycin resistant enterococci (VRE), whenever provided at an appropriate concentration.[17] In addition to the antimicrobial properties, silver also appears to have anti-inflammatory properties, as suggested by the loss of rubor in chronic wounds treated with colloidal silver.[18] Nanoparticles (NPs) are particles having one or more dimensions in the order of 100 nm or less. Silver NPs (Ag NPs) have been shown to possess unusual physical, chemical and biological properties.[19-21]

However, recently, the effectiveness of Ag NP containing dressings has been widely tested *in vitro*, and demonstrated that these dressings have a fast and broad spectrum antibacterial activity against both Gram-positive and -negative bacteria.[22-23] Further the use of hydrogels achieves a more effective autolytic debridement. Hydrogel dressings are used to maintain a moist environment and to induce autolytic debridement of necrotic debris within the ulcer area.[24] Autolytic debridement is the process by which the body attempts to shed devitalised tissue by the use of moisture. This process is helped by the presence of enzymes called matrix metalloproteinases (MMPs), which are produced by damaged tissue and which disrupt the proteins that bind the dead tissue to the body. This process can be enhanced by the application of wound management products which promote a moist environment. [25]

The unique feature of hydrogels is due to the presence of hydrophylic polymers in their content. The amorphous gel formed by hydrogel dressings maintains a moist and hydrated environment within the ulcer.[24] This provides a good environment for autolytic debridement. Also autolytic debridement is more selective and may require less frequent dressing changes. Less frequent dressing changes reduce the manpower costs associated with wound care, although the supply cost for autolytic debridement may be higher than for wet-to-dry gauze dressings. The high cohesion makes Gel stay in place. The gel is easy to apply to the wound. Due to its viscous texture, the gel will not run. Even after absorption of debris and excess exudates, the gel will remain cohesive and counteract leakage, can absorb significant fluid volume without significant increase in size. Semi permeable to fluids and vapors. No adherent to wound base. Frequent dressing changes required every 1 to 3 days, depending on amount of exudates.

However data on topical silver with hydrogel in treatment of chronic wounds is lacking as nanosilver being a new generation of nanoproduct in biomedical applications. Hence the present study was planned to know the efficacy of amorphous hydrogel dressings with silver nano particles versus conventional dressing for treating diabetic foot ulcers.

OBJECTIVES

The objective of the present study was to know the efficacy of amorphous hydrogel dressings with silver nano particles versus conventional dressing for treating diabetic foot ulcers with special emphasis on wound culture and slough.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus (DM) is a chronic metabolic disorder of impaired metabolism of carbohydrates, fats, and proteins, characterised by hyperglycaemia resulting from decreased utilisation of carbohydrate and excessive glycogenolysis and gluconeogenisis from amino acids and fatty acids.[26]

It is one of the first diseases described with an Egyptian manuscript mentioning “too great emptying of the urine”.[27,28] Indian physicians around the same time identified the disease and classified it as “Madhumeha” or “Honey urine”, noting the urine would attract ants. The term “diabetes” or “to pass through” was first used in 230 BC by the Greek Apollonius of Memphis. Galen named the disease “diarrhoea of the urine” (diarrhoea urinosa).[29]

Classification

Diabetes is classified into four broad categories viz. type 1, type 2, gestational diabetes and other specific types. The "other specific types" are a collection of a few dozen individual causes.[30]

Type 1 DM is characterized by loss of the insulin producing beta cells of the islets of langerhans in the pancreas, leading to insulin deficiency. The majority of type 1 diabetes is of the immune-mediated nature, in which a T- cell- mediated autoimmune attack leads to the loss of beta cells and thus insulin. Traditionally it is termed as juvenile diabetes because a majority of these diabetes cases were in children.[30]

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. In the early stages of type 2, the predominant abnormality reduced insulin sensitivity. At this stage, hyperglycaemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. Type 2 diabetes is due primarily to genetics and lifestyle factors including obesity, lack of physical activity, poor diet, stress and urbanization. A lack of exercise is believed to cause 7% of cases.[30]

Gestational DM (GDM) involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery.[30]

Prevalence

Worldwide

The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. There are 382 million people living with diabetes worldwide. The worldwide prevalence of diabetes in adults (aged 20-79 years) was estimated to be 135, 285 million in 1995 and 2010 respectively and is expected 300 million in 2025 and 439 million in 2030. Statistics showed significant increase (155 million) of diabetes in adults from 1995 to 2010. By 2035, 592 million people or 1 in 10 people will have diabetes and 316 million people are currently at high risk of developing type 2 diabetes, with the number expected to increase to almost 500 million within a generation.[6,30-36]

According to the International Diabetes Federation survey in the year of 2013, nearly 98.4 million people with diabetes (at 20 - 79 years) live in China, is the top most country and India is the second i.e., nearly 65.1 million. Table 1 presents survey of the year 2013 on diabetes affected top 10 countries and their number of diabetic people at age group of 20-79.[6,30-35]

Top ten countries with diabetes and number of people with age 20–79 years[37]

Serial number	Country / territory	Number (Million)
1.	China	98.40
2	Indian	65.10
3	United states of America	24.40
4	Brazil	11.90
5	Russian federation	10.90
6	Mexico	8.70
7	Indonesia	8.50
8	Germany	7.60
9	Egypt	7.50
10	Japan	7.20

Geographical distribution

The prevalence of diabetes is higher in developed than in developing countries. By the year 2025, more than 75% of people with diabetes will reside in developing countries, as compared with 62% in 1995. Europe has the highest prevalence of type 1 diabetes in children but in South-East Asia, almost half of people with diabetes are undiagnosed. 11% of people with diabetes live in Middle

East and North Africa where as it was 6% in Africa but in Africa, 76% of deaths due to diabetes are in people under the age of 60. North America and the Caribbean spent more on healthcare for diabetes than in any other region.[6,30-35]

Sex predilection

The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. [6,30-35]

Mortality

In 2012 it resulted in 1.5 million deaths worldwide making it the 8th leading cause of death and more than 80% of diabetic deaths occurring in low and middle-income countries. More than 21 million live births were affected by diabetes during pregnancy and > 79,000 children developed type 1 diabetes in 2013. [6,30-35]

Indian scenario

According to The International Diabetes Federation (IDF) estimation India will have rise in people living with diabetes up to 87.0 million by 2030 from 50.8 million (2010), making it the 'Diabetes Capital' of the world.[38-40]

This prevalence is increasing not only in urban but also in rural area. According to the World Health Organization (WHO) criteria, the prevalence of known diabetes was 5.6% and 2.7% among urban and rural areas, respectively.[41]

Recently, in Karnataka, Rao CR. et al.[42] reported overall prevalence of diabetes as 16%. Increasing age showed two-fold, four-fold, and six-fold higher odds for 40 – 49, 50 – 59, and ≥ 60 years age group, respectively, as compared to the

30 - 39 year age group (p< 0.001). Nineteen percent of the males had diabetes, (OR = 1.38, 95% confidence interval [CI] = 1.01 – 1.88). In the high socioeconomic strata, 32% of the subjects had diabetes (*P* = 0.018 unadjusted odds ratio 3.29, 95% CI = 1.40 – 7.74).

In India, diabetes mellitus is considered to be a disease of grave concern not only because of rapidly increasing prevalence of this disease, but also because various studies have shown rising prevalence of diabetes in young and middle aged people. This is mainly due to the economic transition, rapid urbanization and changing lifestyles, tobacco use, excessive alcohol consumption, and insufficient physical activity which are the major risk factors for diabetes mellitus.[43]

Risk factors for Type 2 Diabetes Mellitus[38]

- Family history of diabetes (i.e. parent or sibling with type 2 diabetes)
- Obesity (body mass index [BMI] ≥25 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- History of GDM or delivery of baby > 4kg (>9 Ib)
- Hypertension (blood pressure ≥ 140/90 mm Hg)
- High density lipoprotein (HDL) cholesterol level ≤ 35mg/dL (0.90mmol/L) and / or a triglyceride level ≥ 250mg/dL (2.82 mol/L)
- Polycystic ovary syndrome or acanthosis nigricans.

- History of vascular disease.

Symptoms

Symptoms are similar in both types of diabetes but they vary in their intensity. Symptoms develop more rapidly in type 1 diabetes and more typical. The symptoms of diabetes include frequent urination, extreme thirst and/or hunger, weight loss, fatigue, numbness and increased infections. People with diabetes have an increased risk of developing a number of serious health problems.[38]

Pathophysiology

Hyperglycemia results from lack of endogenous insulin, which is either absolute, as in type 1 diabetes mellitus, or relative, as in type 2 diabetes mellitus. Relative insulin deficiency usually occurs because of resistance to the actions of insulin in muscle, fat, and the liver and an inadequate response by the pancreatic beta cell. Insulin resistance, which has been attributed to elevated levels of free fatty acids in plasma,[44] leads to decreased glucose transport in muscle, elevated hepatic glucose production, and increased breakdown of fat.

Presumably, the defects of type 2 diabetes mellitus occur when a diabetogenic lifestyle (ie, excessive caloric intake, inadequate caloric expenditure, obesity) is superimposed upon a susceptible genotype. The body mass index at which the risk for diabetes increases varies with different racial groups. For example, compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight.[45] A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

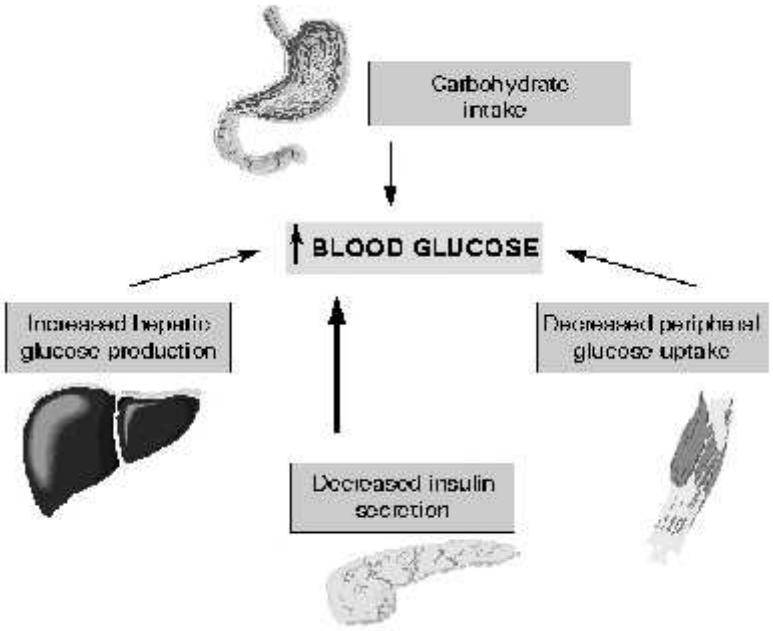


Figure 1. Pathophysiology of type 2 diabetes mellitus[1,46]

Hyperglycemia appears to be the determinant of microvascular and metabolic complications. However, glycemia is much less related to macrovascular disease. Insulin resistance with concomitant lipid (i.e., small dense low-density lipoprotein [LDL] particles, low high-density lipoprotein-cholesterol [HDL-C] levels, elevated triglyceride-rich remnant lipoproteins) and thrombotic (ie, elevated type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen) abnormalities, as well as conventional atherosclerotic risk factors (e.g., family history, smoking, hypertension, elevated low-density lipoprotein-cholesterol [LDL-C], low HDL-C), determine cardiovascular risk.[1,46]

Diagnosis

The National Diabetes Data Group and World Health Organization (WHO) have issued diagnostic criteria for DM based on the following premises:[1]

Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose 7.0 mmol/L (126 mg/dL)[b] *or*
- Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Complications

Poor control of diabetes can lead to an increased risk of heart disease, high blood pressure, stroke, nerve disease, kidney and bladder failure, gum disease, blindness, foot and leg infections, sexual dysfunctions, pregnancy complications. Uncontrolled diabetes can lead to biochemical imbalance that can cause life-threatening events, such as diabetes ketoacidosis and hyperosmolar coma.[30]

Chronic Complications of Diabetes Mellitus[47-53]

The chronic complications of DM affect many organ systems and those may be responsible for the majority of morbidity and/or mortality associated with the disease.

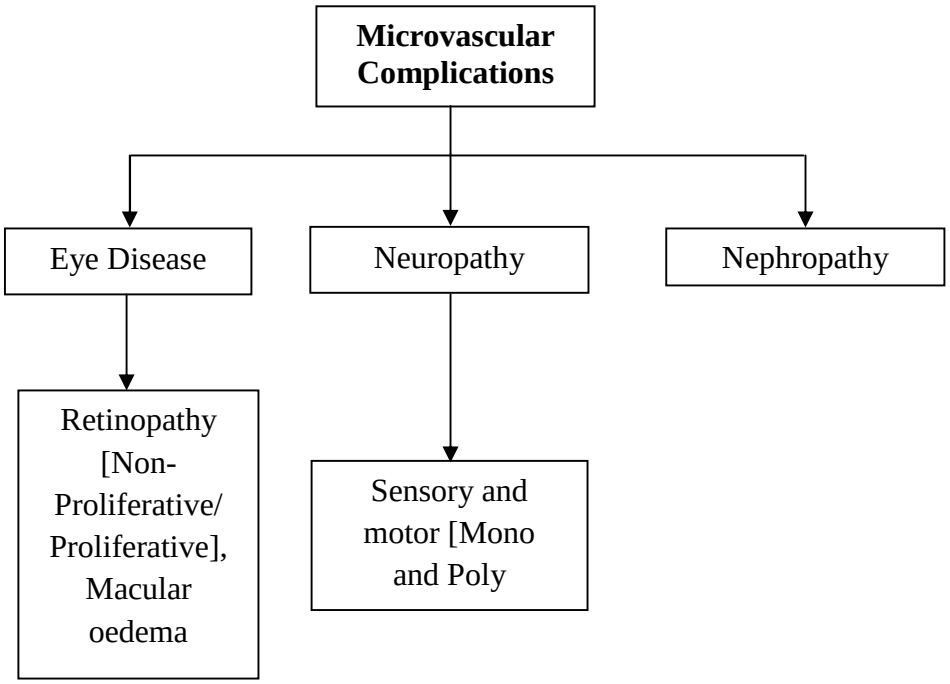


Figure 2. Microvascular complications seen in diabetes mellitus

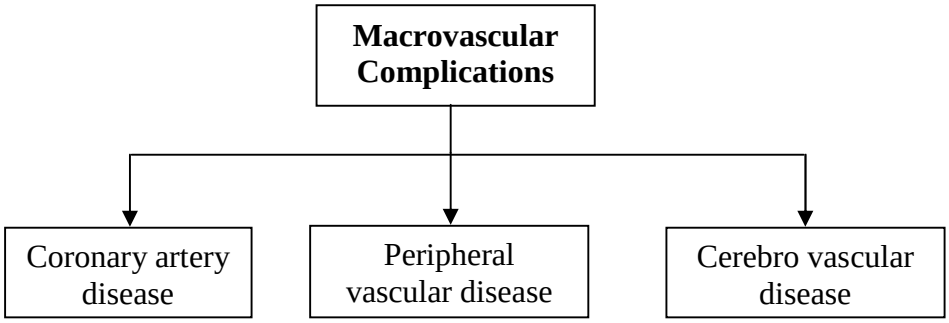


Figure 3. Macrovascular complications seen in diabetes mellitus

Other complications seen in diabetes mellitus:[47-53]

- Gastro-intestinal problems [Gastroparesis, diarrhea]
- Genitor-urinary problems [Uropathy / Sexual dysfunction]
- Dermatologic problems.
- Infections.
- Cataracts and Glaucomas.

Microvascular complications in both type 1 and type 2 diabetes mellitus, results from chronic hyperglycemia.

Complications in lower extremities and diabetes mellitus:[47-53]

- Foot ulcers and infections are major and important source of morbidity in persons with DM.
- The reasons for the increased incidence of these disorders in DM is because of the interaction of several pathogenic factors:
    - Neuropathies.
    - Peripheral arterial diseases.
    - Abnormal foot biomechanics.

Neuropathy:

Neuropathy is present in over 80% of the patients with foot ulcers.

Peripheral sensory neuropathy:

It interferes with normal protective mechanisms and allows the patient to sustain major or minor trauma to the foot repeatedly, often without knowledge of the injury to the patient.

Motor and sensory neuropathy:

It generally leads to abnormal foot muscle mechanics and structural changes in the foot [e.g., hammer toe, claw toe deformity, prominent metatarsal heads, Charcot arthropathy].

DIABETIC FOOT ULCER

Diabetic foot ulcer (DFU) is the most common complication of diabetes mellitus that usually fail to heal, and leading to lower limb amputation. DFU is a common complication of DM that has shown an increasing trend over previous decades.[54]

A diabetic foot infection is most simply defined as any inframalleolar infection in a person with diabetes mellitus. These include paronychia, cellulitis, myositis, abscesses, necrotizing fascitis, septic arthritis, tendonitis, and osteomyelitis. The most common and classic lesion, however, is the infected diabetic "mal perforans" foot ulcer.[55] Wound infection is the deposition and multiplication of bacteria in tissue with colony count of more than 10^5 bacteria per gram of tissue with an associated host reaction.[56]

Diabetic foot ulcers occur as a result of various factors, such as mechanical changes in conformation of the bony architecture of the foot, peripheral neuropathy, and atherosclerotic peripheral arterial disease, all of which occur with higher frequency and intensity in the diabetic population.

Anatomy of the foot[38,39]

The human foot acts as a pliable platform to support the body weight in the upright posture and as a lever to propel the body forwards in walking, running or jumping. It has 26 bones, 29 joints, 42 intrinsic muscles, various ligaments, 4 mm thick skin, exquisite nerve supply and abundant vascularity with good collaterals. These component works together to provide the body with support, balance with mobility.

Parts

Structurally the foot has three main parts;

1. *The fore foot:* It is composed of phalanges and metatarsals. They are connected together by metatarso phalangeal joint at the balls of the foot. The fore foot bears the half of the body weight and balance pressure on the balls of the foot.
2. *The mid foot:* It is composed of five tarsals bones. It forms the foot's arch and serves as a shock absorber.
3. *The hind foot:* It links the mid foot to ankle. It is composed of two long bones of the lower leg, the tibia and the fibula which forms ankle joint with talus. This subtalar joint is formed between talus and calcaneum which is cushioned inferiorly by a fat layer.

Arches

The foot consists of three arches.

1. Medial longitudinal arch
    - It is the highest and the most important arch of the foot.
    - It is composed of calcaneum, talus, navicular, cuneiforms and first three metatarsal bones. The submit of the arch is formed by talus.
    - It acts as a shock absorber.
2. Lateral longitudinal arch
    - It is characteristically low arch.

- It is composed of calcaneum, cuboid, fourth and fifth metatarsal bones. The submit of the arch is formed by calcaneum.
- It transmits the body weight and thrust to the ground.

3. Transverse arch

- It is a continuous structure formed by cuboid, three cuneiforms and the bases of the metatarsal bones.

Factors responsible for the maintenance of the arches

1. Ligaments and plantar aponeurosis.
2. Action of extrinsic and intrinsic muscles of the foot.
3. Structure of the bones.

Functions of the arches of the foot

1. They distribute body weight to the weight bearing areas of the sole mainly heel and the base of the toes (first and fifth).
2. They act as a springs chiefly the medial longitudinal arch which helps in walking and running.
3. They also act as a shock absorbers in stepping and jumping.
4. The concavity of the arches protects the soft tissue of the sole against pressure.

Sole

The skin of the sole is about 4 mm thick. It is adapted for weight bearing. There are subcutaneous concentrations of the fat over the weight bearing areas such

as heel, lateral margin of the sole and across the plantar aspect of the metatarsal heads. Numerous fibrous bands between the skin and the plantar aponeurosis prevent undue movement of sole during walking.

Muscles

Intrinsic

- Origin and insertion are located within the foot.
- They include plantar flexors, dorsiflexors, abductors and adductors of the toes.
- They also support the arches of the foot.

Extrinsic

- Origin of these muscles are in the lower leg.
- They have long tendon that crosses the ankle to insert on the bones of foot except the talus.
- They are responsible for the movement at the ankle, foot and toes.
- They also support the arches of the foot.

Major joints and movements

- Ankle joint – Dorsiflexion and plantar flexion.
- Subtalar joint – Inversion and eversion.
- Midtarsal joint – Abduction and adduction.

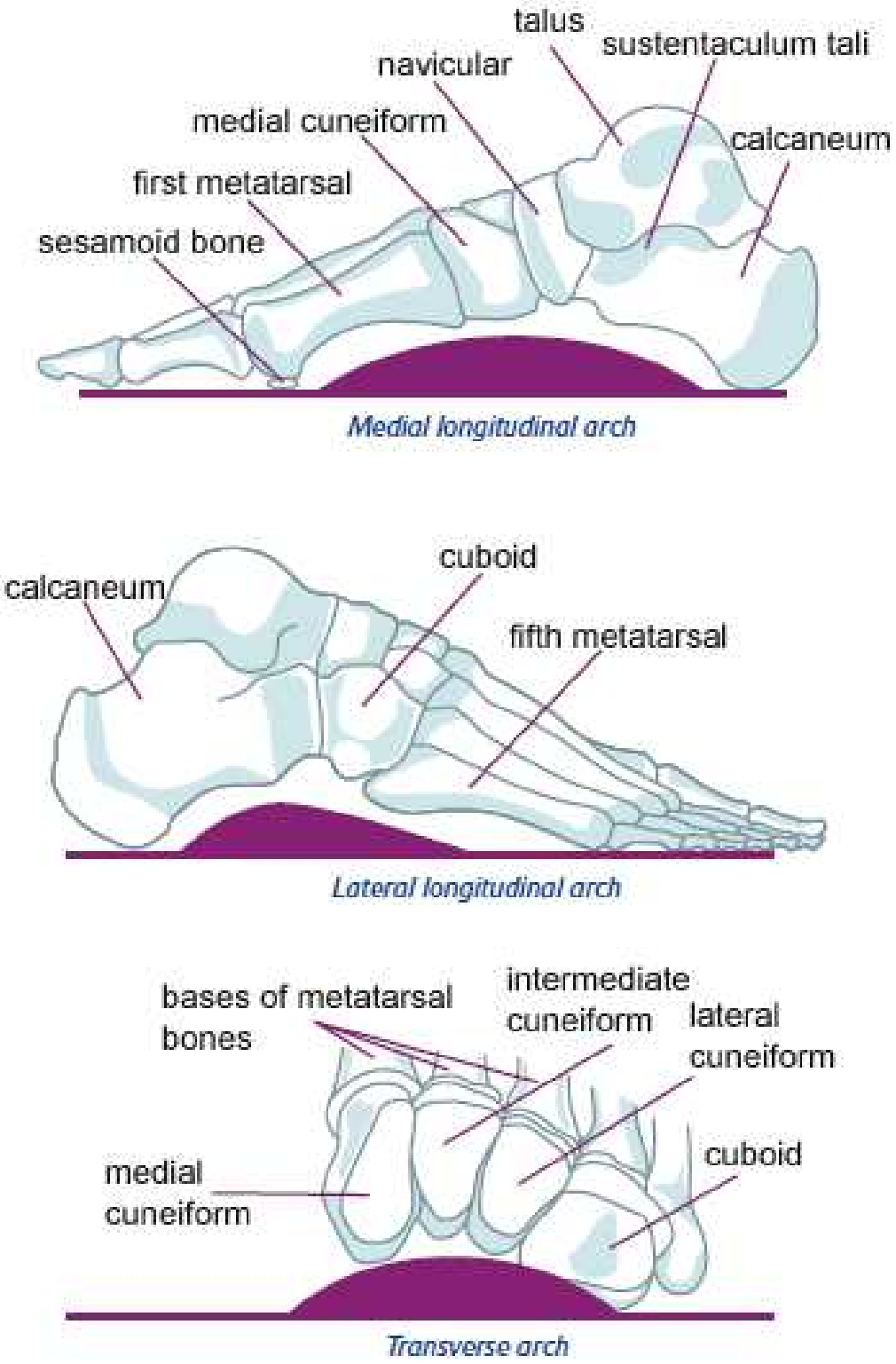


Figure 4. Arches of the foot[59,60]

Blood supply

Anterior tibial artery continues as a dorsalis pedis artery in the foot. Dorsalis pedis artery gives off a arcuate artery that along with its branches supplies the outer four toes. The dorsalis pedis artery continues down to supply the great toe. Posterior tibial artery in the sole of the foot divides into two branches, the lateral and medial plantar arteries that supplies the sole of the foot. The peroneal artery descends down and supply posterior and the outer aspect of the heel.

Nerve supply

Sensory nerve supply

Dorsum

- The saphenous nerve: It supplies the medial border of the foot upto the ball of the great toe.
- The superficial peroneal nerve: It supplies entire dorsum of the foot except the lateral border, medial border and the cleft between the first and second toe.
- The sural nerve: It supplies the lateral border of the foot upto the tip of the little toe.
- The deep peroneal nerve: It supplies the cleft between the first and the second toes.
- The digital branch of the medial and lateral plantar nerve supplies the distal part of the dorsum of the toes.

Sole

- Medial calcanean branch of tibial nerve: It supplies posterior and medial portion of the sole.
- Medial plantar nerve: It supplies the anteromedial portion of the sole and medial three and half digits.
- Lateral plantar nerve: It supplies anterolateral portion of the sole and lateral one and half digits.

Motor nerve supply

- Deep peroneal nerve.
- Superficial peroneal nerve.
- Tibial nerve - Medial plantar nerve; Lateral plantar nerve.

Epidemiology

Approximately 15% of all patients with diabetes will develop a peripheral ulcer. 20% of all patients with diabetes admitted to a hospital will have a skin ulcer. The risk of amputation in a patient with diabetes is 15–40 times higher than in a patient without diabetes. The presence of an ulcer in a diabetic patient has a deep impact on the quality of life for the patient and on the delivery of care. The cost of care for diabetic ulcers and the associated amputations is staggering. Although the prevalence of chronic ulcers has been estimated to be 120/100,000 people between 45–64 year of age, the prevalence increases to more than 800/100,000 people over the age of 75 year. Persons with diabetes have up to a 40-fold greater risk of lower extremity amputation than their nondiabetic counterparts. There were approximately

86,000 hospital discharges for diabetes-related nontraumatic amputations in the United States in 1996. The 5-year survival rate after amputation of a diabetic limb is less than 50%. These grim statistics reflect an increased prevalence of peripheral lesions in diabetes, but also delayed healing.[47,61]

In total, it is estimated that 15% of patients with diabetes will suffer from DFU during their lifetime. Although accurate figures are difficult to obtain for the prevalence of DFU, the prevalence of this complication ranges from 4%-27%.[54]

To date, DFU is considered as a major source of morbidity and a leading cause of hospitalization in patients with diabetes. It is estimated that approximately 20% of hospital admissions among patients with DM are the result of DFU. Indeed, DFU can lead to infection, gangrene, amputation, and even death if necessary care is not provided. On the other hand, once DFU has developed, there is an increased risk of ulcer progression that may ultimately lead to amputation. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than patients without diabetes. It is estimated that approximately 50%-70% of all lower limb amputations are due to DFU. In addition, it is reported that every 30 s one leg is amputated due to DFU in worldwide. Furthermore, DFU is responsible for substantial emotional and physical distress as well as productivity and financial losses that lower the quality of life.[54]

Risk factors

Risk factors for foot ulcers or amputation include male sex, diabetes >10 years' duration, peripheral neuropathy, abnormal structure of foot (bony

abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation and poor glycemic control.[54]

Etiology

Recent studies have indicated multiple risk factors associated with the development of DFU. These risk factors are as follows: gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index, and other comorbidities such as retinopathy, diabetic peripheral neuropathy, peripheral vascular disease, glycated hemoglobin level (HbA_1C), foot deformity, high plantar pressure, infections, and inappropriate foot self-care habits.[54]

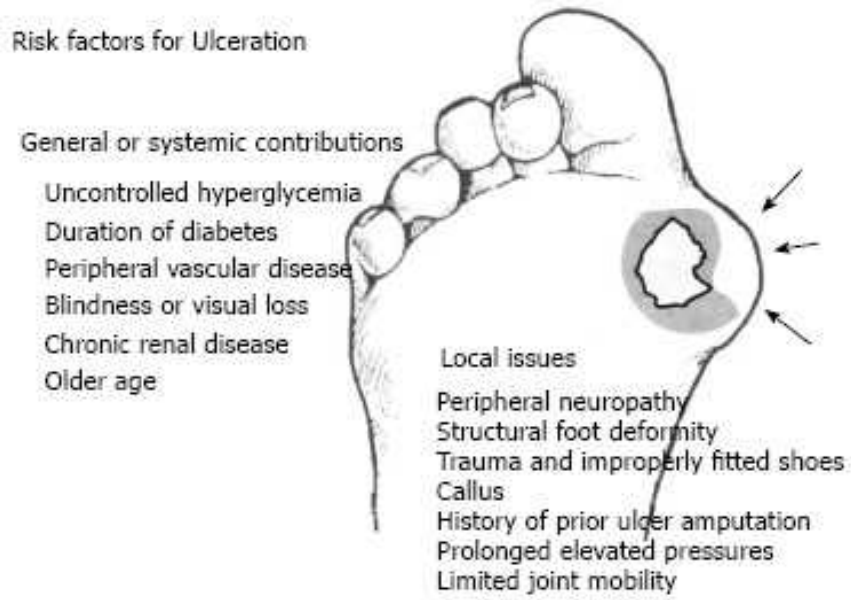


Figure 5. The risk factors for diabetic foot ulcer. Ulcers may be distinguished by general or systemic considerations *vs* those localized to the foot and its pathology[62]

Although the literature has identified a number of diabetes related risk factors that contribute to lower-extremity ulceration and amputation, to date most DFU has been caused by ischemic, neuropathic or combined neuroischemic abnormalities. Pure ischemic ulcers probably represent only 10% of DFU and 90% are caused by neuropathy, alone or with ischemia. In recent years, the incidence of neuroischemic problems has increased and neuroischemic ulcers are the most common ulcers seen in most United Kingdom diabetic foot clinics now.[54]

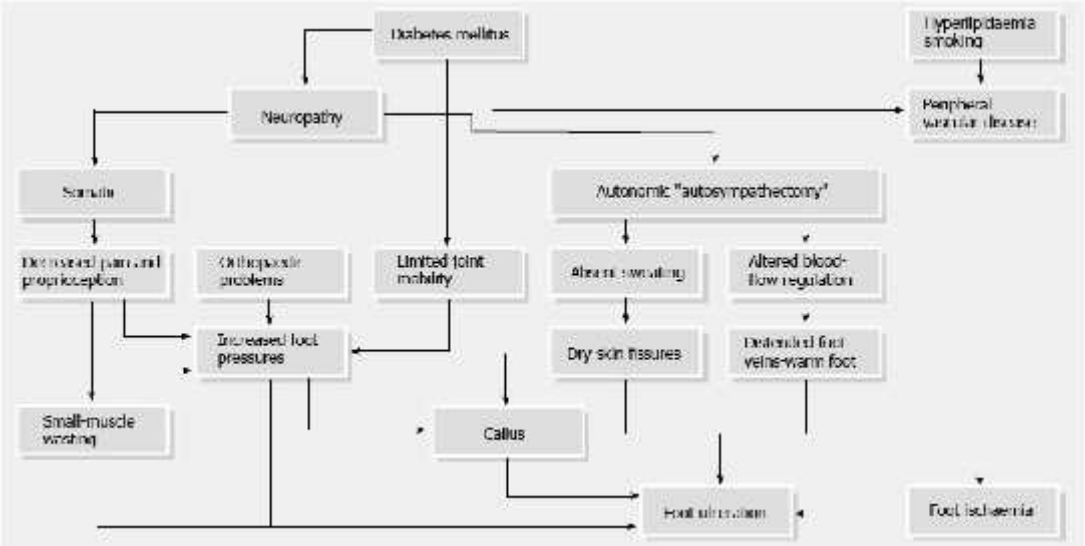


Figure 6. Etiology of diabetic foot ulcer[63]

In total, the most common pathway to develop foot problems in patients with diabetes is peripheral sensori-motor and autonomic neuropathy that leads to high foot pressure, foot deformities, and gait instability, which increases the risks of developing ulcers. Today, numerous investigations have shown that elevated plantar pressures are associated with foot ulceration. Additionally, it has been demonstrated that foot defor-mities and gait instability increases plantar pressure, which can result in foot ulceration.[63]

Pathophysiology

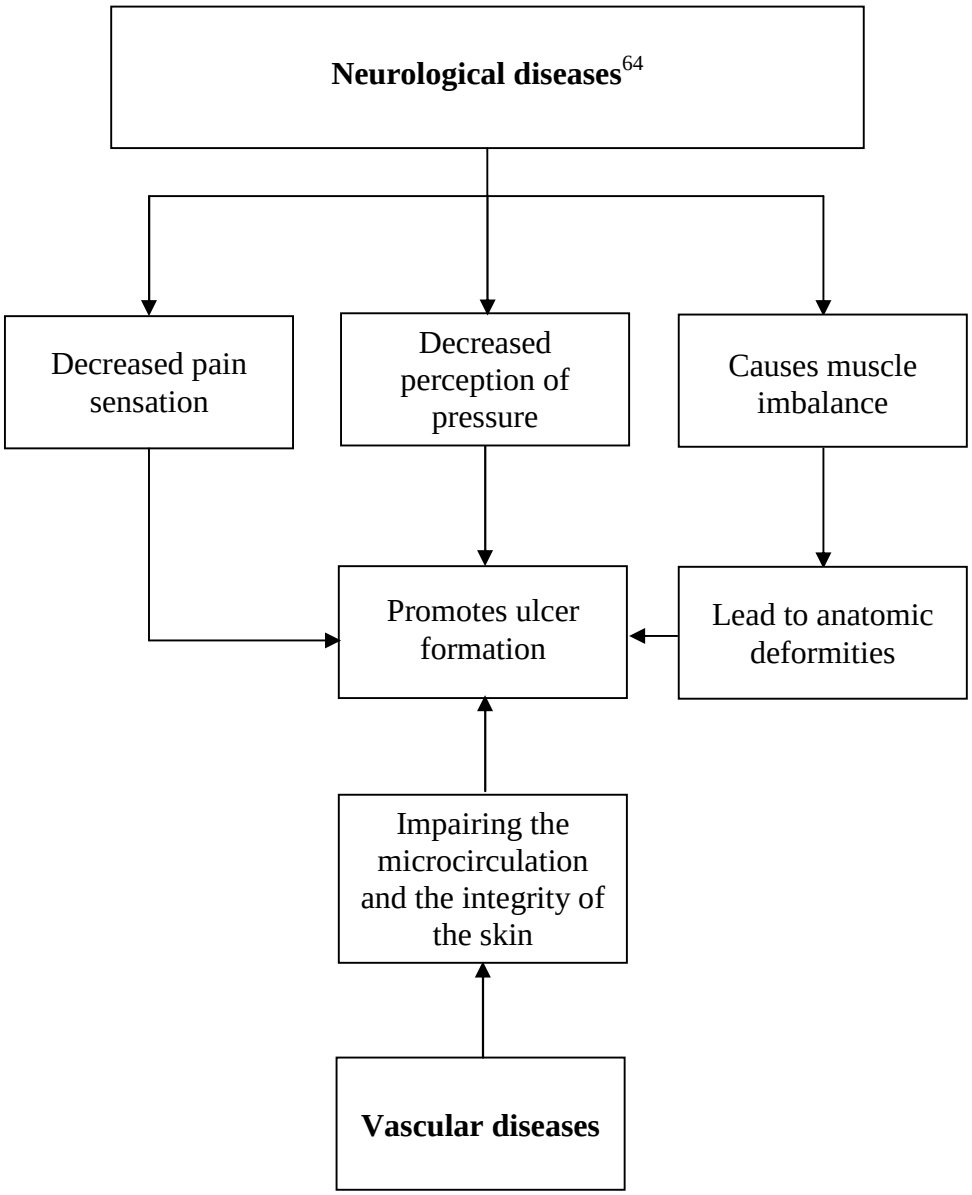


Figure 7. Pathogenesis of Diabetic Foot

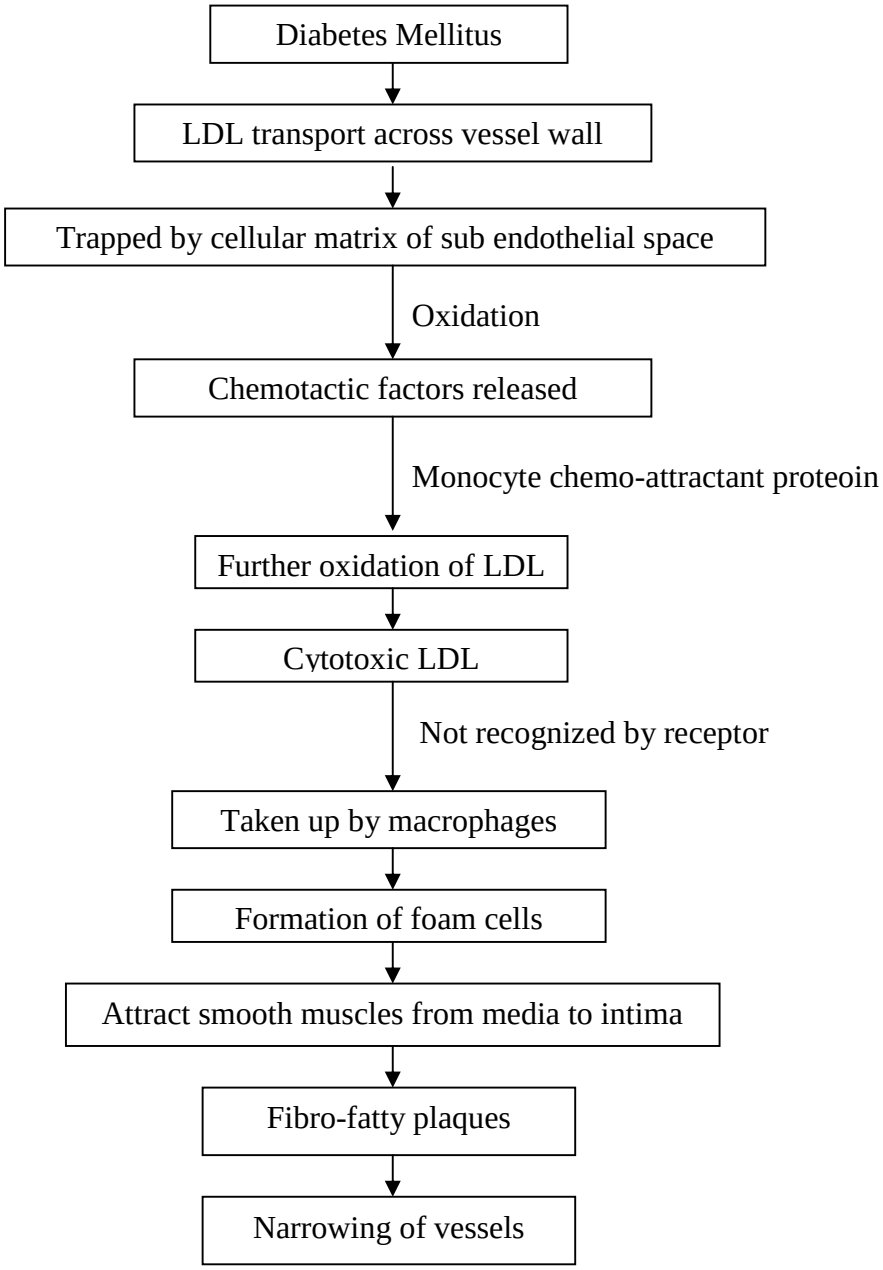


Figure 8. Pathophysiology of diabetic vasculopathy

Atherosclerosis and peripheral neuropathy occur with increased frequency in persons with DM. Development of atherosclerosis is accelerated in DM leading to

increased morbidity and mortality. All the large vessels are involved in this process and clinical manifestations are apparent as a result of atherosclerotic narrowing and thrombosis of coronary, cerebral and leg vessels.

The pathophysiology of diabetic peripheral neuropathy is multifactorial and is due to vascular disease occluding the vasa nervorum; endothelial dysfunction; deficiency of myoinositol-altering myelin synthesis and diminishing sodium-potassium adenine triphosphatase (ATPase) activity; chronic hyperosmolarity, causing edema of nerve trunks; and effects of increased sorbitol and fructose.[65]

The result of loss of sensation in the foot is repetitive stress; unnoticed injuries and fractures; structural foot deformity, such as hammertoes, bunions, metatarsal deformities, or Charcot foot; further stress; and eventual tissue breakdown. Unnoticed excessive heat or cold, pressure from an ill- fitting shoe, or damage from a blunt or sharp object accidentally left in the shoe may cause blistering and ulceration. These factors, combined with poor arterial inflow, confer a high risk of limb loss on the patient with diabetes.

The infection and related issues

The source of infection is usually the contamination of the break in the skin, which may be imperceptible like cracks or fissures, puncture wounds or a major wound in a neuropathic foot due to trauma of any cause. Staphylococcus aureus and beta haemolytic streptococci rapidly colonise the break in the skin. A high frequency of anaerobic infection has also been reported.[66] The devastating developments subsequent to an infected ulcer that lead to the development of gangrene, necrotizing fascitis and life threatening situations like multi organ failure should be guarded

against. The pathophysiology of these events can be constructed in the following sequence.

In persons with diabetes, infection results in microthrombi formation in the smaller vessels unlike persons without diabetes where it results in vasodilatation. This impairs blood flow in diabetes, converting the small arteries of the toes into end arteries resulting in gangrene of the toes. Osteomyelitis can be difficult to diagnose and remains a focus of untreated infection and fails to indicate to the physician the need for longer antibiotic regimen. The diagnosis of Osteomyelitis was missed in as many as two thirds of bone culture proven case. Excessive reliance on plain X rays by primary care physicians does not help. Simple probing the bone can make a diagnosis of Osteomyelitis, while scanning techniques are not always successful, some like Tc99 lack specificity, but magnetic resonance imaging (MRI) is proving helpful.

The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in persons who do not have diabetes mellitus. Foot infections are the most common complications of diabetic foot and plays a main role in the development of moist gangrene.[67] In general, people with diabetes have infections that are more severe and take longer to cure than infections in other people. The infection leads to the early development of complication even after a trivial trauma, the disease progresses and becomes refractory to antibacterial therapy.[68] It is essential to assess the magnitude of bacterial infection of the lesions to avoid further complications and save the diabetic foot. Early diagnosis of microbial infections is aimed to provide the appropriate antibacterial therapy and to avoid further complications.[69]

However, these infections are difficult to treat because these patients have impaired microvascular circulation, which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues. Although infection is rarely implicated in the etiology of diabetic foot ulcers, the ulcers are susceptible to infection once the wound is present.

Microbiologic features of diabetic foot

Aerobic Gram-positive cocci are the predominant bacteria that colonize and acutely infect breaks in the skin. *Staph aureus* and the hemolytic streptococci (groups A, C, and G, but especially group B) are the most commonly isolated pathogens.[70] Chronic wounds develop a more complex colonizing flora, including enterococci various Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa*, and nonfermentative Gram-negative rods.[71] Hospitalization, surgical procedures, and, especially, prolonged or broad-spectrum antibiotic therapy may predispose patients to colonization and/or infection with antibiotic-resistant organisms (*MRSA* or *vancomycin-resistant enterococci* [VRE]).[72] Although *MRSA* strains have previously been isolated mainly from hospitalized patients, community associated cases are now becoming common and are associated with poor outcomes in patients with diabetic foot infections.[73]

The impaired host defenses around necrotic soft tissue or bone may allow low-virulence colonizers, such as *coagulase-negative staphylococci* and *Corynebacterium* species ("*diphtheroids*"), to assume a pathogenic role. Acute infections in patients who have not recently received antimicrobials are often monomicrobial (almost always with an aerobic Gram-positive coccus), whereas

chronic infections are often polymicrobial. Cultures of specimens obtained from patients with such mixed infections generally yield 35 isolates, including Gram-positive and Gram-negative aerobes and anaerobes.[74] The pathogenic role of each isolate in a polymicrobial infection is often unclear.

Pathogens associated with various clinical foot-infection syndromes[75]

Foot- infection syndrome	Pathogens
Cellulitis without an open skin wound.	*Beta-hemolytic streptococcus** and *Staph aureus*
Infected ulcer and antibiotic naïve (X).	*Staph aureus* and *beta-hemolytic streptococcus**
Infected ulcer that is chronic or was previously treated with antibiotic therapy (Y).	*Staph aureus, beta-hemolytic streptococcus*, and *Enterobacteriaceae*
Ulcer that is macerated because of soaking (Y).	*Pseudomonas aeruginosa* (often in combination with other organisms)
Long-duration nonhealing wounds with (Y, Z) prolonged broad-spectrum antibiotic therapy	Aerobic gram-positive cocci (*Staph aureus, coagulase-negative staphylococci, and enterococci*), *diphtheroids, Enterobacteriaceae, Pseudomonas species, nonfermentative gram-negative rods, and, possibly, fungi*
"Fetid foot": extensive necrosis or gangrene or malodorous (Z)	Mixed aerobic gram-positive cocci, including *enterococci, gangrene, malodorous Enterobacteriaceae, nonfermentative gram-negative rods,* and *obligate anaerobes*

*Groups A, B, C, and G; X Often monomicrobial; Y Usually polymicrobial; Z Antibiotic-resistant species (eg, *MRSA, vancomycin-resistant enterococci*, or *extended-spectrum beta-lactamase–producing gram-negative rods*) are common.

Evaluation

- Characteristics: Size, depth, appearance, discharge and location.
- Etiological assessment: Neuropathic, ischemic, or neuro-ischemic.
- Screening for neuropathy.
    - Pressure of a 5.07 (10-g) Semmes Weinstein monofilament.
    - Vibration sensation with the use of standard tuning fork (128 cycles per second)
    - Neurologic reflex hammer.
- Probing of ulcer for underlying osteomyelitis.
- Culture sensitivity of the discharge.
- Radiograph for underlying osteomyelitis.
- Colour Doppler study for vascular pathology.
- MRI for Charcots neuropathy.

Management of diabetic foot ulcers

A Baseline Approach in Managing the Acute Problem of the Diabetic Foot

1. Appraise problem
    a. Careful inspection with emphasis on webspaces and back of heels.
    b. Record pulses, venous filling time, rubor
    c. Record sensation.
2. Describe lesion
3. Describe Necrotic tissue, probe sinuses with sterile probe to determine the extent of disease.
4. Culture pus for aerobic and anaerobic organisms

5. Begin broad spectrum antibiotic until appropriate antibiotics can be given according to culture and sensitivity.
6. Medical Management of Diabetes - Blood sugar monitoring and anti diabetic measures to achieve good glycemic control, Doppler study of vessels.
7. X-ray both feet to exclude osteomyelitis.
8. No weight bearing
    a. Hospitalize with absolute bed rest when indicated.
    b. Crutches or walker when feasible.
9. Surgical Management of the Problem
    a. No soaks
    b. Antibiotics
    c. Medical Management of diabetes
    d. Dressing change atleast once daily.
    e. Surgical debridement, frequently if necessary.
    f. Consideration for possible arterial reconstruction
    g. Drainage or open amputation.
10. Rehabilitation
    a. Podiatrist for patient education, preventive maintenance orthotics, healing sandals and special shoes.
    b. Nutritionist to advice on diet needs.
    c. Surgeon to ensure proper wound healing and proper prosthetics
    d. Physician to make final decision about diabetes management.
    e. Psychiatrist to return to normal activity.

Principles of Medical Management[56,76]

1. Pus from ulcers sent for culture and sensitivity.
2. Careful monitoring of the blood glucose levels.
3. Appropriate antidiabetic measures either insulin preparations or oral hypoglycemic drugs.
4. Broad spectrum antibiotics to be started at the onset and change over to other antibiotics depending on the culture and sensitivity report.
5. Patients with limb threatening infections require hospitalization. It is most prudent initially to administer antibiotics parenterally to ensure adequate serum levels.

Principles of Surgical Management[56,76]

1. Early recognition and prompt intervention.
2. Control of blood glucose
3. Complete rest of injured area.
4. Careful but complete debridement and drainage of all involved areas.
5. Appropriate antibiotic coverage
6. Wound care and dressings
7. Appropriate vascular reconstructions
8. Careful follow up including podiatric appliances and modified footwear.
9. More experienced consultation as necessary.

Wound care management

Historical aspects

The earliest documentation concerning wound management is found in the Papyrus Ebers, which dates from around BC 1500 indicating crude treatments based on oiled frog skins, honey, lint and animal grease were commonly used by the Egyptians as wound coverings. An early Hindu document, the Susrutu Sanhita reported skin grafts being used as early as BC 700. Jeter and Tintle report that spider webs, new-born puppies boiled in oil of white lilies, and red-hot pokers to cauterize wounds have been used at various times throughout history. George states that the Sumerians were the first to fashion occlusive dressings, which are capable of maintaining a moist environment, using clay.[77]

In the 19th century, Pasteur advocated that wounds should be covered and kept dry because he believed this would keep them 'germ' free. The dressings developed at this time, made from cloth, cotton and gauze, have dominated wound management in recent history and in some countries they continue to be the main products used. The first manufactured dressings were probably Gamgee wadding and tulle gras. Gamgee discovered that degreased cotton wrapped in bleached lint would absorb fluids, and he introduced his first dressing in the 19th century. During the 1914-18 war, Lumiere in France developed a cotton gauze that was impregnated with paraffin to prevent the dressing sticking to the wound. Wound management technology did not progress significantly beyond these early developments until the 1960s, when comparisons were made of wound healing in dry and moist environments. Although initial attempts were made to only alter the moisture at the

surface of a wound, researchers are now investigating the whole wound healing process in order to establish what factors impede wound healing and what characteristics of the environment could be manipulated to accelerate healing.[77]

Physiology of wound healing

When the skin is wounded, a complex series of cellular and chemical events are initiated which act on the damaged tissues – blood vessels, dermis, and epidermis. Wounds that results in limited tissue loss, such as surgical wounds, have a tendency to heal rapidly on the surface as opposing edges of the wound are in close proximity for cellular and structural repair. The wound is healed in about a week, but will continue to mature for a year or more. During this time the structural architecture of the wound changes, the scar usually flattens, and the skin regains most of its pre-wound tensile strength.[77]

In wounds where significant tissue loss occurs the damaged edges are usually unsuitable for primary closure. In this case, the tissue defect must be made up before the wound can heal. To facilitate healing, dressings are applied to try to protect the wound from contamination and keep the wound surface moist to maintain the integrity of the cells present in the defect. In a dry wound environment, dividing cells at the wound edges are unable to migrate into those areas occupied by dry scab material.[77]

Chronic wound occurs where healing is protracted as a result of significant tissue loss (as in deep pressure sores) or due to underlying pathology (venous leg ulcers). Although not initially chronic in nature, both surgical wounds and pilonidal sinuses can develop into chronic wounds if they fail to heal by primary intention.

Wound healing process

The biological mechanism associated with wound healing is complex and still not well understood. Although there is much to learn about the detail of the processes involved, some of the general concepts of healing are understood.[78]

Chronic open wounds, such as leg ulcers and pressure sores, heal by secondary intention or granulation, rather than primary intention (the means by which a surgical incision heals). Platelet aggregation during haemostasis liberates a number of soluble mediators, including platelet-derived growth factor, which initiate the healing process.[78]

Haemostasis is followed by an early inflammatory phase that is characterised by vasodilatation, increased capillary permeability, complement activation and polymorphonuclear (PMN) and macrophage migration into the wound.[78]

Polymorphonuclears predominate during the first days of post wound occurrence, with the macrophage becoming the predominant inflammatory cell within 3 days. Macrophages are large, mobile and actively phagocytic, engulfing bacteria and devitalized tissue and acting effectively as the body's own debridement system. Additionally, macrophages are considered to play a key role in regulating subsequent events in the healing process. This is achieved by secretion of a number of factors that regulate their own and other cell functions. These factors are responsible for the chemotactic attraction of more macrophages and the migration and induction of proliferation by fibroblasts and endothelial cells. The increasing number of fibroblasts and endothelial cells forming granulation tissue around the fifth day post-injury heralds the 'proliferative phase'.[78]

Fibroblasts are the 'factory cells' of the wound healing module. They are rich in mitochondria, endoplasmic reticulum, and Golgi apparatus essential for protein synthesis. Fibroblasts synthesize collagen and ground substance (proteoglycans and fibronectin), which support new cells, and the fragile capillary buds, which appear around this time (angiogenesis). The endothelial buds become canalised, and are thus able to increase the vascularity and hence oxygen tension of the new tissue, so responding to the large metabolic demand of tissue repair. Epithelialisation requires the migration of epithelial cells across the granulation tissue, to close the epidermal defect.[78]

Collagen synthesis continues for many months after wound closure, but also undergoes continous lysis, so a delicate balance exists between the two processes. This final remodelling phase, accompanied by increasing tensile strength of the wound, and a decreasing cellularity, may continue for up to a year.[78]

Little research has been carried out to investigate the differences between acute and chronic wounds, though this comparison is now becoming the focus of recent work. Most studies of the wound healing process have been undertaken on acute wounds, usually in experimental animals. How closely the healing of a chronic wound follows the healing pattern of an acute wound is not clear. The question of what makes a chronic wound 'chronic' has yet to be answered.[79]

The healing process is considered to be regulated by cytokines and growth factors, and recent studies have demonstrated that the cytokine environment in a healing chronic wound is different from that in a non-healing wound.[80] However, the precise nature of the defect(s) leading to non-healing remain to be defined.

Phases of healing

Wound healing and repair are complex processes that involve dynamic series of events.

Coagulation

- Helps in preventing blood loss, covering wound surface and holding the wound edges together and thus contributing to the healing process
- It is shown that equivocally that fibrin and platelates play an important role in initiating the wound healing.

Granulation phase of wound healing

Granulation tissue[81]

"This is a highly vascular tissue, contains largely of;

1. Fibroblast.
2. Endothelial cells lining capillaries of newly spouting blood vessels.
3. Macrophages.
4. Pleuripotent pericytes.

Above all are embedded in a matrix consisting.

1. Fibronectin
2. Proteoglycans rich in Hyaluronic acid and collagen [This collagen is at first mainly of Type-III, changing later to Type I].

The term granulation tissue derived from it, is pink, soft, granular appearance on the surface of wound.[81]

Functions

- Fill the gap of the wound
- Supports the growing and migrating epithelial cells – The nutritive substrate is formed by connective tissue matrix of granulation tissue, over which regenerating epidermis can migrate and is gradually replaced by scar tissue.

Imporant factors for granulation tissue formation

- Chemotactic factor.
- Growth factor.
- Structural molecules.
- Proteases [Digests connective tissue matrix].

Angiogenesis or neo-vascularisation

It is most important part of proliferative phase of wound healing and repair.[82]

Without angiogenesis**,** invasion of the wound bed by macrophages and fibroblasts would cease due to lack of oxygen and nutrients.[82]

In the initial stages, these vessels lack basement membrane and have loose cellular junction and are fragile in nature. Because of this even on slightest touch, the vessels bleed profusely which is a characteristic feature of newly formed capillaries. The leakage facilitates the movement of cells and macromolecules into wound site.[82]

There are four steps in angiogenesis:[81,82]

- *Step-1* Proteolytic degradation of basement membrane of parent vessel is to allow formation of capillary sprout and subsequent cell migration.[83] Angiogenic factors acts on capillary endothelial cells releases collagenase. This enzyme degrades the collagen of basement membrane.[81]

- *Step-2* Fragmentation of the collagen of basement membrane, permits the migration of endothelial cells into peri-vascular spaces.[50,84]

- *Step-3* Endothelial cells migrate into the peri-vascular spaces where they form buds.[82]

- *Step-4* Maturation of endothelial cells and organisation into capillary loops**.**

    - Functional capillary loops: During dermal repair, these buds grow rapidly towards the free surface and branch at their tips to unite and form functional capillary loops.

    - Superficial capillary plexus: On these loops, new buds develop, so that, a superficial capillary plexus rapidly forms in the granulation tissue.

    - Canalization: Proliferation and branching of cords of endothelial cells later become canalized to form growing capillary buds of healing wound.

    - Fusion: Capillaries originating from opposite sides of the wound fuse and establish a complete circulation within the wound.

Remodelling of the vasculature

There is constant remodelling of the vasculature, which involves obliteration of many of the capillaries.Each capillary loop becomes functional bringing nutrient and oxygen to nearby cells, enabling the fibroblast to secrete materials for the matrix, through which macrophages and other cells migrate further. As the scar maturation proceeds, capillaries gradually regress and the red vascular rich wound tissue transforms into a white and relatively avascular poor scar. The above proliferative and migratory processes are repeated sequentially, until wound bed is filled with granulation tissue.

Macrophagia[82]

- It is the point at which protecting and clearing functions of inflammatory response are linked to starting of repair process:

  Macrophagia is;

  1. Migration of Monocyte [from blood] to the site of tissue injury.
  2. Conversion of monocyte to Macrophage after migration to tissue injury site.
     - They are key cells in dermal repair
     - Wound macrophages, which appear subsequent to the cells, play pivotal role in healing by liberating various factors.

Functions of macrophages:[85]

- Take over the function of phagocytes that is debridement.
- Release matrix metalloproteinases (MMP).

- Macrophages secrete numerous cytokines.
- Macrophages also release growth factors that stimulate fibroblast, endothelial cells and keratinocyte proliferation.
- Promote angiogenesis by liberating endothelial growth factor [EGF].
- Macrophage-secreted platelet derived growth factor (PDGF) stimulate collagen and proteoglycan synthesis.

Fibroplasia[85]

After injury, sparse fibroblasts are chemoattracted to the inflammatory site, divide and produce the components of the extra cellular matrix (ECM). After stimulation by macrophage and platelet derived cytokines and growth factors, the fibroblast which is normally arrested in G_0 phase, undergoes replication and proliferation.

The primary function of fibroblsts is to synthesize collagen. The rate of collagen synthesis declines after 4 weeks and eventually balances the rate of collagen destruction by collagenase (MMP-1). At this point the wound enters a phase of collagen maturation. The maturation phase continues for months or even years.

Moisture and wound healing

In 1962, Winter[86] published his seminal text on the effect of occlusion on wound healing. Winter made experimental wounds in Large-White pigs, and covered half with occlusive film and left the other half exposed to the air. The occluded, and hence moist wounds, had an epithelialisation rate twice that of those left to form a scab. Experimental, acute wounds in humans and animals appear to

heal more rapidly in a moist environment. The relevance of this to chronic, pathological wounds is unclear.

Role of oxygen in wound healing

Oxygen is essential for cell metabolism, and demand is increased by synthetic processes such as those occurring during wound healing. Shortly after injury, the oxygen tension in a wound falls, so that by day 3, the pO_2 in the dead space of a wound is below 10 mmHg. This fall in oxygen tension is accompanied by an increase in the concentration of CO_2, and a fall in pH. A low pO_2 provides optimal conditions for fibroblast regeneration, possibly stimulating the process and increasing the rate of advance of granulation tissue.[87]

The concept that hypoxia stimulates healing was further supported by Knighton and co-workers[88] who demonstrated a positive relationship between a steep oxygen gradient between capillaries and hypoxic tissue, and angiogenesis.

pH and wound healing

Few studies have examined the effect of pH on wound healing. In 1973, Leveen[89] demonstrated that the acidification of wound surfaces increased healing. Varghese and co-workers[90] found wound fluid to be more acidic under a Granuflex dressing than under an Opsite dressing, the more acidic pH being compatible with *in vitro* antibacterial activity. However, there are no high-quality randomized controlled trials (RCTs) examining the effects of wound pH on ulcer healing.

Micro-organisms and ulcer healing

The effect of micro-organisms on ulcer healing remains an area of intense debate. That chronic wounds are usually colonised by bacteria is accepted, and an important distinction should be made between colonisation and infection. Infection is characterised by the stigmata of pain, inflammation, purulent exudates and heat by the more objective measures of a PMN response and tissue concentrations of organisms in excess of 10^5/g. The effect of occlusive dressings on infection rates is controversial.[77]

Local treatment

Uncontrolled diabetes affects infection and infection adversely affects diabetes. The basic rules in treating any foot infection are;[77]

1. Absolute bed rest
2. Regulation of diabetes
3. Adequate culturing of wound
4. Administration of appropriate antibiotics
5. Adequate drainage of all infection
6. Appropriate wound care.

Different kind of debridement for patients with diabetic foot ulcer[54]

The method of debridement depends on chara-cteristics, preferences, and practitioner level of expertise. When surgical or sharp debridement is not indicated, then other types of debridement could be used.

An older debridement type that is categorized as biological debridement is maggot debridement therapy (MDT), which is also known as maggot therapy or larval therapy. In this method, sterile and live forms of the Lucilia sericata larvae are applied to the wound to achieve debridement, disinfection, and ultimately wound healing. Indeed, larvae secrete a powerful autolytic enzyme that liquefies necrotic tissues, stimulates the healing processes, and destroys bacterial biofilms. This technique is indicated for open wounds and ulcers that contain gangrenous or necrotic tissues with or without infection. To date, paucity of RCTs show efficacy of this method with DFU; however, some of retrospective; and prospective studies have shown MDT as a clinically effective treatment for DFU. These studies reported that MDT can significantly diminish wound odor and bacterial count, including *Methicillin-Resistant Staphylococcus Aurous*, prevent hospital admission, and decrease the number of outpatient visits among patients with DFU.

Despite the advantages of debridement, adequate debridement must always precede the application of topical wound healing agents, dressings, or wound closure procedures, which may be expensive.

Different types of debridement for patients with diabetic foot ulcer[54]

Method	Explanation	Advantages	Disadvantages
Surgical or Sharp	Callus and all nonviable soft tissues and bone remove from the open wound with a scalpel, tissue nippers, curettes, and curved scissors. Excision of necrotic tissues should extend as deeply and proximally as necessary until healthy, bleeding soft tissues and bone are encountered	Only requires sterile scissors or a scalpel, so is cost-effective	Requires a certain amount of skill to prevent enlarging the wound
Mechanical	This method includes wet to dry dressings, high pressure irrigation, pulsed lavage and hydrotherapy, and commonly used to clean wounds prior to surgical or sharp debridement	Allows removal of hardened necrosis	It is not discriminating and may remove granulating tissue; It may be painful for the patients
Autolytic	This method occurs naturally in a healthy, moist wound environment when arterial perfusion and venous drainage are maintained[18	It's cost-effective; It is suitable for an extremely painful wound	It's time consuming and may require an equivocal time for treatment
Enzymatic	The only formulation available in the United Kingdom contains Streptokinase and Streptodornase (Varidase Topical® Wyeth Laboratories). This enzyme aggressively digests the proteins fibrin, collagen and elastin, which are commonly found in the necrotic exudate of a wound	They can be applied directly into the necrotic area	Streptokinase can be systemically absorbed and is therefore contraindicated in patients at risk of an MI; It's expensive
Biological	Sterile maggots of the green bottle fly (Lucilia sericata) are placed directly into the affected area and held in place by a close net dressing. The larvae have a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue	They discriminate between the necrotic and the granulating tissue	There may be a reluctance to use this treatment by patients and clinicians; It's expensive

Offloading

The use of offloading techniques, commonly known as pressure modulation, is considered the most important component for the management of neuropathic ulcers in patients with diabetes. Recent studies have provided evidence indicating that proper offloading promotes DFU healing.

Although many offloading modalities are currently in use, only a few studies describe the frequency and rate of wound healing with some of the methods frequently used clinically. The choice of these methods is determined by patient physical characteristics and abilities to comply with the treatment along with the location and severity of the ulcer.

Common offloading techniques[54]

Casting techniques	Footwear related techniques	Surgical offloading techniques	Other
TCC	Shoes or half shoes	ATL	Bed rest
iTCC	Sandals	Liquid silicone injections/tissue augmentation	Crutches/Canes/Wheelchairs
RCW	Insoles	Callus debridement	Bracing (patella tendon bearing, ankle-foot orthoses)
Scotch-cast boots	In-shoe orthoses	Metatarsal head resection osteotomy/ arthroplasty/os ectomy/ exostectomy	Walkers
Windowed casts Custom splints	Socks	External fixation	Offloading dressings Custom splints Felted foam/padding Plugs

The most effective offloading technique for the treatment of neuropathic DFU is total contact casts (TCC). Total contact casts is minimally padded and molded carefully to the shape of the foot with a heel for walking. The cast is designed to relieve pressure from the ulcer and distribute pressure over the entire surface of the foot; thus, protecting the site of the wound. Mueller et al conducted an RCT that showed TCC healed a higher percentage of plantar ulcers at a faster rate when compared with the standard treatment. In addition, a histologic examination of ulcer specimens has shown that patients treated with TCC before debridement had better healing as indicated by angiogenesis with the formation of granulation tissue than for patients treated with debridement alone as indicated by a predominance of inflammatory elements. The contributory factors to the efficacy of TCC treatment are likely to be due to pressure redistribution and offloading from the ulcer area. In addition, the patient is unable to remove the cast, which thereby forces compliance, reduces activity levels, and consequently improves wound healing. However, the frequency of side effects referred to in the literature and minimal patient acceptance make this approach inappropriate for wide applications.

Fife et al has shown that TCC is vastly underutilized for DFU wound care in the United States. Based on this study, only 16% of patients with DFU used TCC as their offloading modalities. The main disadvantage of TCC was the need for expertise in its application. Most centers do not have a physician or cast technician available with adequate training or experience to safely apply TCC. In addition, improper cast application can cause skin irritation and in some cases even frank ulceration. Also, the expense of time and materials (the device should be replaced weekly), limitations on daily activities (*e.g.*, bathing), and the potential of a rigid

cast to injure the insensate neuropathic foot are considered other disadvantages. Furthermore, TCC does not allow daily assessment of the foot or wound, which is often contraindicative in cases of soft tissue or bone infections.

In some cases, it is suggested to use other kinds of offloading techniques such as a removable cast walker (RCW) or Instant TCC (iTCC).

An RCW is cast-like device that is easily removable to allow for self-inspection of the wound and application of topical therapies that require frequent administration. The application of this method allows for bathing and comfortable sleep. In addition, because RCW is removable, they can be used for infected wounds as well as for superficial ulcers. However, in a study that compared the effectiveness of TCC, RCW, and half-shoe, this method did not show equivalent healing time (mean healing time: 33.5, 50.4, and 61.1 d, respectively), and a significantly higher proportion of people with DFU were healed after 12 wk wearing a TCC compared with the two other widely used offloading modalities.

Instant total contact casts, which involves simply wrapping a RCW with a single layer of cohesive bandage, Elastoplast or casting tape, is another offloading technique that is shown to be more effective than TCC and RCW. This technique forces the patient to adhere to advice to immobilize the foot while allowing for ease of application and examination of the ulcer as needed. A preliminary randomized trial of TCC *vs* iTCC in the management of plantar neuropathic foot ulcers has confirmed equivalent efficacy of the two devices and that iTCC is cheaper, quicker to apply, and has fewer adverse effects than traditional TCC. As this device does not require a skilled technician to apply it, it could revolutionize the future management

of plantar neuropathic ulcers. It has been suggested that iTCC will dramatically change the treatment of non-ischemic, neuropathic, diabetic plantar ulcers, and has the potential to replace TCC as the gold standard for offloading plantar neuropathic ulcers.

Advanced dressing

A major breakthrough for DFU management over the last decades was the demonstration of novel dressings. Ideally, dressings should confer moisture balance, protease sequestration, growth factor stimulation, antimicrobial activity, oxygen permeability, and the capacity to promote autolytic debridement that facilitates the production of granulation tissues and the re-epithelialization process. In addition, it should have a prolonged time of action, high efficiency, and improved sustained drug release in the case of medicated therapies. Hence, no single dressing fulfills all the requirements of a diabetic patient with a foot ulcer. The choice of dressing is largely determined by the causes of DFU, wound location, depth, amount of scar or slough, exudates, condition of wound margins, presence of infection and pain, need for adhesiveness, and conformability of the dressing.

Wound dressing can be categorized as passive, active, or interactive. Passive dressings are used as protective functions and for acute wounds because they absorb reasonable amounts of exudates and ensure good protection. Active and interactive dressings are capable of modifying the physiology of a wound by stimulating cellular activity and growth factors release. In addition, they are normally used for chronic wounds because they adapt to wounds easily and maintain a moist environment that can stimulate the healing process. The main categories of dressings

used for DFU are as follows: films, hydrogels, hydrocolloids, alginates, foams, and silver-impregnated.

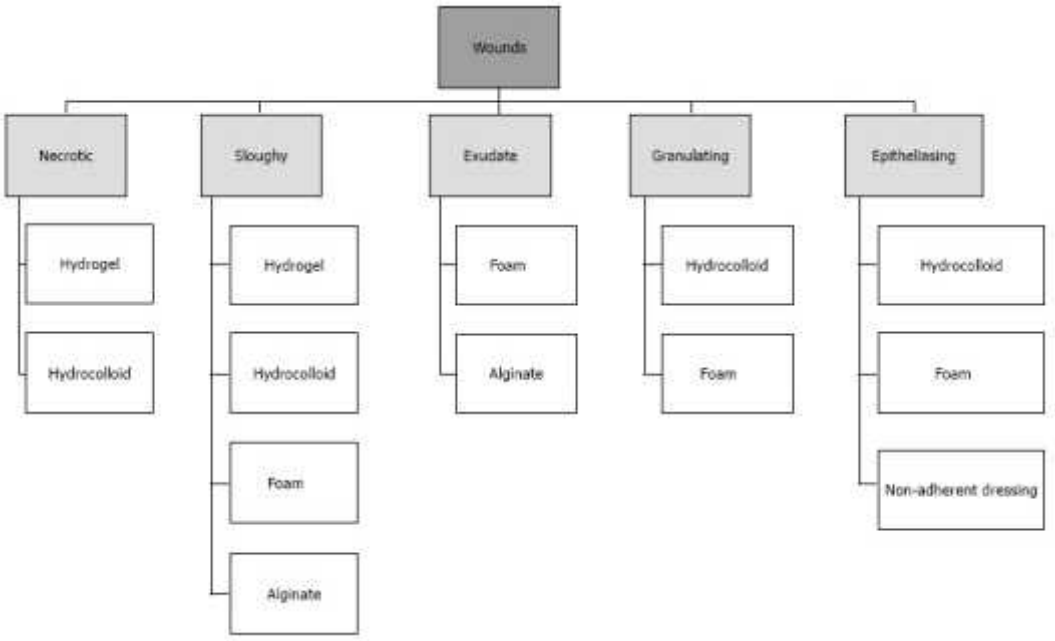


Figure 9. Classification of advanced wound dressings used for diabetic foot ulcers healing[54]

Today, all dressings are commonly used in clinical practice, while the efficacy of these products has been a challenge for researchers and clinicians, and there are controversial results regarding their use. However, dressings are used based on DFU characteristics, hydrogels have been found to be the most popular choice of dressing for all DFU types. Some studies dealing with the incorporation of these products show great potential in the treatment of DFU. However, these findings do not represent a practical option since the application of these compounds is expensive and difficult to regulate.

Classification of the different advanced dressing types usually used in diabetic foot ulcer treatment[91]

Type	Example	Description	Advantages	Disadvantages
Hydrocolloids	Duoderm, Granuflex, Comfeel	These kind of dressings usually composed of a hydrocolloid matrix bonded onto a vapor permeable film or foam backing; When in contact with the wound surface this matrix forms a gel to provide a moist environment	Absorbent Can be left for several days Aid autolysis	Concerns about use for infected wounds May cause maceration Unpleasant odor
Hydrogels	Aquaform, Intrasite Gel, Aquaflo	These dressings consist of cross-linked insoluable polymers (i.e., starch or carboxymethylcellulose) and up to 96% water; These dressings are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels; They are supplied in either flat sheets, an amorphous hydrogel or as beads	Absorbent; Donate liquid Aid autolysis	Concerns about use for infected wounds May cause maceration using for highly exudative wounds
Foams	Allevyn, Cavicare, Biatain, Tegaderm	These dressings normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface	Highly absorbent and protective Manipulate easily; Can be left up to seven days Thermal insulation	Occasional dermatitis with adhesive; Bulky; May macerate surrounding skin
Films	Tegaderm Opsite	Film dressings often form part of the construction of other dressings such as hydrocolloids, foams, hydrogel sheets and composite dressings, which are made up of several materials with the film being used as the outer layer	Cheap; Manipulate easily; Permeable to water vapor and oxygen but not to water microorganisms	May need wetting before removal; Aren't suitable for infected wounds; Nonabsorbent If fluid collects under film it must be drained or the film replaced
Alginates	Calcium Alginate Dressing, Kaltostat Sorbalgon, Medihoney	The alginate forms a gel when in contact with the wound surface which can be lifted off with dressing removal or rinsed away with sterile saline; Bonding to a secondary viscose pad increases absorbency	Highly absorbent; Bacteriostatic; Hemostatic; Useful in cavities	May need wetting before removal
Silver impregnated	Acticoat, Urgosorb Silver	These dressing used to treat infected wounds as silver ions are thought to have antimicrobial properties	Antiseptic Absorbent; Reduce odor; Improved pain-related symptoms; Decrease wound exudates; Have a prolonged dressing wear time	High cost

Nevertheless, they have longer wear times, greater absorbency, may be less painful, and are typically less traumatic when removed. Moreover, in certain patients, they are cost effective because of the lowered frequency of dressing changes and not requiring extensive nursing time.

Broadly, the treatment of diabetic foot ulcers includes pressure relief (or off-loading) by resting the foot or wearing special footwear or shoe inserts (or both); the removal of dead cellular material from the surface of the wound (debridement or desloughing); infection control; and the use of wound dressings. Other general strategies in the treatment of diabetic foot ulcers include: patient education; optimisation of blood glucose control; correction (where possible) of arterial insufficiency; and surgical interventions (debridement, drainage of pus, revascularisation, amputation).[92]

Dressings are widely used in wound care, both to protect the wound and to promote healing. Classification of a dressing normally depends on the key material used. Several attributes of an ideal wound dressing have been described, including:[92]

- The ability of the dressing to absorb and contain exudate without leakage or strike-through;
- Lack of particulate contaminants left in the wound by the dressing;
- Thermal insulation;
- Permeability to water and bacteria;
- Avoidance of wound trauma on dressing removal;
- Frequency with which the dressing needs to be changed;
- Provision of pain relief; and

- Comfort.

There is a vast choice of dressings available to treat chronic wounds such as diabetic foot ulcers.

Basic wound contact dressings[92]

Low-adherence dressings and wound contact materials: usually cotton pads which are placed directly in contact with the wound. They can be either non-medicated (e.g. paraffin gauze dressing) or medicated (e.g. containing povidone iodine or chlorhexidine). Examples are paraffin gauze dressing, BP1993 and Xeroform (Covidien) dressing - a non-adherent petrolatum blend with 3% bismuth tribromophenate on fine mesh gauze. Absorbent dressings: applied directly to the wound or used as secondary absorbent layers in the management of heavily exuding wounds.

Advanced wound dressings[92]

Hydrogel sheet and amorphous dressings

They consist of a crosslinked insoluable polymers (i.e. starch or carboxymethylcellulose) and up to 96% water. These dressings are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels. They are supplied in either flat sheets, an amorphous hydrogel or as beads.

Films - permeable film and membrane dressings

These are permeable to water vapour and oxygen but not to water or microorganisms.

Soft polymer dressings

Dressings composed of a soft silicone polymer held in a non-adherent layer. They are moderately absorbent.

Hydrocolloid dressings

They are occlusive dressings usually composed of a hydrocolloid matrix bonded onto a vapour-permeable film or foam backing. When in contact with the wound surface this matrix forms a gel to provide a moist environment.

Fibrous alternatives have been developed which resemble alginates and are not occlusive but which are more absorbant than standard hydrocolloid dressings: Aquacel.

Foam dressings:

Normally contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface. There are various versions and some foam dressings that include additional absorbent materials, such as viscose and acrylate fibres or particles of superabsorbent polyacrylate, or which are silicone-coated for non-traumatic removal.

Alginate dressings:

Highly absorbent and come in the form of calcium alginate or calcium sodium alginate and canbe combined with collagen. The alginate forms a gel when in contact with the wound surface which can be lifted off with dressing removal or

rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency.

Capillary-action dressings

Consist of an absorbent core of hydrophilic fibres held between two low-adherent contact layers.

Odour-absorbent dressings

Dressings that contain charcoal and are used to absorb wound odour. Often these types of wound dressings are used in conjunction with a secondary dressing to improve absorbency.

Antimicrobial dressings[92]

Honey-impregnated dressings

Contain medical-grade honey which is proposed to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds.

Iodine-impregnated dressings:

Release free iodine when exposed to wound exudate, which is thought to act as a wound antiseptic.

Silver-impregnated dressings:

used to treat infected wounds as silver ions are thought to have antimicrobial properties. Silver versions of most dressing types are available (e.g. silver foam, silver hydrocolloid etc).

Other antimicrobial dressings

These dressings are composed of a gauze or low-adherent dressing impregnated with an ointment thought to have antimicrobial properties.

Amorphous hydrogel dressings with silver nano particles[93]

With the establishment of the first synthetic Hydrogels by Wichterle and Lim in 1954, the hydrogel technologies may be applied to food additives, pharmaceuticals, biomedical implants4 tissue engineering and regenerative medicines, diagnostics, cellular immobility, separation of biomolecules or cells and barrier materials to regulate biological adhesions, Biosensor and BioMEMs devices and drug carriers. Additionally the ever growing spectrum of functional monomers and macromeres widen its applicability.[93]

Hydrogels are hydrophilic polymeric network of three dimensional cross linked structures that absorb substantial amount of water. Cross linking facilitates insolubility in water because of ionic interaction and hydrogen bonding. It also provides required mechanical strength and physical integrity to the Hydrogels.[93]

Modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol (PVA) together with blood coagulants are formulated.[93]

Silver compounds and ions have been extensively used for both hygienic and healing purposes, due to their strong bactericidal effects, as well as a broad spectrum antimicrobial activity.[93,94]

As early as 1000 B.C., the antimicrobial properties of silver in rendering water potable were appreciated.[95]

The topical antimicrobial agent silver has been used for hundreds of years in wound care4. For example, silver has been used to prevent or manage infection in its solid elemental form (eg silver wire placed in wounds), as solutions of silver salts used to cleanse wounds (eg silver nitrate solution), and more recently as creams or ointments containing a silver– antibiotic compound (silver sulfadiazine (SSD) cream). Silver nitrate solution is less widely used nowadays, but SSD cream has been an important part of burns management for many years. SSD cream, however, is relatively short-acting, requires reapplication at least daily, and is time-consuming and messy to apply and remove.[93]

In recent years, a wide range of wound dressings that contain elemental silver or a silver releasing compound have been developed. These dressings have overcome some of the problems associated with the first silver preparations. They are easier to apply, may provide sustained availability of silver, may need less frequent dressing changes, and may provide additional benefits such as management of excessive exudate, maintenance of a moist wound environment, or facilitation of autolytic debridement. [93]

The use of silver dressings in wound care has recently been faced with considerable challenges. These include a perceived lack of efficacy and cost effectiveness, and questions about safety. In some healthcare settings, these challenges have led to restrictions in the availability or complete withdrawal of

silver dressings. This has left some clinicians in the frustrating position of not being able to use silver dressings for patients who may find them beneficial.[93]

In the context of increasing resistance to antibiotics and the dramatic fall in the number of antibiotics in development, restriction of other potentially useful antimicrobial treatments such as silver dressings is particularly unfortunate. Topical antiseptics, such as silver, differ from antibiotics: they have multiple sites of antimicrobial action on target cells and therefore a low risk of bacterial resistance. As a result, antiseptics have the potential to play an important part in controlling bio-burden in wounds while limiting exposure to antibiotics and reducing the risk of development of further antibiotic resistance.[93]

Silver is found in dressings in a number of forms:

- Elemental silver (Silver metal, nanocrystalline silver)
- An inorganic compound (Silver oxide, silver phosphate, silver chloride, silver sulfate, silvercalcium-sodium phosphate, silver zirconium compound, SSD)
- An organic complex (Silver-zinc allantoinate, silver alginate, silver carboxymethylcellulose).

The silver component of dressings may appear:

- As a coating – on one or both external surfaces of the dressing (elemental or nanocrystalline silver).
- Within the structure of the dressing – either as a coating on dressing materials (elemental or compound silver), within the spaces of the dressing

materials (elemental or compound silver), or as a compound that forms part of the dressing structure (silver alginate)

- As a combination of these.

Silver on the surface of the dressing may come into contact with the wound where it exerts the antimicrobial action. Silver within the dressing structure acts on bacteria absorbed into the dressing with wound exudate, but is likely also to diffuse to some extent into the wound. The total amount of silver in dressings varies considerably, but in a wound environment the interaction of silver ions with wound components such as chloride ions and proteins, means that the amount of silver delivered to a wound does not correlate with the amount of silver contained in the dressing. In addition, although in some laboratory experiments very low concentrations, eg one part per million (1ppm) of silver ions or less, have been shown to be effective against bacteria, it is unclear how silver content and availability measured in experimental settings relate to clinical performance.[93]

In metallic (elemental) form, silver is unreactive and cannot kill bacteria. To become bactericidal, silver atoms (denoted as Ag or Ag0) must lose an electron and become positively charged silver ions (Ag+). Elemental silver ionises in air, but ionises more readily when exposed to an aqueous environment such as wound exudate. In contrast, silver compounds contain positive silver ions bound to negatively charged ions or molecules. When exposed to aqueous environments, some of the silver ions become detached from the compound. [93]

Silver ions are highly reactive and affect multiple sites within bacterial cells, ultimately causing bacterial cell death. They bind to bacterial cell membranes,

causing disruption of the bacterial cell wall and cell leakage. Silver ions transported into the cell disrupt cell function by binding to proteins and interfering with energy production, enzyme function and cell replication. Silver ions are active against a broad range of bacteria, fungi and viruses, including many antibiotic resistant bacteria, such as meticillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococci (VRE). [93]

Studies of the effects of silver dressings on experimental models of biofilms have suggested that silver may reduce bacterial adhesion and destabilise the biofilm matrix, as well as kill bacteria within the matrix and increase susceptibility of bacteria to antibiotics.[95]

Some laboratory studies have suggested that silver may have beneficial effects on wound healing other than the control of bioburden alone. For example, silver nitrate, nanocrystalline silver, and some silver-containing dressings have been found to have anti-inflammatory effects and to encourage blood vessel formation (neovascularisation). The clinical relevance of these findings is not yet known.[96]

Only a small proportion of silver presented to a wound site in a dressing is involved in antimicrobial action. Most of the rest remains within the dressing or binds to proteins in the wound or wound debris. Very little is systemically absorbed. Even if absorbed systemically, silver is excreted mainly via the biliary route in faeces. Some is also excreted in urine. Silver is not absorbed into the central or peripheral nervous systems.[93]

The major roles for antimicrobial dressings such as silver dressings in the management of wounds are to:[93]

- Reduce bioburden in acute or chronic wounds that are infected or are being prevented from healing by microorganisms

- Act as an antimicrobial barrier for acute or chronic wounds at high risk of infection or re-infection.

Silver dressings may be used on acute wounds, such as traumatic wounds (including burns) or surgical wounds, and chronic wounds that present with localised (overt or covert), spreading or systemic infection. Inflamed wounds may be particularly suited to management with silver dressings because of the anti-inflammatory effects.[93]

Antimicrobial dressings such as silver dressings may be used as a barrier to microorganisms in wounds at high risk of infection or re-infection. Examples of such wounds may include burns, surgical wounds, pressure ulcers near the anus, wounds with exposed bone, or wounds in patients who are immunocompromised, have poor circulation, unstable diabetes or neoplastic disease. There may also be a role for antimicrobial dressings in preventing entry of bacteria to medical device entry/exit sites such as tracheostomy sites, externally placed orthopaedic pins, postsurgical drains, chest drains, nephrostomy sites, central venous lines, dialysis catheters, and epidural catheters. The use of silver dressings in this way is yet to be fully defined and evaluated. When a silver dressing is used for prophylaxis, the rationale should be fully documented in the patient's health records and use of the dressing reviewed regularly (every two weeks).[93]

Differentiating between the many silver dressings that are available can be perplexing because of the variety of antimicrobial testing methods and clinical

endpoints used and the complexity of comparing the data derived. In practice, the factors most likely to influence choice of a silver dressing are: [93]

- Availability and familiarity
- The additional needs of the patient and the wound, eg level of exudate production and condition of the wound bed
- Whether a secondary dressing is required
- Patient preference.

High absorbency would be preferable for a wound producing high levels of exudate, activated charcoal for odour, and low adherence for a patient who experiences pain at dressing change. In addition, if a patient has an irregular wound bed, enhanced dressing conformability may prevent the formation of pools of exudate where bacteria might flourish beneath the dressing.[93]

The duration of silver availability may also be important. In general, silver dressings are intended to provide sustained delivery of silver over several days, so reducing the need for frequent dressing changes. If dressing changes are planned to take place once weekly, use of a dressing that is known to continue releasing silver for seven days would be advisable. When choosing a silver dressing, it is important to balance the needs of the patient, the wound and the environment, and to consider how the overall characteristics of the silver dressing meet the other needs of the patient, eg in terms of exudate handling, adherence and frequency of dressing change.[93]

Silver has been shown in vitro to have antimicrobial activity against a wide range of microorganisms, including resistant forms such as MRSA and VRE, and

fungi and anaerobes. The techniques used to test antimicrobial efficacy are often not standardized. Hence the comparisons between different studies may not be possible as it may lead to incorrect conclusions. Direct comparisons of several different dressings have revealed differences in silver content, silver availability, and scope and degree of antibacterial efficacy.[93]

One study found no correlation between silver content or amount of silver released and antimicrobial activity in an in vitro dissolution assay, indicating that silver dissolution from a dressing is not a predictor of antimicrobial activity.[97]

Although silver content is important, many other factors influence the ability of a dressing to kill microorganisms, eg the distribution of silver within the dressing, the availability of silver from the dressing, the ability of a dressing to closely contact the wound surface (dressing conformability), the dressing's ability to absorb fluid, the construction of the dressing, and its chemical and physical form.[98]

In vitro tests of the antimicrobial efficacy of silver dressings are unlikely to be truly representative of performance in a wound because of the complexity of the wound environment. Silver dressings have been assessed in many different types of studies. RCTs have been performed in a range of acute and chronic wounds using a number of different endpoints. Some studies have found silver dressings to have positive effects on wound healing parameters, whereas others have found no significant difference from comparators.[93]

Difficulties in interpreting and comparing studies arise from the small number of patients in some studies (which may cause issues of insufficient study power and problems with randomisation), and the wide range of different inclusion

criteria, study protocols and endpoints used. It is therefore not surprising that some systematic reviews and meta-analyses have come to differing conclusions or have failed to find sufficient comparable data.[93]

Also many of the studies of silver dressings have included endpoints related to healing. However, more appropriate endpoints for silver dressings may relate to measurement of microbial burden or assessment of clinical indicators of infection.[99]

A study which examined pre-specified indicators of infection found that significantly more wounds treated with a silver dressing had no signs of heavy bacterial colonisation after four or eight weeks of treatment in comparison with the control ($p<0.05$).[100]

Another smaller study, which used clinical infection scores, found no significant difference between a silver and a control dressing after two weeks of treatment and observation.[101]

A particularly influential and controversial study of silver dressings has been the VULCAN study. This study randomised 213 patients with venous leg ulcers to receive either one of a number of silver-containing dressings or a clinician-selected non-antimicrobial control dressing. The main outcome measured was the rate of complete healing at 12 weeks. The study concluded that there was no statistically significant difference between the use of silver containing dressings and the control dressings for the proportion of ulcers healed, time to healing or rates of recurrence. The cost-effectiveness analysis found a higher cost associated with the silver dressings.[102,103]

Many commentators have been concerned that, despite the care involved in the study design, the conclusions are potentially misleading. The major concern is that the study did not use silver dressings in line with current recommendations, and so could not be expected to provide clinically relevant information on efficacy.[93]

METHODOLOGY

This randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period, from January 2013 to December 2013.

Study design

The study design was a randomized controlled trial.

Study period and duration

This study was carried out for the duration of one year from January 2014 to December 2014.

Place

This study was done under the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care teaching hospital attached to KLE University's Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients presenting with diabetic foot ulcers measuring more than one cms with slough, foul smell and minimal granulation tissue were enrolled.

Sample size

The present study was comprised of 60 cases divided into two groups of 30 each.

Sampling procedure

As the effect size was not available, by applying thumb rule a total of 60 cases divided into two groups of 30 each was planned.

Selection criteria

Inclusion

- Diabetic patients between the age group of 25 to 70 years.
- Patients having ulcers measuring more than one cms below ankle in dorsum of foot
- Patients with grade I and II ulcers based on Wegener's classification.

Exclusion

- Patients with grade III, IV and V ulcers of Wegener's classification.
- Patients with absent peripheral pulses, dorsal pedis artery, posterior tibial artery, anterior tibial artery.
- Patients who were not on regular follow-up.
- Patients not willing to participate in the study.

Ethical clearance

The study was approved from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

The eligible patients who fulfilled the selection criteria were informed in detail about the nature of the study and a written informed consent was obtained (Annexure I).

Method of collection of data

The demographic data was obtained through an interview. Patients were asked for the past history, ulcer duration, diabetic history and treatment history. Further these patients were subjected to clinical examination. The wound observation was performed for ulcer characteristics such as site, size, shape, edge, margin, floor, base, discharge, surrounding skin and slogh / necrotic tissue.

Assessment for the grade and severity of wound was done based on Wagner's classification and the wound was graded as below.

- Grade 0: No ulcer in a high risk foot.
- Grade 1: Superficial ulcer involving the full skin thickness but not underlying tissues.
- Grade 2: Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
- Grade 3: Deep ulcer with cellulitis or abscess formation, often with osteomyelitis.

- Grade 4: Localized gangrene.
- Grade 5: Extensive gangrene involving the whole foot.

These findings were noted on a predesigned and pretested proforma (Annexure II).

Investigations

The patients underwent following investigations.

- Complete blood count.
- Fasting blood sugar
- Blood Urea
- Serum Creatinine
- Urine analysis (Routine and microscopy)
- X-Ray foot – Antero-posterior and Lateral view
- Tissue culture.

Randomization

The patients were divided into two groups of 30 each viz. Group A and group B based on computer generated random numbers.

Treatment

All the patients underwent the derangement of wound. Empirical antibiotics viz. Cefotaxim and Metranidazole or Ceftriaxone and Metranidazole were started and changed to sensitive antibiotics after culture and sensitivity report.

Photograph 1. Dressing material for hydrogel with silver nano particles

Photograph 2. Amorphous hydrogen with colloidal silver

Photograph 3. Dressing material for conventional dressing

In both the groups povidine iodine was used as an antiseptic. The dressing and topical management was done as below.

Group A

In this group, patients underwent dressing and topical management using hydrogel with silver nano particles

Group B

The dressing and topical management was done using povidone iodine in group B.

Outcome

Ulcer was assessed by the investigator at the beginning of the study. Ulcer mapping was made and size was recorded. Area of the slough was assessed at the beginning, fifth, tenth and fifteenth day. To calculate and compare slough area, wounds were photographed with help of Sony 8 MP camera, after placing a scale next to the wound. This picture was then analyzed using Image J™ software. The image was linearly calibrated done using the 'ruler' and it was possible to derive the exact size of the marked area (slough) over the wound. Outcome was measured in terms of reduction in slough area and wound culture between the two groups.

Follow up

The patients were followed at the end of fifth, tenth and fifteenth day for the assessment of slough are and culture.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel Spreadsheet. The categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test and Fisher's exact test. Continuous data was expressed as mean ± standard deviation and the independent sample 't' test was used for comparison. A 'p' value of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

The present randomized controlled trial was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period of one from January 2014 to December 2014. A total of 60 patients were studied. Patients were divided into two groups of 30 each as below.

- Group A (n=30): Patients in this group underwent dressing and topical management using hydrogel with silver nano particles.

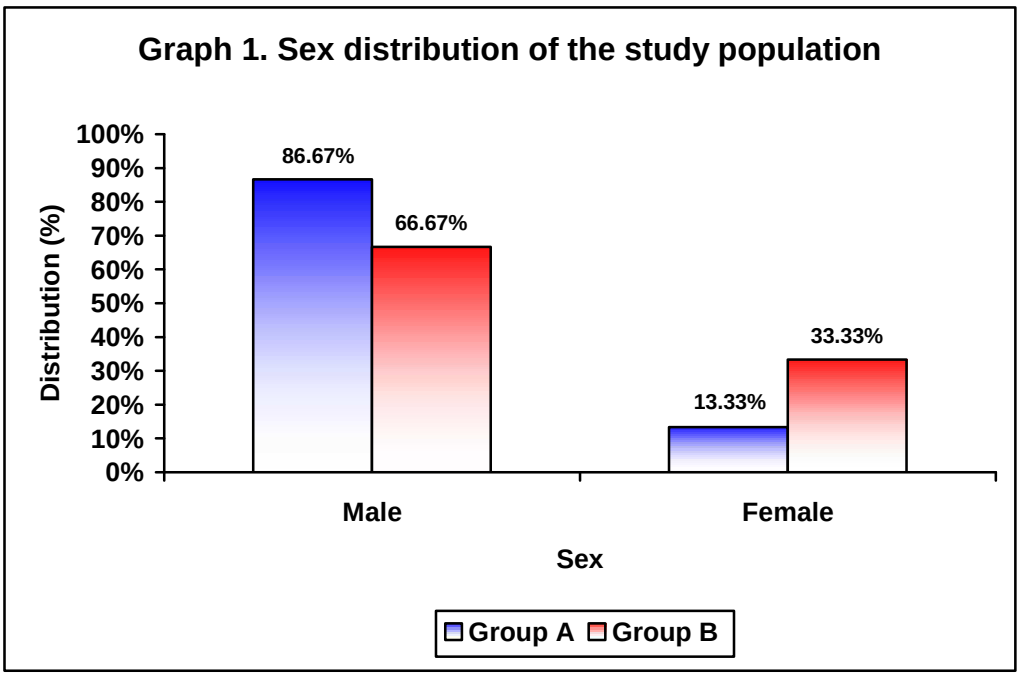
- Group B (n=30): In this group, dressing and topical management was done using povidone iodine.

The data obtained was coded and entered into the master chart. The data was analysed and the final results were tabulated as below.

Table 1. Sex distribution of the study population

Sex	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Male	26	86.67	20	66.67
Female	4	13.33	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

p =0.067

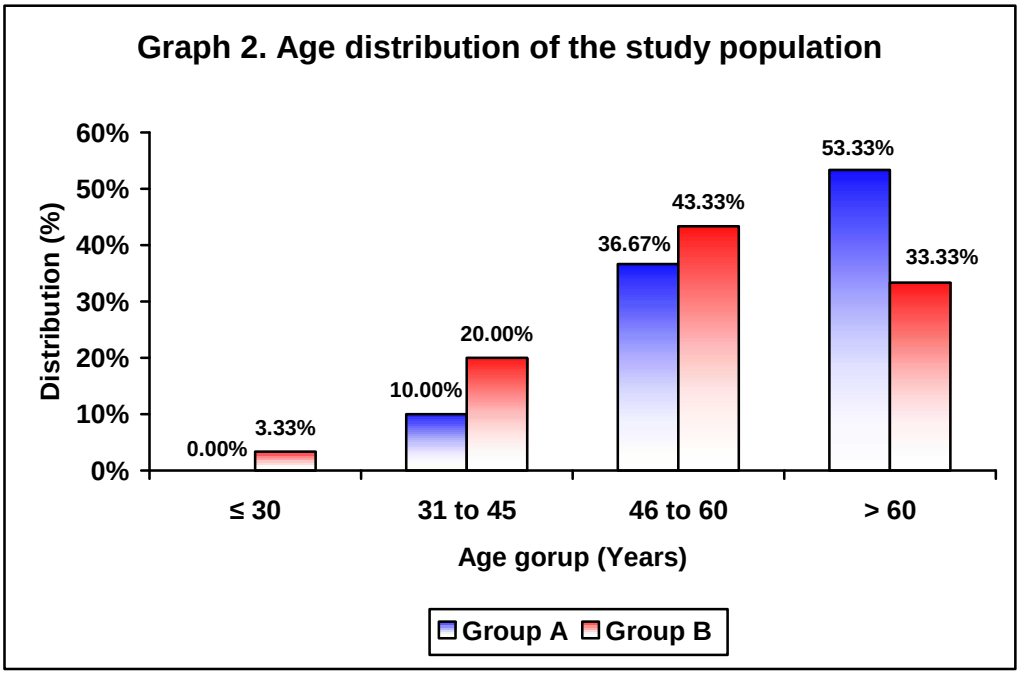


In the present study 86.67% and 66.67% of the patients in group A and B were males respectively. The male to female ratio in group A was 6.5:1 compared to 2:1 in group B. However the sex distribution in group A and B was comparable (p=0.067).

Table 2. Age distribution of the study population

Age group (Years)	Group A (n=30)		Group B (n=30)	
	No.	%	No.	%
≤ 30	0	0.00	1	3.33
31 to 45	3	10.00	6	20.00
46 to 60	11	36.67	13	43.33
> 60	16	53.33	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.315



In this study 53.33% of the patients in group A were aged > 60 years while in group B, 43.33% were aged from 46 to 60 years. However no statistically significant difference was noted with regard to age distribution (p=0.315).

Table 3. Comparison of mean age

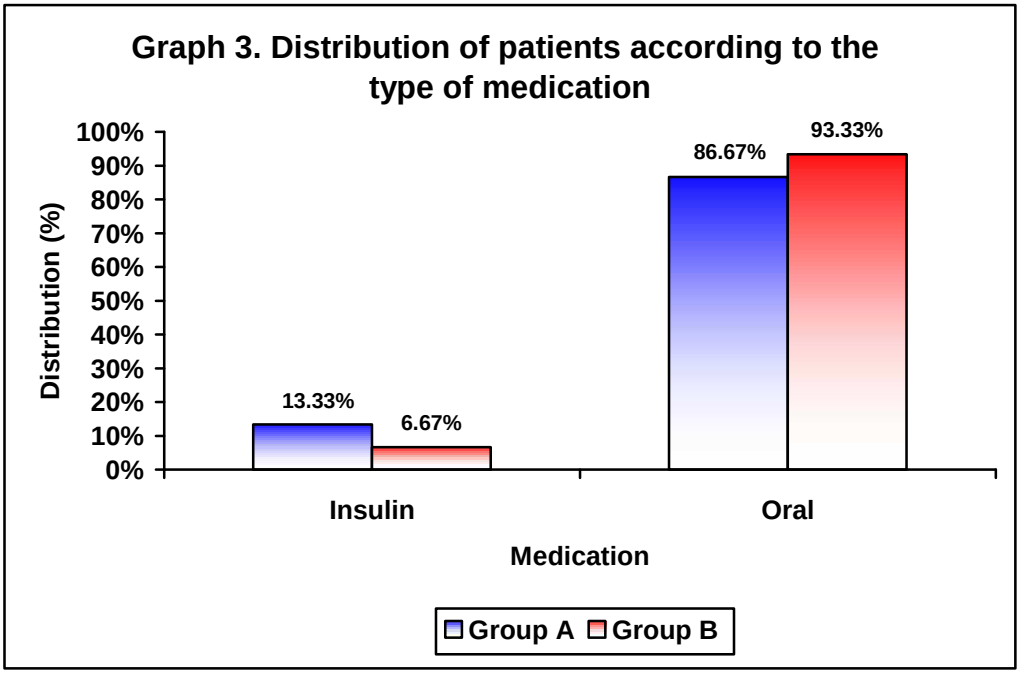
Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	60.23	9.27	55.13	12.06	0.072

In the present study the mean age in group A was slightly high (60.23 ± 9.27 years) compared to group B (55.13 ± 12.06 years) but difference was statistically not significant (p=0.072)

Table 4. Distribution of patients according to the type of medication

Medication	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Oral	26	86.67	28	93.33
Insulin	4	13.33	2	6.67
Total	**30**	**100.00**	**30**	**100.00**

p = 0.335

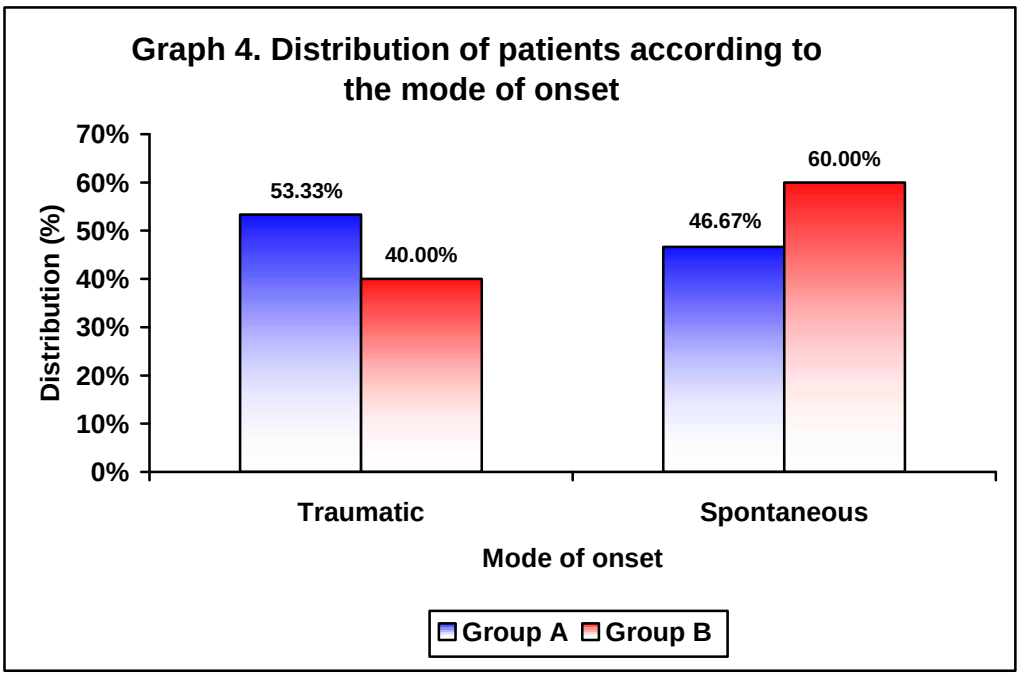


In this study, maximum patients in group A (86.67%) and B (93.33%) were on oral hypoglycaemic agents for the treatment of diabetes mellitus (p=0.335).

Table 5. Distribution of patients according to the mode of onset

Mode	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
Traumatic	16	53.33	12	40.00
Spontaneous	14	46.67	18	60.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.301

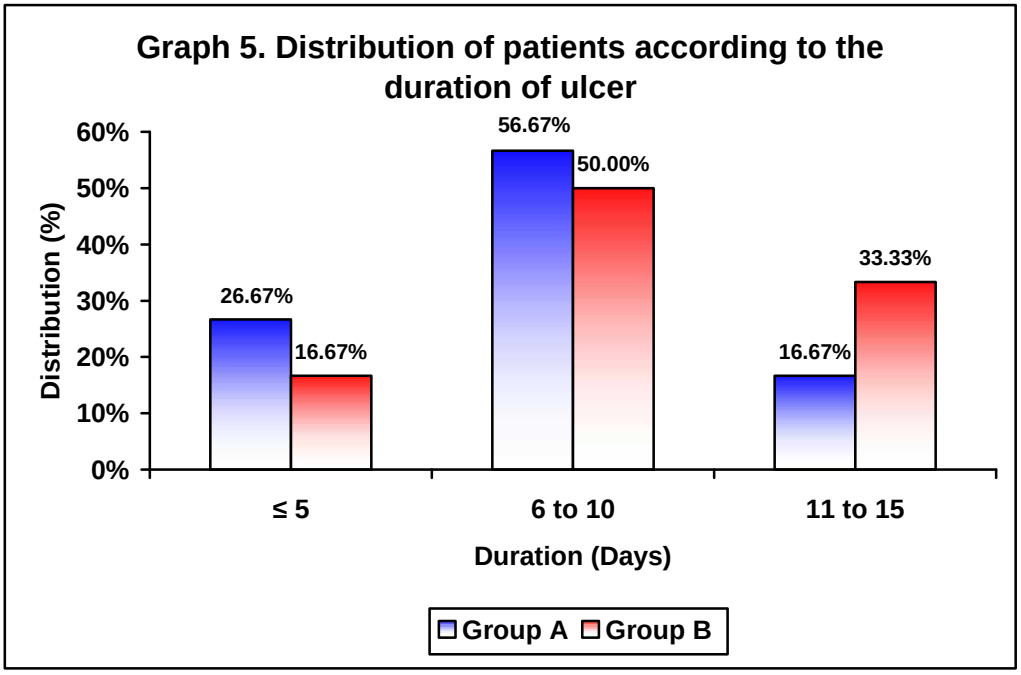


In the present study, most of the patients in group A had traumatic mode of onset (53.33%) while in group B, the common mode of onset was spontaneous (60%) (p=0.301)

Table 6. Distribution of patients according to the duration of ulcer

Duration (Days)	Group A (n=30)		Group B (n=30)	
	No.	%	No.	%
≤ 5	8	26.67	5	16.67
6 to 10	17	56.67	15	50.00
11 to 15	5	16.67	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.289



In this study 56.67% and 50% of the patients from group A and B reported duration of ulcer from 6 to 10 days (p=0.289).

Table 7. Comparison of mean duration of ulcer

Duration	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Duration (Days)	7.60	2.75	8.63	3.69	0.224

In the present study mean duration in group A and B was comparable (7.60 ± 2.75 days vs. 8.63 ± 3.69 days; p=0.224).

Table 8. Distribution of patients according to the ulcer characteristics

Characteristics	Findings	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Site	Left side	14	46.67	15	50.00	0.796
	Right side	16	53.33	15	50.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Shape	Circular	3	10.00	0	0.00	0.222
	Irregular	18	60.00	18	60.00	
	Oval	2	6.67	3	10.00	
	Rectangular	5	16.67	3	10.00	
	Round	2	6.67	6	20.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Edge	Indurated	8	26.67	12	40.00	0.490
	Edematous	5	16.67	3	10.00	
	Sliding	17	56.67	15	50.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Floor	Granular	0	0.00	2	6.67	0.329
	Pale	11	36.67	11	36.67	
	Rough	4	13.33	7	23.33	
	Smooth	15	50.00	10	33.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Surrounding skin	Indurated	13	43.33	8	26.67	0.099
	Normal	2	6.67	0	0.00	
	Edematous	15	50.00	22	73.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Necrotic tissue	Present	16	53.33	13	43.33	0.438
	Absent	14	46.67	17	56.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Grade (Wagner classification)	I	13	43.33	19	63.33	0.121
	II	17	56.67	11	36.67	
	Total	**30**	**100.00**	**30**	**100.00**	

Table 8 shows distribution of patients according the ulcer characteristics. It was observed that, the distribution of ulcer characteristics including site (p=0.796),

shape (p=0.222), edge (p=0.490), floor (p=0.329), surrounding skin (p=0.099), necrotic tissue (p=0.438) and ulcer grades (p=0.121) were comparable in both the groups.

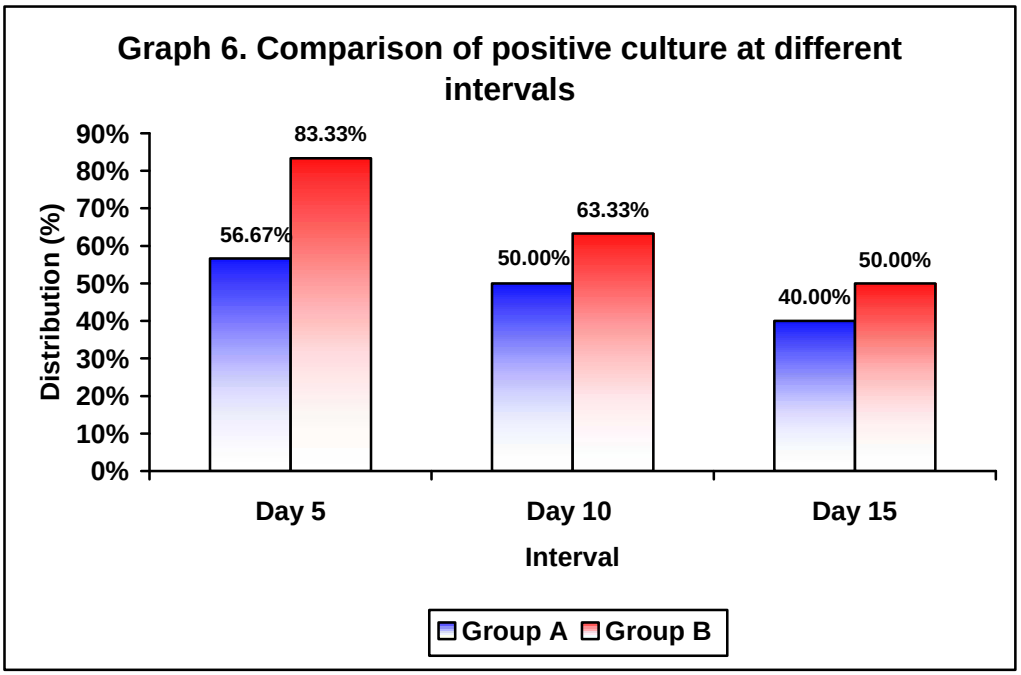
Table 9. Comparison of mean haemoglobin, fasting blood sugar and blood urea nitrogen

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Haemoglobin (gm%)	10.51	1.81	10.95	1.94	0.367
Fasting blood sugar (mg/dL)	259.30	62.89	233.97	81.31	0.183
Blood urea nitrogen (mg/dL)	36.83	10.01	30.82	17.49	0.109

In this study, the mean haemoglobin levels (10.51 ± 1.81 gm% vs. 10.95 ± 1.94 gm%; p=0.367), fasting blood sugar levels (259.30 ± 62.89 mg/dL vs. 233.97 ± 81.31 mg/dL; p=0.183) and blood urea nitrogen (36.83 ± 10.01 mg/dL vs. 30.82 ± 17.49 mg/dL; p=0.109) did not differ significantly.

Table 10. Comparison of culture at different intervals

Interval	Findings	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Fifth day	Positive	17	56.67	25	83.33	**0.024**
	Negative	13	43.33	5	16.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Tenth day	Positive	15	50.00	19	63.33	0.297
	Negative	15	50.00	11	36.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Fifteenth day	Positive	12	40.00	15	50.00	0.436
	Negative	18	60.00	15	50.00	
	Total	**30**	**100.00**	**30**	**100.00**	



In the present study significantly lower number of patients in group A had positive culture (56.67%) on day fifth compared to group B (83.33%) ($p=0.024$). However on day 10 and 15, in group A, 50% and 40% of the patients had positive culture respectively compared to 63.33% and 50% in group B respectively. However this difference was statistically not significant ($p>0.050$).

Table 11. Comparison of organisms at different intervals

Intervals	Organisms	Group A (n=30)		Group B (n=30)	
		No	**%**	**No**	**%**
Enrolment	*Proteus vulgaris*	10	33.33	9	30.00
	Pseudomonas	7	23.33	9	30.00
	Escherichia coli	7	23.33	6	20.00
	MRSA	6	20.00	6	20.00
	Total	**30**	**100.00**	**30**	**100.00**
Fifth day	*Escherichia coli*	5	16.67	4	13.33
	MRSA	4	13.33	6	20.00
	Pseudomonas	4	13.33	9	30.00
	Proteus vulgaris	4	13.33	6	20.00
	NOGC	13	43.33	5	16.67
	Total	**30**	**100.00**	**30**	**100.00**
Tenth day	*Escherichia coli*	4	13.33	2	6.67
	MRSA	4	13.33	6	20.00
	Pseudomonas	4	13.33	8	26.67
	Proteus vulgaris	3	10.00	3	10.00
	NOGC	15	50.00	11	36.67
	Total	**30**	**100.00**	**30**	**100.00**
Fifteenth day	*Escherichia coli*	3	10.00	2	6.67
	MRSA	2	6.67	6	20.00
	Pseudomonas	4	13.33	5	16.67
	Proteus vulgaris	3	10.00	2	6.67
	NOGC	18	60.00	15	50.00
	Total	**30**	**100.00**	**30**	**100.00**

The comparison of organisms in group A and B at different intervals is as shown in table 11.

Table 12. Comparison of mean slough at different intervals

Interval	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Enrolment	36.25	14.38	34.04	14.38	0.553
Day five	29.32	14.21	29.67	13.02	0.920
Day ten	21.04	11.42	24.94	10.39	0.171
Day fifteen	14.68	9.10	18.14	7.40	0.112

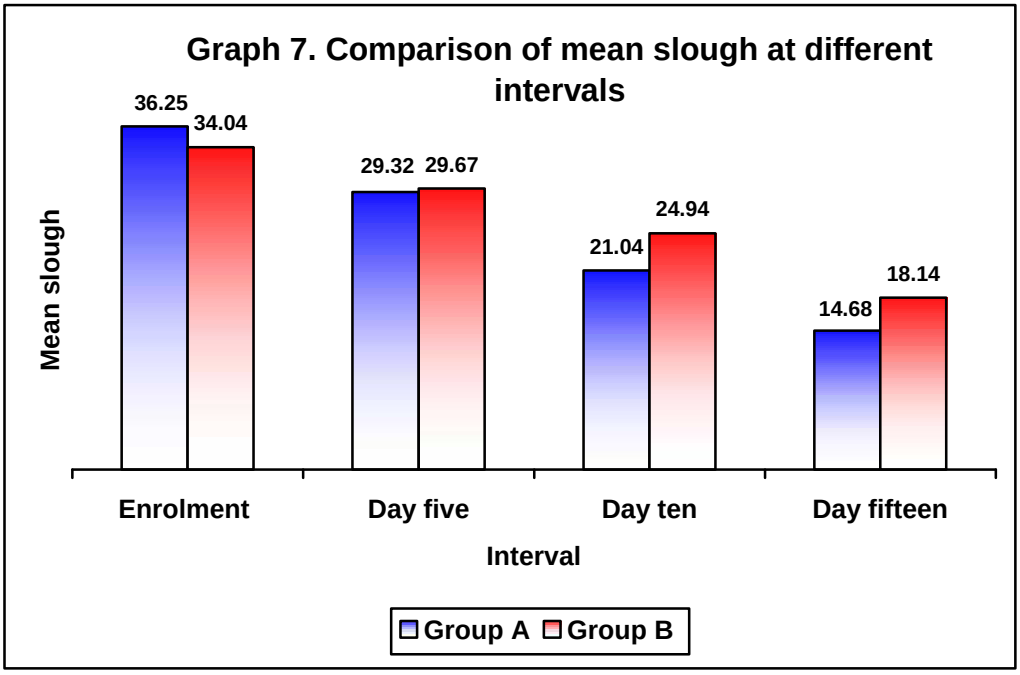
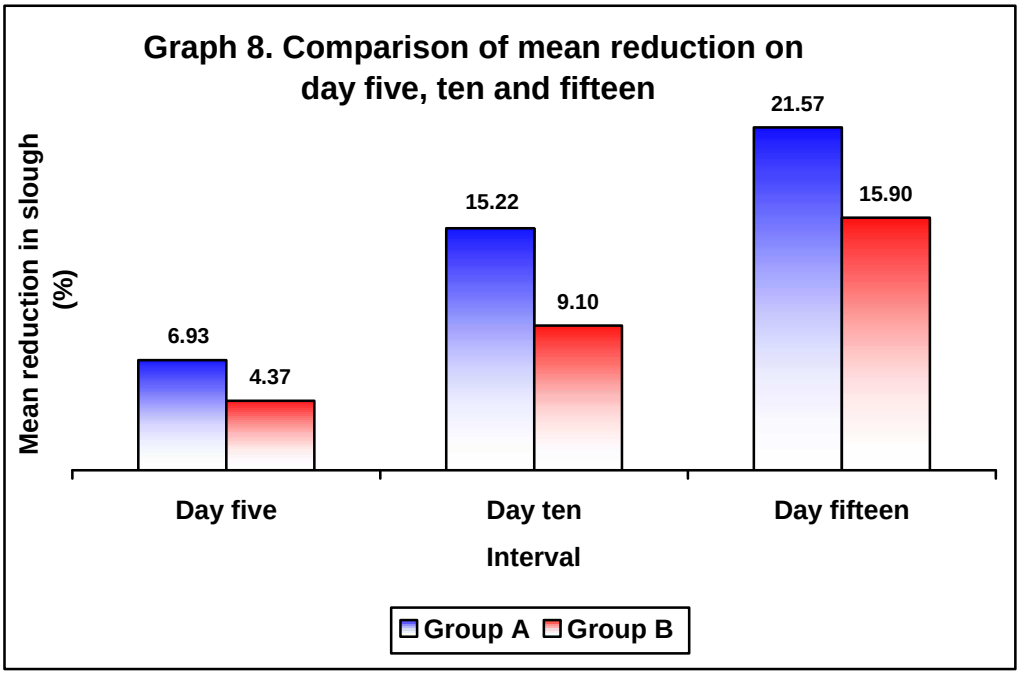


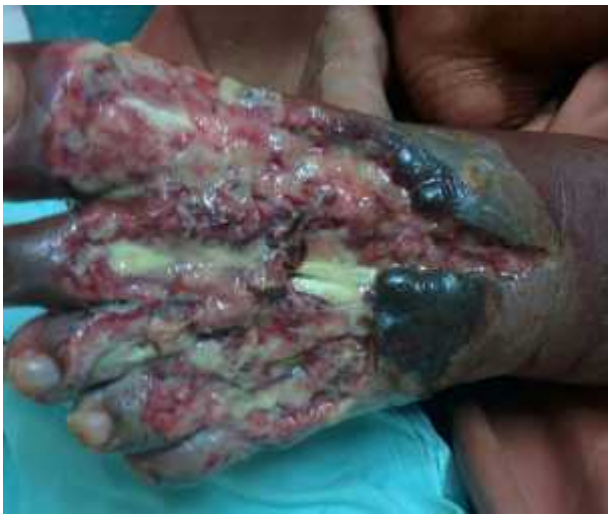
Table 12 shows the comparison of mean slough from enrolment to day fifteen. It was observed that, the mean slough was comparable at all the intervals ($p>0.050$).

Table 13. Comparison of mean reduction on day five, ten and fifteen

Interval	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Day five (%)	6.93	6.14	4.37	2.96	**0.045**
Day ten (%)	15.22	7.40	9.10	7.00	**0.002**
Day fifteen (%)	21.57	8.71	15.90	8.11	**0.012**

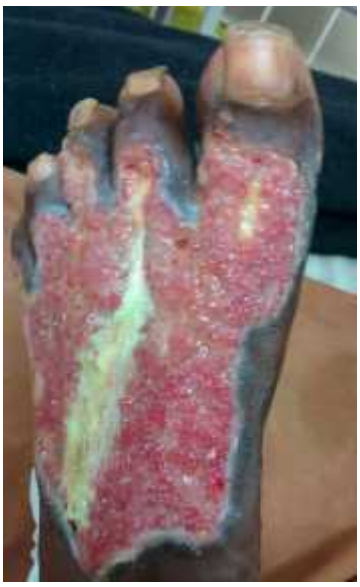


In the present study, among the patients with group A, the mean reduction of slough on day five (6.93 ± 6.14% vs. 4.37 ± 2.96%; p=0.045), day ten (15.22 ± 7.40% vs. 9.10 ± 7.00%; p=0.002) and day fifteen (21.57 ± 8.71% vs. 15.90 ± 8.11%; p=0.012) was significantly high compared to group B.



Photograph 4. Diabetic foot ulcer at enrolment

Photograph 5. Diabetic foot ulcer on tenth day



Photograph 6. Diabetic foot ulcer on fifteenth day

DISCUSSION

Chronic wounds are injuries produced as a result of specific diseases such as diabetes, tumors and severe physiological contaminations. Healing of these wounds could take long time and there are chances of recurrence. For effective healing of wound, suitable material had to be used to cover the wound so as to prevent infection. To achieve the highest rate of healing and the best aesthetic repair of the wound, the design of a wound bandage, characteristics of the wound type, wound healing time, physical, mechanical, and chemical properties of the bandage are important aspects which must be taken into consideration.[104]

Historically, honey pastes, plant fibers, and animal fats were used as wound dressing materials. Nowadays, with new biopolymers and fabrication techniques, a wound dressing material is expected to have extraordinary properties which enhance the healing process of a wound.[104]

Amorphous hydrogel dressings consist of a crosslinked insoluable polymers (starch or carboxymethylcellulose) and water. They are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels. Silver is a broad-spectrum antimicrobial agent which controls yeast, mold, and bacteria if provided in an appropriate proportion[17] and has also anti-inflammatory properties.[18] Silver NPs (Ag NPs) have unusual physical, chemical and biological properties.[19-21]

However nano-silver being a new generation of nanoproduct, data is lacking on effect of healing of chronic wound such as diabetic foot ulcers. This prompted us to find the efficacy of amorphous hydrogel dressings with silver nano particles

versus conventional dressing for treating diabetic foot ulcers with special emphasis on wound culture and slough area.

This one year randomized controlled trial was done under the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 60 patients who presented with diabetic foot ulcer measuring more than one cm. with slough, foul smell and minimal granulation tissue were studied. These patients were divided into two groups of 30 to receive treatment with dressing and topical management using hydrogel with silver nano particles (Group A) and dressing and topical management using povidone iodine (Group B).

Several researchers[105,106] have reported that diabetic foot ulcers mostly occur among males. Similar to these findings, in the present study males constituted 86.67% in group A and 66.67% in group B with male to female ratio of 6.5:1 in group A and 2:1 in group B. The male preponderance observed in the present study was consistent with an epidemiological study from Varanasi to determine risk factors for foot ulceration (71.13% of the patients males and 28.86% females).[107]

In this study most of the patients who presented with diabetic foot ulcer were elderly. In group A 53.33% of the patients and in group B 43.33% of the patients were aged > 60 years. Though the mean age in group A was slightly high compared to group B (60.23 ± 9.27 years vs. 55.13 ± 12.06 years) but difference was statistically not significant (p=0.072). Similar to these findings several other reports have showed occurrence of diabetic foot ulcers mostly in middle aged patients.[108] A

study[107] from Varanasi to determine risk factors for foot ulceration reported mean age of the patients with diabetic foot ulcers as 55.25 years.

Though there was male preponderance and most of the patient were elderly the distribution of demographic pattern of the study population in group A and B was comparable (p>0.050).

In this study, with regard to diabetic characteristics, majority of the patients in group A (86.67%) and in group B (93.33%) were on oral hypoglycaemic agents (p=0.335). Further the mean duration of diabetes in group A and B was also comparable (7.60 ± 2.75 days vs. 8.63 ± 3.69 days; p=0.224). The fasting blood sugar levels were slightly high in group A (259.30 ± 62.89 mg/dL) compared to group B (233.97 ± 81.31 mg/dL) but the difference was statistically not significant (p=0.183). These findings suggest that, the diabetic features in group A and group B were comparable.

In the present study pertaining to the ulcer characteristics, 53.33% of the patients in group A had traumatic mode of onset compared to 40% in group B (p=0.301). The duration of ulcer was in nearly half of the study population was between 6 to 10 days (group A 56.67% and group B 50%; p= 0.289). The other ulcer characteristics including site (p=0.796), shape (p=0.222), edge (p=0.490), floor (p=0.329), surrounding skin (p=0.099), and necrotic tissue (p=0.438) were comparable in both the groups.

In the present study wound culture at enrolment was positive in all the patients in group A and B (100%). The commonest organism isolated was *Proteus*

vulgaris in group A (33.33%) as well as group B (30%). Also the slough area in group A (36.25 ± 14.38) and group B (34.04 ± 14.38) was comparable (p=0.553).

Overall these findings suggest that, the demographic characteristics of the study population, history of diabetes, ulcer characteristic in patients with group A and B were comparable ruling out bias in the outcome.

It is reported that, anaerobic bacteria are almost always isolated with aerobes from diabetic foot infections. Aerobic gram-positive cocci are the predominant microorganisms that colonize and acutely infect breaks in the skin. *S. aureus* and the beta-hemolytic streptococci (groups A, C, and G, but especially group B); nterococci, Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa,* nonfermentative gram-negative rods; Antibiotic-resistant organisms (e.g., MRSA or vancomycinresistant enterococci); and Coagulase negative staphylococci and *Corynebacterium* species (diphtheroids) are a major therapeutic challenge both in hospital and community settings. The pathogenic role of each isolate in a polymicrobial infection is often unclear.[109]

In the present study significantly higher number of patients had negative wound culture in group A (43.33%) compared to group B (16.67%) (p=0.024) on fifth day. Similar trend was noted on day 10 and 15, where the negative wound culture was noted in 50% and 60% of the patients in group A as against 36.67% and 50% in group B respectively but the difference was statistically not significant (p=0.297 and 0.436 respectively). Further the treatment was more effective in reducing wound culture with *Proteus vulgaris* followed by pseudomonas, *Escherichia coli* and *MRSA*. These findings suggest that dressing and topical management using

hydrogel with silver nano particles resulted in effective management of wound though reduction in organisms. However this effect was limited to initial period only.

In this study, there was reduction in mean slough area from 36.25% ± 14.38% at enrolment to 14.68% ± 9.10% till day 15 in group A resulting in reduction of mean slough area of 21.57% ± 8.71%. Similar findings were noted in group B also that is, the mean slough area at enrolment was 34.04% ± 14.38% which reduced to 18.14% ± 7.40% and the reduction was noted as 15.90% ± 8.11%. Though there was considerable reduction in mean slough area in both the groups at different intervals, the mean reduction in slough area was significantly high in group A compared to group B. Among the patients with group A, the mean reduction of slough on day five (6.93% ± 6.14% vs. 4.37% ± 2.96%; p=0.045), day ten (15.22% ± 7.40% vs. 9.10% ± 7.00%; p=0.002) and day fifteen (21.57% ± 8.71% vs. 15.90% ± 8.11%; p=0.012) was significantly high compared to group B. These findings suggest that, dressing and topical management using hydrogel with silver nano particles favours wound healing as measured by slough area compared to dressing and topical management using povidone iodine.

The early wound healing process observed in the present study can be explained by the combined mechanism of action with topical management using silver nano particles and amorphous hydrogel dressings.[93]

Hydrogels consist of a matrix of insoluble polymers with up to 96% water content enabling them to provide water molecules to the wound surface and to maintain a moist environment at the wound bed. As the polymers are only partially hydrated, hydrogels have the ability to absorb a degree of wound exudate, the

amount varying between different brands. They transmit moisture vapour and oxygen, but their bacterial and fluid permeability is dependent on the type of secondary dressing used.[104,110]

Hydrogels promote wound debridement by rehydration of non-viable tissue, thus facilitating the process of natural autolysis. Amorphous hydrogels are the most commonly used and are thick, viscous gels. Hydrogels are considered to be a standard form of management for sloughy or necrotic wounds. They are not indicated for wounds producing high levels of exudate or where there is evidence of gangrenous tissue, which should be kept dry to reduce the risk of infection. [104,110]

Silver on the surface of the dressing may come into contact with the wound where it exerts the antimicrobial action. Silver within the dressing structure acts on bacteria absorbed into the dressing with wound exudate, but is likely also to diffuse to some extent into the wound. In one part per million (1ppm) of silver ions or less, have been shown to be effective against bacteria. However, it is unclear how silver content and availability measured in experimental settings relate to wound healing performance.[93]

Silver ions are highly reactive and affect multiple sites within bacterial cells, ultimately causing bacterial cell death. They bind to bacterial cell membranes, causing disruption of the bacterial cell wall and cell leakage. Silver ions transported into the cell disrupt cell function by binding to proteins and interfering with energy production, enzyme function and cell replication. Silver ions are active against a broad range of bacteria, fungi and viruses, including many antibiotic-resistant

bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).[93]

To date limited numbers of studies have assessed the role of silver nano particle in patients with diabetic foot ulcers.

Jude EB, et al.[111] compared AQUACEL Ag (silver Hydrofiber) versus Algosteril (alginate) for 8 weeks or until healing (n=134) in patients with Non-ischaemic diabetic foot ulcers. Ulcer depth in the silver group reduced significantly more than in the control group (p=0.04). Overall improvement and less deterioration was greater in the silver group (p=0.058), and particularly in the subset using antibiotics (p=0.02). The mean time to healing was not significantly different between the two groups.

The VULCAN study[102,103] randomised 213 patients with venous leg ulcers to receive either one of a number of silver-containing dressings or a clinician-selected non-antimicrobial control dressing. The main outcome measured was the rate of complete healing at 12 weeks. The study concluded that there was no statistically significant difference between the use of silver-containing dressings and the control dressings for the proportion of ulcers healed, time to healing or rates of recurrence.

Overall the present study showed that treatment with dressing and topical management using hydrogel with silver nano particles in selected patients with diabetic foot ulcers results in favourable outcome through reduction in slough area and microorganisms.

CONCLUSION

Based on the results of this study it may be concluded that, diabetic foot ulcers treated with amorphous hydrogel dressings with silver nano particles are efficacious in terms of reduction in slough resulting in early wound healing compared to conventional dressing. However the reduction in microorganism resulted in patients who were treated with amorphous hydrogel dressings remains controversial as the reduction pattern was significant only during first five days.

SUMMARY

The silver-containing preparations have bactericidal properties and it has been tried in the treatment of chronic ulcers. The present study was aimed to find the effect of amorphous hydrogel dressings with silver nano particles versus conventional dressing on wound culture and slough in patients with diabetic foot ulcers.

This one year randomized controlled trial was done in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 60 patients with chronic diabetic foot ulcers from January 2014 to December 2014were enrolled. Patients were divided into two groups of 30 each as group A (dressing and topical management using hydrogel with silver nano particles) and group B (dressing and topical management with povidone iodine).

Most of the patient sin group A (86.67%) and B (66.67%) were males (p=0.067). The mean age in group A was 60.23 ± 9.27 years compared to 55.13 ± 12.06 years in group B (p=0.072). The diabetic history, wound characteristics and culture in group A and B were comparable (p>0.050). On day five, maximum number of patients had negative wound culture in group A (43.33% vs 16.67%) compared to group B (p=0.024). The mean slough was comparable at all the intervals (p>0.050) in group A and B. Among the patients with group A, the mean reduction of slough on day five (6.93 ± 6.14 vs. 4.37 ± 2.96; p=0.045), day ten (15.22 ± 7.40 vs. 9.10 ± 7.00; p=0.002) and day fifteen (21.57 ± 8.71 vs. 15.90 ± 8.11; p=0.012) was significantly high compared to group B.

From the findings of this study it may be concluded that, diabetic foot ulcers treated with amorphous hydrogel dressings with silver nano particles are efficacious in terms of reduction in slough compared to conventional dressing and reduce the micro-organisms during first five days.

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ANNEXURE I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. / Mrs. / Miss. _____ we are requesting you to enroll yourself in study titled "**A COMPARATIVE STUDY OF AMORPHOUS HYDROGEL DRESSINGS WITH SILVER NANO PARTICLES VERSUS CONVENTIONAL DRESSING FOR TREATING DIABETIC FOOT ULCERS – A RANDOMISED CONTROLLED TRIAL"** conducted by Dr. **** ****** Post Graduate in M.S. General Surgery under the guidance of Dr. ***** *******. Associate Professor, Department of General Surgery, Jawaharlal Nehru Medical College, Belgaum under KLE University, Belgaum.

Respected Sir / Madam We request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with Jawaharlal Nehru Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of research is to know efficacy of silver particles on chronic ulcer.

Purpose of the study

The clinical use of amorphous Hydrogel with Silver dressing as an alternative to conventional dressing gauze dressings is limited by lack of scientific evidence regarding antimicrobial activity and debridement in diabetic ulcers. The

purpose of this experimental research, therefore, is to compare the effect of amorphous hydrogel dressings with silver nano particles versus conventional dressing for treating diabetic foot ulcers.

Procedure Involved

If you agree to enroll yourself in my study, I will ask your present past and family history. Then you will be clinically examined in detail and routine investigations like Hb, TC, DC, Platelet Count, RBS, Blood Urea, Serum Creatinine, Blood Grouping, Chest X-ray, ECG, will be done accordingly. You will be allotted into one of the two groups randomly using a computer rated software. One group is given hydrogel dressings with silver Nano particles dressing and the other group is done with conventional dressing.

Risks

Allergic reaction to silver.

Benefits

Costs same as conventional dressings.

Voluntary Participation / Withdrawal

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at K.L.E. hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Privacy and Confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury related to the study, treatment will be made available through KLES' Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Dr. ***** ****** at Department of General Surgery, KLES Hospital& MRC or by Ph. No: **********

Questions

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. ***** ******, Department of General Surgery, KLES Hospital and MRC, Belgaum, Phone number **** ***** or

Dr. ***** ******* Professor, Dept Of General Surgery, KLES Hospital and MRC, Belgaum

If you have any queries about your rights as a study subject, you may call Dr. ***** ******, Professor, Department of Pathology and Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Phone number ***** ******, or extension ***** at J.N. Medical College, Belgaum.

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

I, Mr. / Ms. / Mrs. _____ voluntarily agree for the participation as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject: _____

Date:

Witness Name : _____

Signature: _____

Date:

Investigators Name: _____

Signature: _____

Date:

Place:

ANNEXURE II – PROFORMA

TITLE: "A COMPARATIVE STUDY OF AMORPHOUS HYDROGEL DRESSINGS WITH SILVER NANO PARTICLES VERSUS CONVENTIONAL DRESSING FOR TREATING DIABETIC FOOT ULCERS – A RANDOMISED CONTROLLED TRIAL"

Patient Identification Data

Group: Case No.:

In Patient /

Out Patient Department No.: Date of Admission:

Name: Date of Surgery:

Sex: Date of Discharge:

Occupation:

Medical History

	Yes	**No**
Peripheral neuropathy		
Nephropathy		
PVD		
CVD		

Diabetic Status

Type

Medication

Drug	Dose	Duration

Complication

	Yes	No
Neuropathy		
Vasculopathy		

Ulcer Detail

1. Mode of onset

Traumatic	
Spontaneous	
Pressure	
Others	

2. Duration

Wound observation

1. Site
2. Size
3. Shape

4. Edge
5. Margin
6. Floor
7. Base
8. Discharge
9. Surrounding Skin
10. Slough /necrotic tissue

Neurological Examination

Vascular Examination

	Right	Left
Femoral a.		
Popliteal a.		
Ant. Tibial a.		
Post Tibial a.		
Dorsalis Pedis a.		

Any Foot Deformity Present

	Yes	No
Bunion		
Charcots foot		
Toe deformity		
Foot drop		

If Debridement Has Been Done

Specify,

Date:

Side / anesthesia:

Investigations

CBC

Fasting Blood Sugar

Date:

Time:

Blood Urea

Serium Creatinine

Urine:

Routine

Microscopy

X-ray Foot

AP view

Lat. View

Tissue culture/ sensitivity

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
Ant.	-	Anterior
AP	-	Antero posterior
Cr	-	Circular
D	-	Days
EC	-	*Escherichia coli*
F	-	Female
gm	-	Gram
I	-	Insulin
in	-	Inflamed
ind	-	Induration
IND	-	Induration
Ir	-	Irregular
L	-	Left
Lat.	-	Lateral
M	-	Male
mg/dl	-	Milligrams per deciliter
MRSA	-	*Methicillin resistant Staphylococcus aureus*
n	-	Normal
N	-	Normal
O	-	Oral
od	-	Odematous

PS	-	*Pseudomonas*
PTV	-	*Proteus vulgaris*
R	-	Right
Rec	-	Rectangle
slo	-	Sloughy
SP	-	Spontaneous
TR	-	Traumatic