“COMPARATIVE STUDY OF EFFECT OF TOPICAL INSULIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A HOSPITAL BASED ONE YEAR RANDOMIZED CONTROLLED TRIAL”

REG NO. BH0110007

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY (M.S.)
in
GENERAL SURGERY

DEPARTMENT OF SURGERY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

APRIL - 2013

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ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF EFFECT OF TOPICAL INSULIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A HOSPITAL BASED ONE YEAR RANDOMIZED CONTROLLED TRIAL"** is a bonafide research work done by **THE CANDIDATE REG NO. BH0110007**.

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LIST OF ABBREVIATIONS USED

AP	- Anteroposterior
ATP	- Adenosine Tri-Phosphate
BMI	- Body mass index
CDC	- Centre for Disease Control and Prevention
DHEA	- Dihydro epiandrosterone
DM	- Diabetes mellitus
DNA	- Deoxyribonucleic acid
ESRD	- End stage renal disease
FPG	- Fasting plasma glucose
GDM	- Gestational diabetes mellitus
HDL	- High density lipoprotein
HNF	- Hepatocyte nuclear transcription factor
IDDM	- Insulin dependent diabetes mellitus
IDF	- International dibates federation
IFG	- Impaired fasting glucose
IGF	- Insulin like growth factor
IGT	- Impaired glucose tolerance
IL	- Interleukin
IPF	- Insulin promoter factor
LDL	- Low density lipoprotein
MODY	- Maturity onset diabetes of the young
MRSA	- Methicillin-resistant Staphylococcus aureus
NIDDM	- Non insulin dependent diabetes mellitus
PAI	- Plasminogen activator inhibitor

PDGF	- Platelet derived growth factor
PEDIS	- Perfusion extent, depth, infection, sensation
PMN	- Polymorphonuclear
RCT	- Randomized controlled trial
TNF	- Tumor necrosis factor
UTI	- Urinary tract infection
VRE	- Vancomycin-resistant enterococci

ABSTRACT

Background and objectives

Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings. The present study was aimed to compare the effect of topical insulin and normal saline dressing in healing of diabetic foot ulcers.

Methodology

The present one year hospital based randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 60 patients with diabetic foot ulcers were studied. Based on the envelop method, patients were divided into two groups of 30 patients each that is group A (topical insulin) and group B (normal saline).

Results

In this males (66.67% in group A and 83.33% in group B) outnumbered females in both the groups with male to female ratio of 2:1 in group A and 4:1 in group B. The mean age in group A was 52.00 ± 11.00 years and in group B it was 57.00 ± 9.80 years (p=1.000). Among patients with group A significant reduction of mean ulcer area was observed (307.23 ± 169.87 mm^2) with higher mean percentage reduction (35.19 ± 19.00 percent) whereas in group B the mean percentage reduction was significantly less (18.82 ± 4.06 percent) with less reduction of mean final ulcer area (149.90 ± 64.45 mm^2) ($p<0.001$).

Conclusion and interpretation

Overall, topical insulin dressing provided favourable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing and it had positive role in reducing the wound infection if present.

Keywords

Diabetic foot ulcers; Normal saline; Topical insulin; Wound healing.

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Chapter 1

Introduction

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.[1]

The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. It is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world. It is a major and growing threat to global public health.[1]

The vast majority of cases of the diabetes fall into two broad categories: those having little or no endogenous insulin secretory capacity (IDDM or type 1 DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM, or Type 2 DM).[1,2]

A 2011 Centers for Disease Control and Prevention (CDC) report estimated that nearly 26 million Americans have diabetes. Type 2 diabetes mellitus (DM) accounts for more than 90% of the diabetic population world wide.[3]

Long term complications of diabetes include retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations and charcot joints and autonomic neuropathy causing gastro intestinal, genitourinary and cardiovascular symptoms and sexual dysfunction.[4]

Diabetic foot ulcers are common and estimated to affect 15% of all diabetic individual during their lifetime. Patient suffering from diabetic ulcer often require hospitalization. One of the major causes of non-healing of ulcer in diabetes is infection. It is caused by a variety of micro-organism. Most common are *Staphylococcus aureus* and *Pseudomonas aeroginosa* which invade the wound and multiply, producing harmful toxic substances, causing destruction of tissue and disturbance in wound healing.[5]

The management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear,[7,8] daily saline or similar dressings to provide a moist wound environment,[9] debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present,[9,10] optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings.[11,12]

It is known that insulin stimulates the growth and development of different cell types, and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts.[13-17] Previous data, although not well controlled, showed that topical insulin accelerates wound healing in the skin of diabetic rats and humans.[13,18-25]

Hence the present study was undertaken to compare the effect of topical insulin and normal saline dressing in healing of diabetic foot ulcers.

Chapter 2

Objectives

OBJECTIVES

The objective of the present study was to compare the effect of topical insulin with normal saline dressing in healing of diabetic foot ulcers.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia.[2] Depending on the etiology of the DM, factors contributing to hyperglycemia include

1. Reduced insulin secretion
2. Decreased glucose utilization
3. Increased glucose production.

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. Diabetes mellitus is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness.[1] It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.

Type 2 diabetes mellitus is a group of disorders characterized by hyperglycemia and associated with microvascular (Retinal, renal, possibly neuropathic), macrovascular (Coronary, peripheral vascular), and neuropathic (autonomic, peripheral) complications.[26] Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent upon insulin for life, even though many of them are ultimately treated with insulin.

Historical aspects

The sweet taste of diabetic urine was noted in the 5th and 6th century AD by the Indian physicians (Sushruta and Charaka) and in the 17th century by Thomas Willis. The term 'Diabetes mellitus', an allusion to the honeyed taste of urine, was first used in the late 18th century by John Rollo and others, to distinguish it from other polyuric states in which urine was tasteless.

The 'ancient' period witnessed the first clinical descriptions of diabetes and complications. The 16th to 18th centuries have been termed the 'diagnostic' period, as diabetes mellitus was then identified as a separate disease entity, while the mid to late 19th century may be regarded as the first 'experimental' period, during which the glucoregulatory role of the pancreas became clear and the biochemical disturbances of diabetes were initially characterized.[27]

In 1893, Edovard Laguesse named the pancreatic islets after Paul Langerhans, who had described them in 1869, and suggested that they produced a glucose lowering substance. This then hypothetical hormone was named 'insulin' by Jean de Meyer in 1909, over a decade before its discovery.

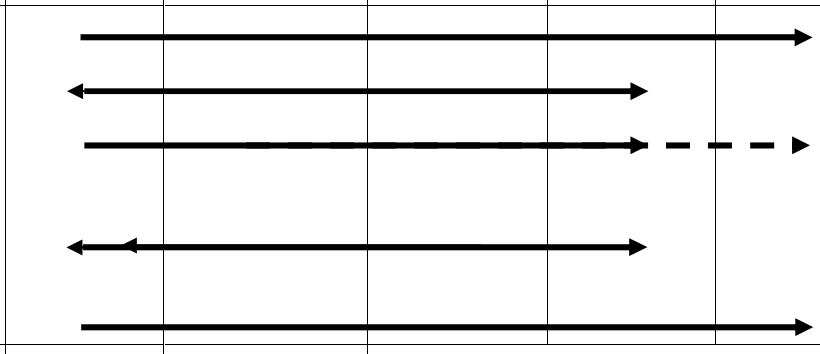
Insulin was discovered at the University of Toronto in 1921, through collaboration between Frederick G. Banting, Charles H. Best, James B. Collip and J.J.R. Macleod.

Finally, the 20th century has seen a dramatic increase in knowledge about diabetes. The discovery of insulin in 1921-22 has had profound scientific, clinical and social consequences.[28]

Classification

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[1] Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy.[4] The two broad categories of DM are designated type 1 and type 2. Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic process progresses. Type 1 diabetes is the result of complete or near-total insulin deficiency.

Spectrum of glucose homeostasis and diabetes mellitus[2]

Type of diabetes	**Normal glucose tolerance**	**Hyperglycemia**			
		Impaired fasting glucose or impaired glucose tolerance	**Diabetes mellitus**		
			No insulin required	**Insulin required for control**	**Insulin required for survival**
Type 1					
Type 2					
Other Specific types					
Gestational diabetes					
Time (years)					
FPG (mg/dl)	< 100	100-125	≥ 126		
2-h pg (mg/dl)	< 140	140 – 199	≥ 200		

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action

and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Etiologic Classification of Diabetes Mellitus[2]

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   a. Immune-mediated
   b. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes.
   a. Genetic defects of β cell function characterized by mutations in:
      i. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1).
      ii. Glucokinase (MODY 2).
      iii. HNF-1 (MODY 3).
      iv. Insulin promoter factor-1 (IPF-1; MODY 4).
      v. HNF-1 (MODY 5).
      vi. NeuroD1 (MODY 6).
      vii. Mitochondrial DNA.
      viii. Subunits of ATP-sensitive potassium channel.

ix. Proinsulin or insulin conversion.

b. Genetic defects in insulin action

i. Type A insulin resistance.

ii. Leprechaunism.

iii. Rabson-Mendenhall syndrome.

iv. Lipodystrophy syndromes.

c. Diseases of the exocrine pancreas-pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase.

d. Endocrinopathies-acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

e. Drug or chemical induced-vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine.

f. Infections - Congenital rubella, cytomegalovirus, coxsackie.

g. Uncommon forms of immune-mediated diabetes "stiff-person" syndrome, anti-insulin receptor antibodies.

h. Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

Epidemiology

Diabetes is fast becoming the epidemic of the 21st century. Type 2 diabetes, which is more prevalent (more than 90% of all diabetes cases) and the main driver of the diabetes epidemic, now affects 5.9% of the world's adult population with almost 80% of the total in developing countries.[29] Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000.[30]

World Health Organization reported that, 346 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high blood sugar. More than 80% of diabetes deaths occur in low- and middle-income countries. WHO projects that, diabetes deaths will double between 2005 and 2030.[31]

Race

The prevalence of type 2 diabetes mellitus varies widely among various racial and ethnic groups. Type 2 diabetes mellitus is becoming virtually pandemic in some groups of Native Americans and Hispanic people. The risk of retinopathy and nephropathy appears to be greater in blacks, Native Americans, and Hispanics.

Sex

Type 2 diabetes mellitus is slightly more common in older women than men.

Age

While type 2 diabetes mellitus traditionally has been thought to affect individuals older than 40 years, it is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese. In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults. Virtually all cases of diabetes mellitus in older individuals are type 2.

Indian scenario

Several epidemiological studies in migrant Indians and India itself show that, the population has a high genetic predisposition for diabetes, which is precipitated by environmental factors such as urbanization.[32] The prevalence of diabetes is four to six fold lower in rural areas, which is probably attributed to a conventional lifestyle which has beneficial effect on glucose tolerance (IGT). National Urban Diabetes Survey done in six cities, found age standardized prevalence rates of 12% for diabetes; with a slight male preponderance and 14% for impaired glucose tolerance. Subjects under the age of 40 years, had a prevalence of five percent for DM and 13% prevalence of impaired glucose tolerance.

The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.[29] It is clear that in the last two decades, there has been a marked increase in the prevalence of diabetes among both urban as well as the rural Indians, with a suggestion that Southern India has seen the sharpest increase. Subsequent studies confirmed this high prevalence of diabetes in urban south India. Although in rural India the prevalence of diabetes is much lower than in the urban population, even here the prevalence rates are rapidly rising, though clearly more studies are needed. Variations in the prevalence rates of diabetes in different urban populations of India are expected because of the large variation in the prevalence of cardiovascular risk factors in different regions and states. It is evident that there is a shift in age of onset to younger age groups, which is alarming and this could have adverse effects on the nation's economy. Hence, the early identification of at-risk individuals and appropriate intervention to increase physical activity, bring about changes in dietary habits could to a great extent help to prevent/ delay, the onset of diabetes and thus reduce the burden due to its associated complications in India.[32]

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,[33] 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 excess weight increases risk for diabetes 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.[34] A simplified scheme for the pathophysiology of abnormal glucose metabolism in type 2 diabetes mellitus is depicted in the image below.

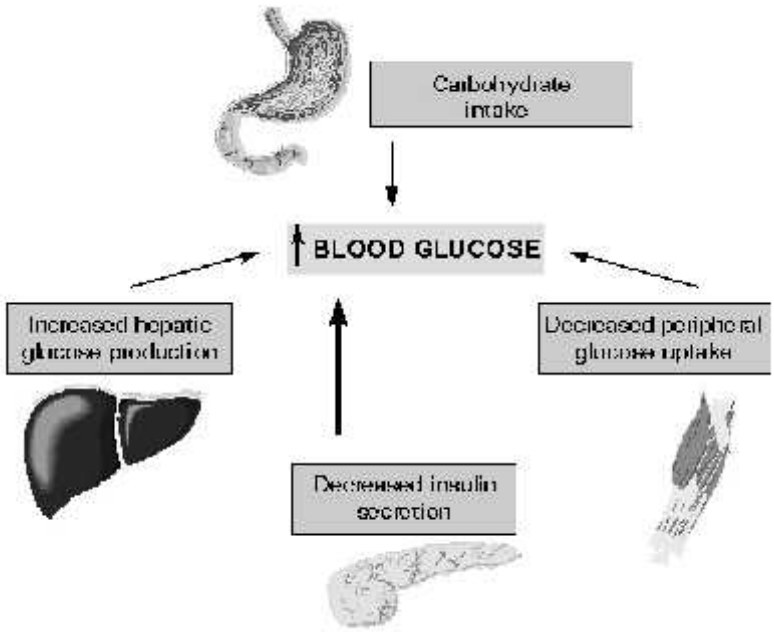


Figure 1. Pathophysiology of type 2 diabetes mellitus

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.

Diagnosis

The National Diabetes Data Group and World Health Organization 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.

Risk factors for Type 2 Diabetes Mellitus

- Family history of diabetes (i.e. parent or sibling with type 2 diabetes)
- Obesity (BMI≥25 kg/m2)
- Habitual physical inactivity

- Race/ethnicity (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified IFG or IGT
- History of GDM or delivery of baby > 4kg (>9 Ib)
- Hypertension (blood pressure ≥ 140/90 mHg)
- 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.

Complications

Diabetes has both acute and long term complications.[1] They are:

Acute

- Diabetic ketoacidosis
- Hyperglycemic Hyperosmolar state
- Hypoglycemia

Long term:

- Retinopathy
- Neuropathy
- Nephropathy
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral vascular disease
- Hypertension.

Others

- ***Infections***
  - UTI
  - Tuberculosis
  - Candidiasis – oral / vulvovaginal
  - Mucor mycosis
  - Necrotising fasciitis
  - Periodontitis
- Dupuytren's contracture
- Pseudogout

Neuropathy and diabetes mellitus[35-41]

- The prevalence of diabetic neuropathy in patients with type 2 diabetes is 32 percent overall and more than 50 percent in patients over 60 years of age.
- Diabetic neuropathy correlates with the duration of diabetes and glycemic control) type 1 and 2 DM.
- May manifest as
  1. Polyneuropathy
  2. Mono-neuropathy
  3. Autonomic Neuropathy
- Both myelinated and unmyelinated nerve fibers are affected.
- Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded.

Poly-neuropathy / Mono-neuropathy

- The most common form of diabetic neuropathy is distal symmetric polyneuropathy.
- It presents as:
    1. Distal sensory loss - most frequent presentation
    2. Hyperesthesia
    3. Paresthesia
    4. Dysesthesia
- Symptoms includes a sensation of following, which begins in the feet & spreads proximally.
    1. Numbness,
    2. Tingling
    3. Sharpness
    4. Burning

Any combination of these symptoms may develop as neuropathy progresses

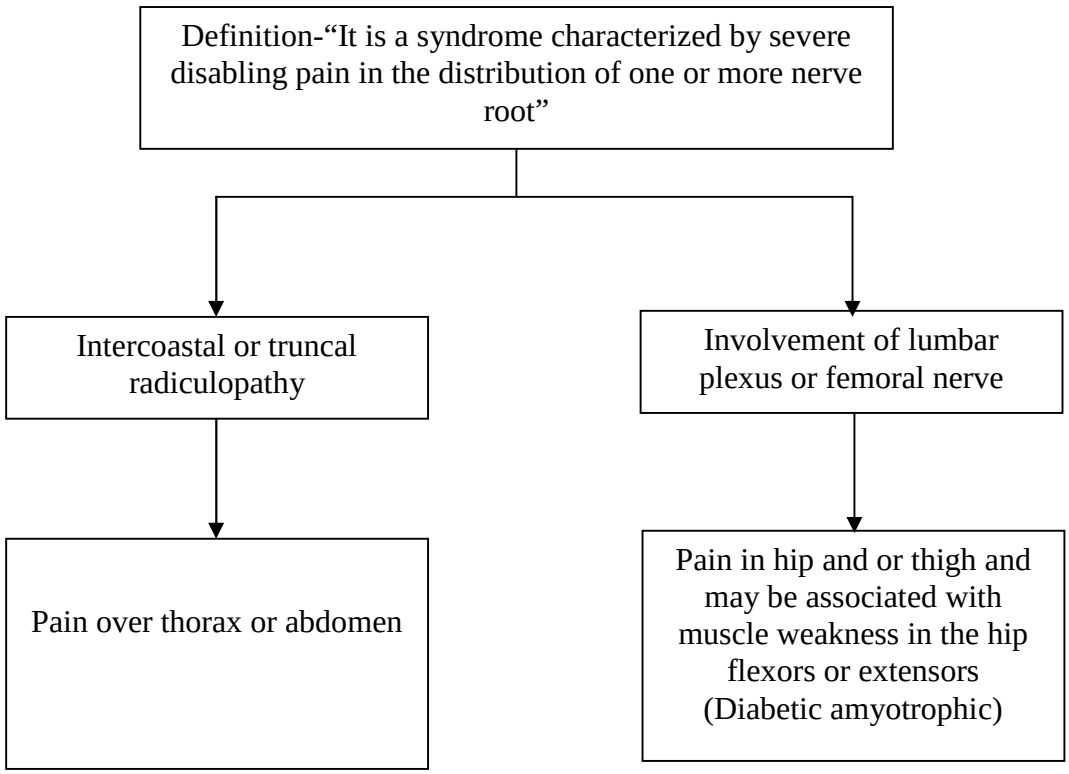
- Physical examination reveals
    1. Sensory loss
    2. Loss of ankle reflexes
    3. Abnormal position sense.
- Pain typically involves lower extremities, is usually present at rest, and worsen at night.
- Both an acute (lasting <12 months) and a Chronic form of painful diabetic neuropathy have been described.

- As diabetic neuropathy progresses, the pain subsides & eventually disappears, but a sensory deficit in the lower extremities persists.
- Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control.

Diabetic Neuropathy

It may be accompanied by - Motor weakness

Figure 2. Diabetic neuropathy



Neuropathy

Neuropathy is present in over 80% of patients with foot ulcers.[42,43]

Peripheral sensory neuropathy

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

Motor and sensory neuropathy

Lead to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint).

Autonomic neuropathy

Results in anhidrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation.

Peripheral arterial disease and poor wound healing

Impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Disordered proprioception

Causes abnormal weight bearing while walking and subsequent formation of callus or ulceration.

Approximately 15% of individuals with DM develop a foot ulcer and a significant subset will ultimately undergo amputation (14 to 24%).

DIABETIC FOOT

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.[44] 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.[45,46]

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[47,48]

The human foot is a marvel of mechanical construction. It acts as a pliable platform to support the body weight in the upright posture 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 aversion.
- Midtarsal joint – Abduction and adduction.

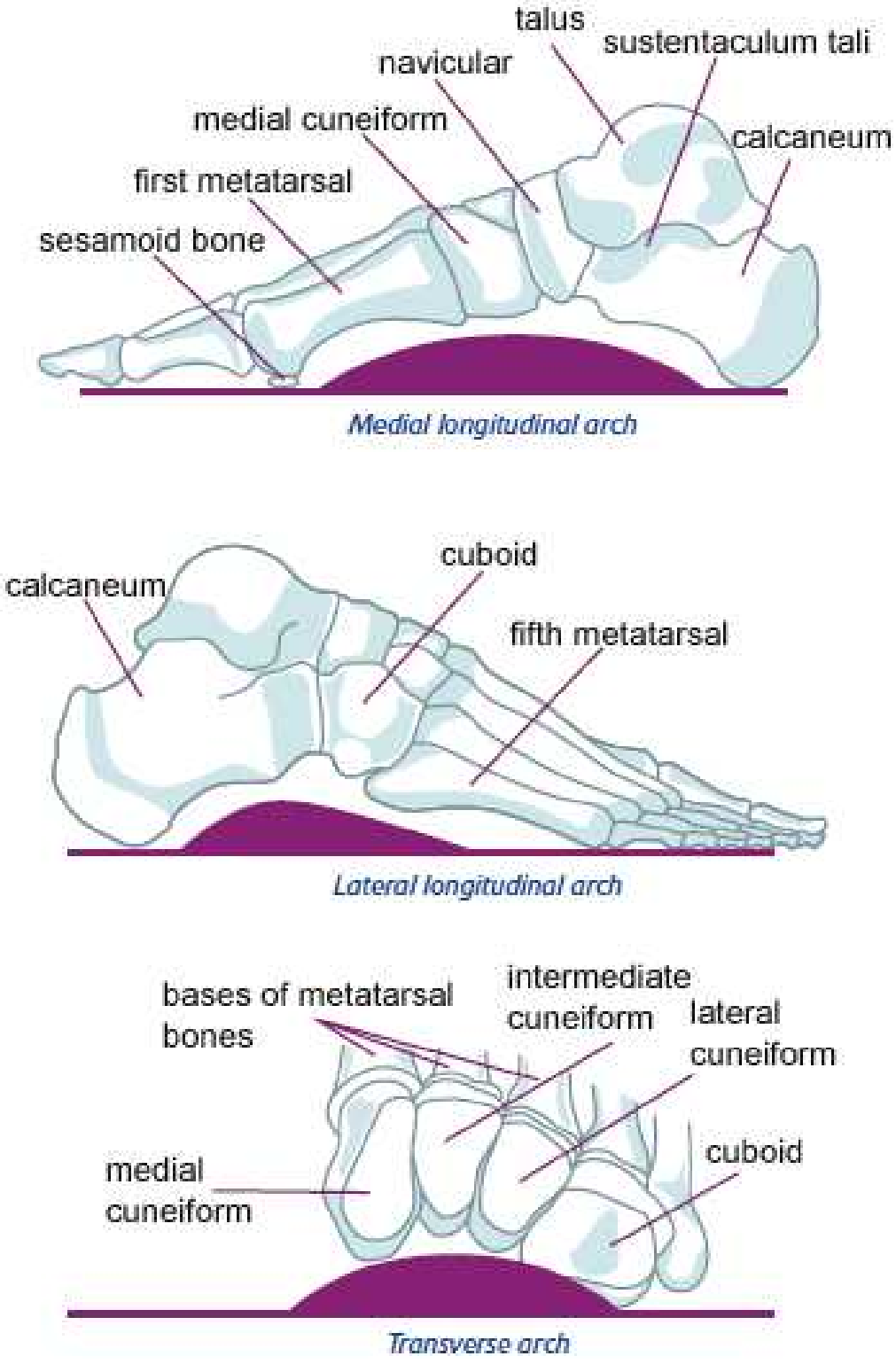


Figure 3. Arches of the foot

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. Twenty percent 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 that in a patient without diabetes. The presence of an ulcer in a diabetic patient has a profound 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.[49]

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.

Etiology

The etiologies of diabetic ulceration include neuropathy,[6] arterial disease,[50] pressure,[35] and foot deformity.[51] Diabetic peripheral neuropathy, present in 60% of diabetic persons and 80% of diabetic persons with foot ulcers, confers the greatest risk of foot ulceration; microvascular disease and suboptimal glycemic control contribute. Sensory neuropathy involving the feet may lead to unrecognized episodes of trauma due to ill-fitting shoes. Motor neuropathy, causing intrinsic muscle weakness and splaying of the foot on weight bearing, compounds this trauma. The result is a convex foot with a rocker-bottom appearance. Multiple fractures are unnoticed until bone and joint deformities become marked. This is termed a Charcot foot (neuropathic osteoarthropathy) and most commonly is observed in diabetes mellitus, affecting about 2% of diabetic persons. If a Charcot foot is neglected, ulceration may occur at pressure

points, particularly the medial aspect of the navicular bone and the inferior aspect of the cuboid bone. Sinus tracts progress from the ulcerations into the deeper planes of the foot and into the bone. Charcot change can also affect the ankle, causing displacement of the ankle mortise and ulceration, which can lead to the need for amputation.

Pathophysiology

Figure 4. Pathogenesis of Diabetic Foot

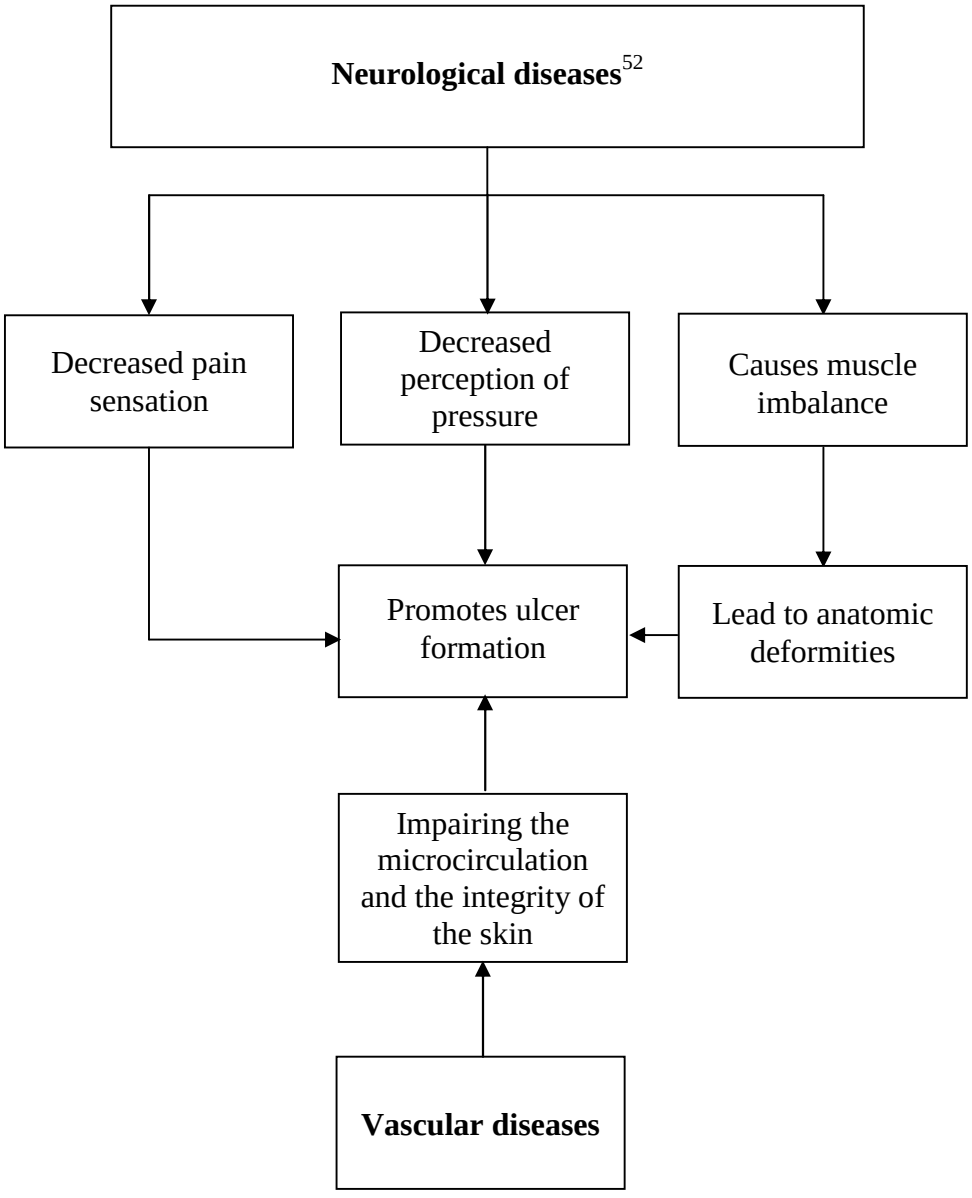
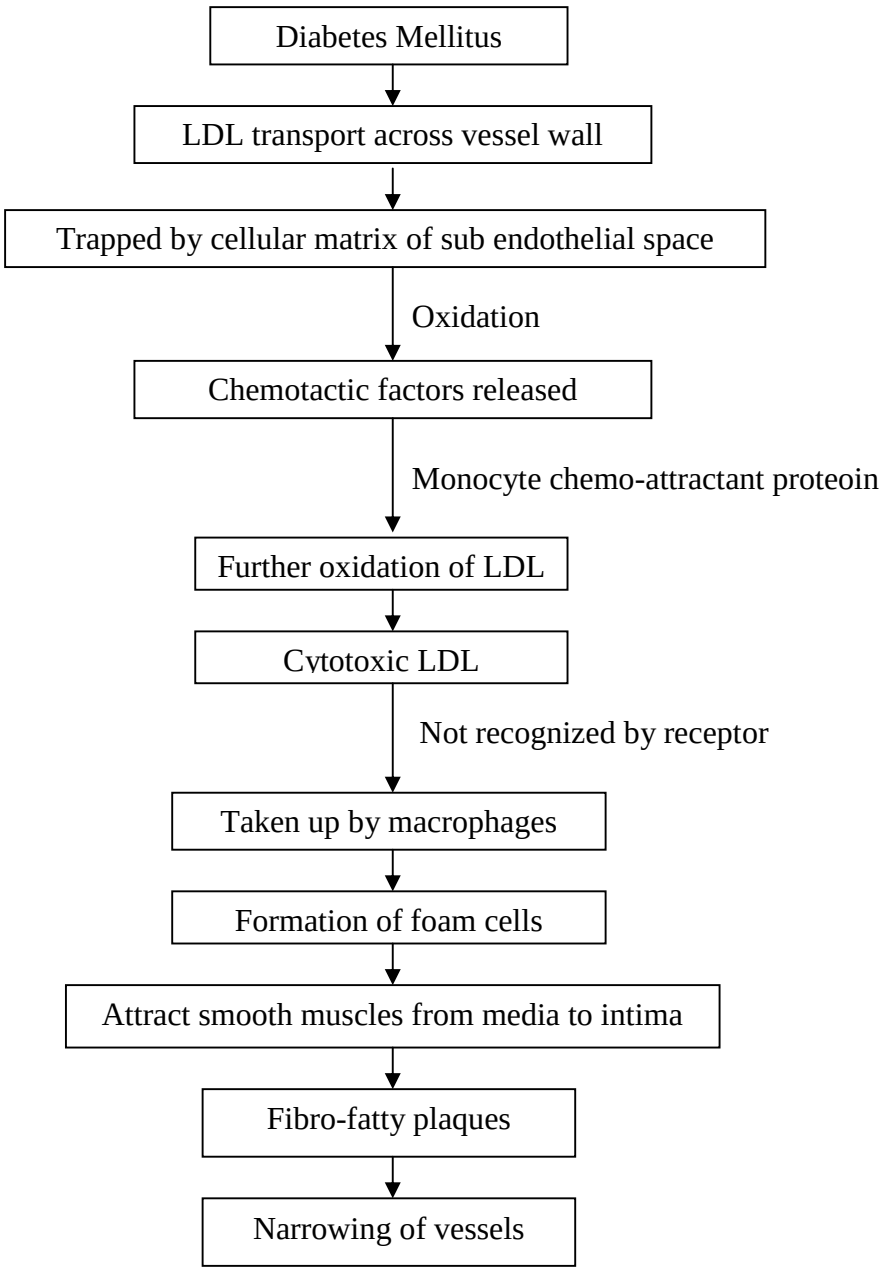


Figure 5. Pathophysiology of diabetic vasculopathy



Atherosclerosis and peripheral neuropathy occur with increased frequency in persons with DM. Chronic inflammatory process that can be converted into acute clinical event by plaque rupture. 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 thought to result from 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.[53]

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 a poorly fitting shoe, or damage from a blunt or sharp object inadvertently 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.[54] 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 uneradicated 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 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.[55] In general, people with diabetes have infections that are more severe and take longer to cure than equivalent 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.[56] 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 institute the appropriate antibacterial therapy and to avoid further complications.[57,58]

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.[58] Chronic wounds develop a more complex colonizing flora, including enterococci various Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa*, and nonfermentative Gram-negative rods.[59] 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]).[60] 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.[61]

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.[62,63] The pathogenic role of each isolate in a polymicrobial infection is often unclear.

Pathogens associated with various clinical foot-infection syndromes[64]

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

Risk Factors for Foot Ulceration and Infection[64]

Risk Factor	Mechanism of Injury or Impairment
Peripheral motor neuropathy	Abnormal foot anatomy and biomechanics, with clawing of toes, high arch, and subluxed metatarsophalangeal joints, leading to excess pressure, callus formation and ulcers.
Peripheral sensory neuropathy	Lack of protective sensation, leading to unattended minor injuries caused by excess pressure or mechanical or thermal injury.
Peripheral autonomic neuropathy	Deficient sweating leading to dry, cracking skin.
Neuro-osteoarthropathic deformities (i.e., Charcot disease) or limited joint mobility	Abnormal anatomy and biomechanics, leading to excess pressure, especially in the midplantar area.
Vascular (arterial) insufficiency	Impaired tissue viability, wound healing, and delivery of neutrophils.
Hyperglycemia and other metabolic derangements	Impaired immunological (especially neutrophil) function and wound healing and excess collagen cross-linking.
Patients disabilities	Patient reduced vision, limited mobility, and previous amputation(s).
Maladaptive patient behaviors	Inadequate adherence to precautionary measures and foot inspection and hygiene procedures, poor compliance with medical care, inappropriate activities, excessive weight-bearing, and poor footwear.
Health care system failures	Inadequate patient education and monitoring of glycemic control and foot care.

Infections and compromise of the foot vessels

Puncture or penetrating wounds of the plantar region or the web space infections may go up in the central non expansible plantar space. The inflammatory exudates that collects causes pressure on the small arteries in the tissues and will lead to thrombosis or obliteration. This will lead to gangrene.[65]

Recognition of wound infection[66]

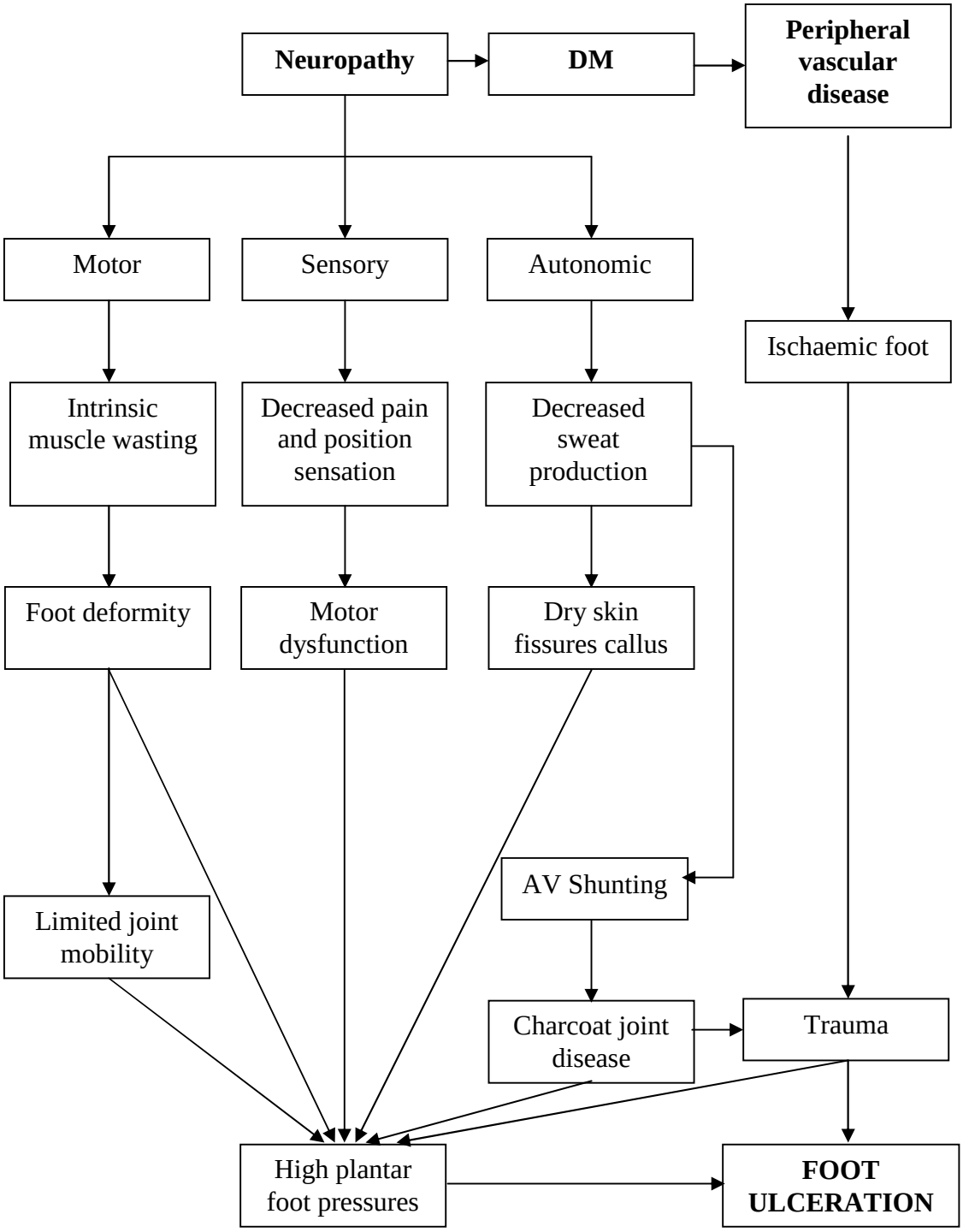
The inflammatory response is a protective mechanism that aims to neutralise and destroy any toxic agents at the site of an injury and restore tissue homeostasis. The classic signs of infection include:

- Localised erythema.
- Localised pain.
- Localised heat.
- Oedema.

Further criteria include:

- Abscess.
- Discharge which may be viscous in nature, discoloured and purulent.
- Delayed healing not previously anticipated.
- Discolouration of tissues both within and at the wound margins.
- Unhealthy granulation tissue.
- Abnormal smell.
- Wound breakdown associated with wound pocketing/bridging at base of wound.

Figure 6. Clinical pathways leading to foot ulceration[67,68]



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 Charcoats neuropathy.

Classification

The Wagner system has been widely used for 25 years for grading of diabetic foot ulcer.[69,70]

Wagner Ulcer Classification System

Grade	Lesion
0	No open lesions; may have deformity or cellulitis.
1	Superficial diabetic ulcer (partial or full thickness).
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis.
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis.
4	Gangrene localized to portion of forefoot or heel.
5	Extensive gangrenous involvement of the entire foot.

Wagner ulcer classification system was developed for the "dysvascular" foot. It was skewed toward severe disease and contains all infections within a single grade.

Consensus is developing that the key issues in classifying a diabetic foot wound are its depth (in particular, which tissues are involved) and whether the wound is complicated by either ischemia or infection. The International Consensus on the Diabetic Foot recently published a preliminary progress report on a diabetic foot ulcer classification system for research purposes.[69,71,72] The key elements are summarized by the acronym PEDIS (perfusion, extent/size, depth/tissue loss, infection, and sensation).

PEDIS Classification

Clinical Manifestations of Infection	Infection Severity	PEDIS Grade*
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of more than or equal to 2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends less than or equal 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but who has one of the following characteristics: cellulitis extending more than two cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (for example, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

*** PEDIS indicates perfusion, extent/size, depth/tissue loss, infection, and sensation.**

MEDICAL AND SURGICAL MANAGEMENT[73]

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

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

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.

Wagner Grade 1 foot

These are patients with superficial ulcers and cellulitis. Infection is controlled with appropriate antibiotics and debridement if required. Ulcers occur because of repetitive pressures Pressure is relieved by complete bed rest, use of total contact cast, walker, braces etc. Associated vascular insufficiency has to be corrected by vascular reconstruction.

Wagner Grade 2 and Grade 3 feet

These are patients with deep ulcers, with or without complications like abscesses and osteomyelitis. Aggressive surgical debridement, excision of the infected bone and vascular reconstruction if necessary is the mainstay of the treatment. To avoid recurrence education about foot care is essential.

Wagner Grade 4 and 5 feet

These are patients with localized or extensive gangrene. Management is by appropriate minor or major amputation followed by vascular reconstruction.

Figure 7. Approach to treating a patient with diabetic foot wound[71]

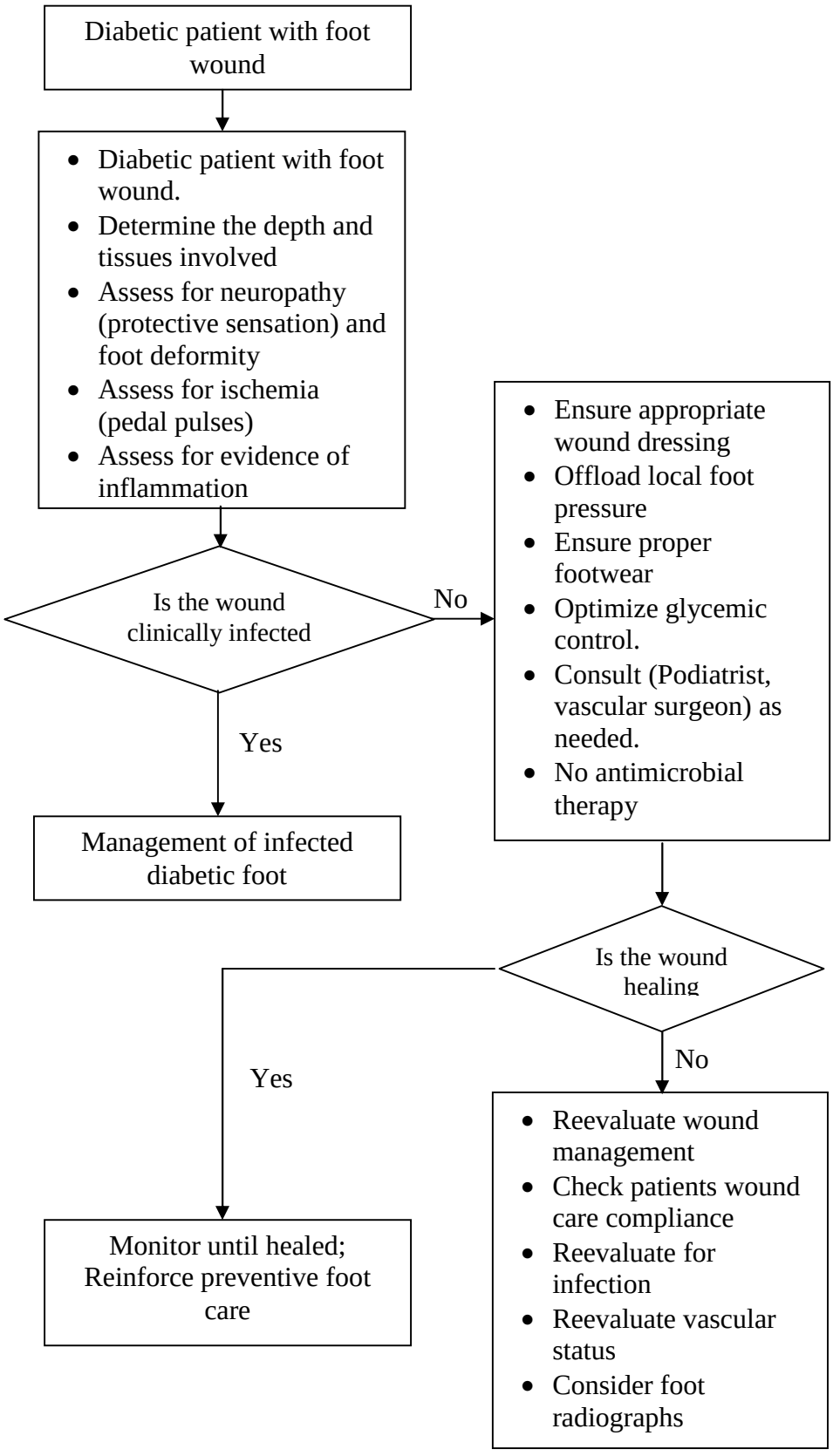


Figure 8. Approach to the management of infected diabetic foot[71]

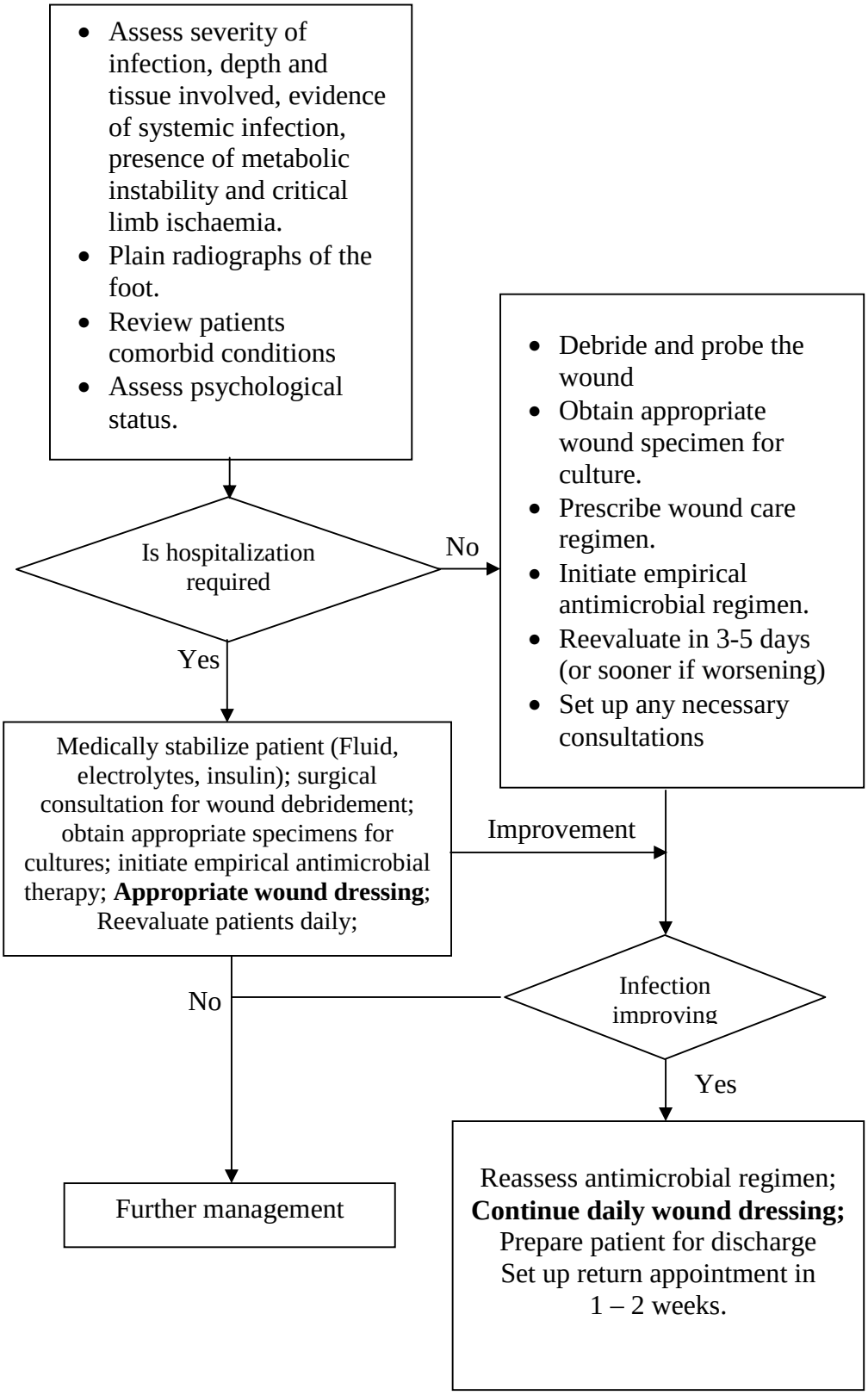
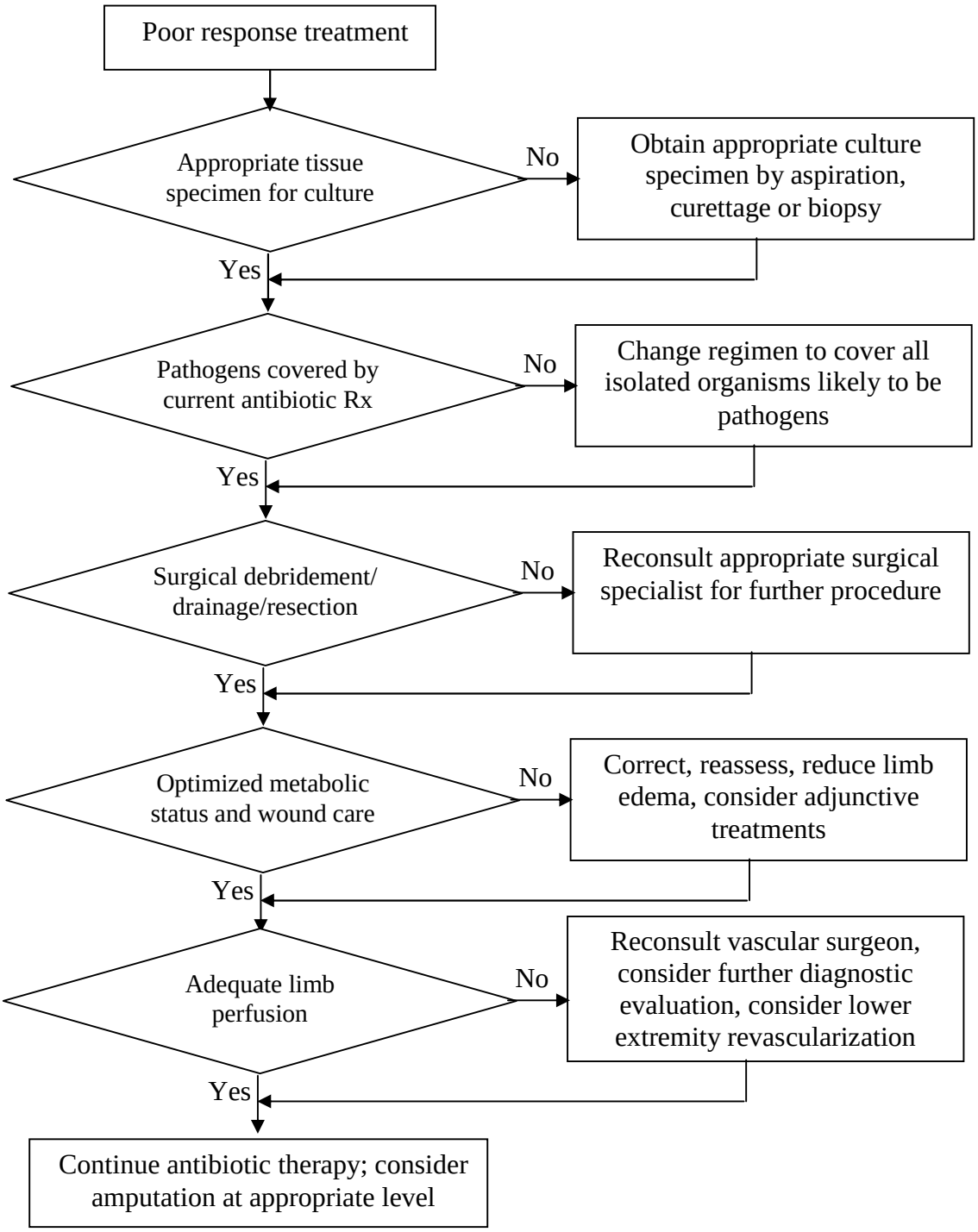


Figure 9. Approach to the patient of infected diabetic foot not responding to the treatment[71]



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 spiders webs, new-born puppies boiled in oil of white lilies, and red-hot pokers to cauterise 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.[74]

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.[74]

Physiology of wound healing[74]

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 result 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.

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.

Where healing is protracted as a result of significant tissue loss (as in deep pressure sores) or due to underlying pathology (venous leg ulcers) chronic wounds occur. 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[75]

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.

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.

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.

PMNs 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 devitalised 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'.[75]

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 synthesise 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.

Collagen synthesis continues for many months after wound closure, but also undergoes continual 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.

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.[76]

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.[77] However, the precise nature of the defect(s) leading to non-healing remain to be defined.

Moisture and wound healing

In 1962, Winter[78] 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 pO2 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 carbon dioxide, and a fall in pH. A low pO2 provides optimal conditions for fibroblast regeneration, possibly stimulating the process and increasing the rate of advance of granulation tissue.[74]

The concept that hypoxia stimulates healing was further supported by Knighton and co-workers[79] 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[80] demonstrated that the acidification of wound surfaces increased healing. Varghese and co-workers[81] 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 exudate and heat, and 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.[74]

Local treatment

Uncontrolled diabetes affects infection and infection adversely affects diabetes. The basic rules in treating any foot infection are;[74]

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.

Drainage

Drainage means opening all abscesses, probing carefully, and laying open all sinus tracts, debriding all necrotic tissue and providing unhindered dependent drainage of pus in the resting foot. The pus must drain down and out. Gas in the tissues can often be felt as crepitus or may be the first detected on x-ray film. This is a serious finding and must be treated immediately by open drainage of all infected spaces and prompt i.v. antibiotics.[74]

Drainage of an infected area may involve amputation of a necrotic toe or toes or even an open amputation. Such amputations are drainage procedures primarily. The avascular joints tolerate infection, badly and ultimately the infected joints in the toes and the feet have to be removed. When an infected area has been enclosed, it is important to plan and attempt to salvage tissue for a possible definitive wound closure.[74]

Dressings

Most foot infections do not require extensive incisions and debridement, yet the principles must always be remembered, Dressings are used to serve the following purposes.[74]

1. Contain wound drainage.
2. Debride a wound
3. Protect an area from trauma
4. Protect an area from contamination
5. Promote proper wound healing

The basic equipment necessary for bedside foot care is

1. Sterile debridement set containing
    a. Sharp scissors for debriding
    b. Blunt ended needle wound probe
    c. Smooth forceps
2. Sterile toenail clippers
3. Sterile guaze dressings
4. Tube guage, paper tape, culture tubes
5. Medicines
    a. Povidone iodine 2.5% - Bactericidal
    b. Dakin’s solution (chlorazene 0.25%)
    c. Bacitracin ointment — antibacterial
    d. Vasceline guage
    e. Normal saline

Patients suffering from diabetic foot ulcers need special care. Infection of the diabetic ulcer can have a serious consequences. The challenges in treating diabetic foot ulcers includes prolonged hospital stay, high morbidities, medical expenses and sometime leads to lower limb amputation. Dressing is one of the important part of the treatment of the diabetic ulcer. The types of wound dressing used in diabetic foot ulcer are;[74]

1. Traditional dressing
    a. Gauze dressing
2. Modern wound dressing (Occlusive / moist wound dressing)
    a. Alginate Dressings
    b. Amorphous hydrogels
    c. Hydrogel Dressings
    d. Hydrocolloid Dressings
    e. Composite Dressings
    f. Transparent Films

INSULIN LIKE GROWTH FACTORS

Recent technological advances offer new interactive therapies that may serve to accelerate wound healing. These include topical growth factors, bioengineered tissue, negative pressure therapy, and many others.[49]

When IGF was discovered, it was found to be somewhat structurally similar to insulin (hence its name). Interestingly, topical insulin accelerated wound healing, perhaps because insulin is chemically similar to IGF-1. Growth hormone secreted by the pituitary gland causes the liver to produce IGF-1, which

encourages cell growth and maintenance and repair in a variety of tissues. Many tissues in the body (including muscle, GI tract, skin, as well as many others) have receptors for IGF-1. IGF-1 and IGF-2 are important in skeletal muscle repair and regeneration. IGF-1 is available, usually at medical research institutions or in medical trials. Topically applied insulin itself accelerates wound healing, perhaps because of its chemical similarity to IGF-1. There are also nutrients like dihydroepiandrosterone (DHEA) that can increase IGF-1 levels.[82]

Growth factors applied topically to wounds can accelerate wound healing by stimulating granulation tissue formation and enhancing epithelialization. This has been suggested by several, different studies of topically applied growth factors. It is clear, however that topical growth factors therapy should not be considered as a substitute for good wound care, including surgical debridement, or revascularization.[83]

Growth factor therapy has shown considerable promise in wound therapy in patients with diabetes. Topically applied growth factors have significantly accelerated wound repair in diabetic wounds. One possible reason for their success is the relative deficiency of growth factors in chronic wound fluid due to decreased supply, increased binding, or increased degradation of the naturally occurring growth factors.[49]

Numerous growth factors are important in wound healing. Platelet-derived growth factor (PDGF), fibroblast growth factor, and epidermal growth factor have been shown to accelerate tissue repair in an experimental wound model. These agents applied locally resulted in a 2-fold increase in

reepithelialization of the wound. Other combinations of growth factors had significant effects on wound healing. In human studies, recombinant PDGF had significant beneficial effect on wound healing. This approach is now accepted therapy for the treatment of peripheral ulcers. Insulin is one of the primary anabolic hormones in the body, and numerous studies have shown beneficial effects of insulin therapy on wound healing. Insulin increases wound tensile strength and stimulates protein anabolism in skin and muscle.[49]

Studies in animals with experimental wounds have defined some abnormalities due to insulin and growth factor action and metabolism. Insulin resistance is a consistent finding, which may be due to postreceptor abnormalities or increased insulin degradation in wound fluid. Growth factor degradation is also increased in experimental wound fluid.[49]

Timely healing moves through a precise stepwise progression dependent on communication and precise interaction between multiple cell types (*e.g.* platelets, neutrophils, macrophages, fibroblasts, endothelial cells, and epithelial cells). The communication is carried out by chemical mediators, such as growth factors (*e.g.* PDGF, insulin, epidermal growth factor, TGF, and keratinocyte growth factor) and cytokines (*e.g.* ILs and TNF). Analysis of wound fluid from both healing wounds and nonhealing wounds shows striking differences. Nonhealing wounds contain higher levels of inflammatory cytokines, fewer active growth factors, and higher levels of proteases. It can be postulated that inadequate growth factors may be partially attributable to the presence of the excessive proteases. Matrix metalloproteases have been shown to be harmful to the wound-healing process, with concentrations of matrix metalloproteases

increased up to 65-fold in biopsies of diabetic foot ulcers. Proteases are necessary in appropriate quantities and at the appropriate times for proper wound healing. Excessive proteolytic activity may be harmful.[49]

Insulin-degrading activity is present in experimental wounds in animals, but no previous study has examined this activity in human wounds. In the present study we show that insulin-degrading activity is present in human wound fluid, and that the activity is higher in subjects with diabetes. The biochemical properties of the wound fluid insulin-degrading activity were consistent with the properties of the insulin-degrading enzyme (insulysin).[49]

A randomized, double-blind, placebo-controlled trial[25] was conducted to determine the safety and efficacy of topical insulin on healing in 45 patients (29 men, mean age for both groups 40.62 years, range 12 to 71 years) with noninfected acute and chronic extremity wounds. Patients were randomly assigned to twice-daily topical application (spray) of 1 cc saline 0.9% for each 10 cm^2 of wound with or without 10 units (0.1 cc) of insulin crystal. The endpoint was complete wound closure. Systemic glucose levels were measured before and 1 hour after treatment application. No patients developed signs or symptoms of hypoglycemia and glucose levels pre- and post-application did not differ significantly. Time to healing did not differ significantly between treatment groups. Healing rates were affected by baseline wound area, patient age, wound type (acute versus chronic), and treatment group. The mean rate of healing was 46.09 mm^2/day in the treatment and 32.24 mm^2/day in the control group ($P = 0.029$), independent of baseline wound size. In this study, the topical application

of insulin was safe and effective. Authors recommended clinical studies with a larger sample on patients with diabetes mellitus.

Literature demonstrates that, despite evidence of a significant role for topical insulin in the promotion of wound healing in several animal models,[18,84-88] there has been little work done in humans.[23] More research is needed to investigate a potential role for topical insulin in the management of wound healing.

Prevention of diabetic foot ulcers

Prevention of ulceration and recurrence once ulceration has occurred are the ultimate goals of any modern team approach to the diabetic foot. Wagner's Grade 0: Foot are the patients who are potentially "at risk" to develop ulcer or infection due to varying degree of neuropathy and joint deformities, They need regular assessment annually for neuropathy and vascular status. Hence the role of proper footwear and hygiene cannot be overemphasized. The diabetic patient and his family must establish a routine for daily foot and shoe inspection and hygiene. Every patient must be taught to shake his shoes at and inspect them prior to wearing. Proper hygiene must become a religion. Washing the feet everyday with mild soap and rinsing and drying thoroughly especially between the toes are adviced. The physician or health care provider must always set the example. Controlling blood glucose, weight, and blood pressure; eliminating smoking; encouraging daily exercises are important, Periodical neurological and vascular examinations are important. Early recognition and prompt reporting of a problem are encouraged.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum over a period, from 1st January 2011 to 31st December 2011.

Study design

The study design was one year hospital based randomized controlled trial.

Study period and duration

The present one year study was conducted during the period of January 2011 to December 2011.

Place

This study was carried out at Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients presenting with diabetic foot ulcers at Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum

Sample size

A total of 60 patients with diabetic foot ulcers were studied.

Sampling procedure

As the effect size is not available, by applying thumb rule a total of 60 cases divided into two groups that is, 30 each in topical insulin (Purified human biosynthetic neutral plain insulin) and normal saline were studied.

Randomization

Based on the envelope method patients were randomized divided into two groups that is;

- Group A (n=30) – Patients in this group underwent dressing with topical insulin (Purified human biosynthetic neutral plain insulin).
- Group B (n=30) – Patients in this group underwent dressing with normal saline.

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 blood glucose levels between 110 and 130 gm/dL.
- Patients with grade I and II ulcers of 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 enroll in the study.

Blinding

Syringes were filled with normal saline and insulin and were labeled by pharmacist and both patient and surgeon who did the dressing were blinded.

Ethical clearance

Prior to the commencement of the study the study was approved from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients satisfying selection criteria were explained about the nature of study and a written informed consent was obtained before enrollment (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. Patients were interviewed for the history and a thorough physical examination was conducted including vitals and systemic examination. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

Routine investigations such as complete blood count, blood urea, fasting blood sugar, serum protein levels, blood urea, serum creatinine and X-ray foot (AP and lateral view) and special investigation such as colour doppler were done.

Procedure

Wound discharge was sent for culture and sensitivity if present. Empirical antibiotics namely ciprofloxacin and metranidazole were started and changed to sensitive antibiotics after sensitivity report. Debridement was done if necessary.

Dressing

Group A

In Group A, one cc normal saline with 10 IU insulin for each 10 cm^2 wound was used

Group B

In group B plain normal saline was used which was one of the standard procedure for ulcer dressings.

Study variables

Ulcer was assessed by the investigator at the beginning of the study and at the end of the study (Investigator being the staff and residents who were blinded to study). Ulcer mapping was made and size was recorded. Size was measured twice and mean of both the measurements were considered as size of the wound.

The dressing was changed every day. Final wound area was measured on 14th day. During the course of dressing wound was observed for granulation, tissue quality, discharge and control of infection at the end of each week and recorded.

Outcome was measured in terms of wound reduction between the two groups. Data was tabulated and the two groups were compared with reference to area and percentage of reduction.

Statistical analysis

The data obtained was tabulated, categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test. Continuous data was expressed as mean ± standard deviation and comparison was done using student unpaired 't' test. A 'p' value of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

The present one year hospital based randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 60 patients with diabetic foot ulcers were studied. Based on the envelope method patients were randomized into two groups that is;

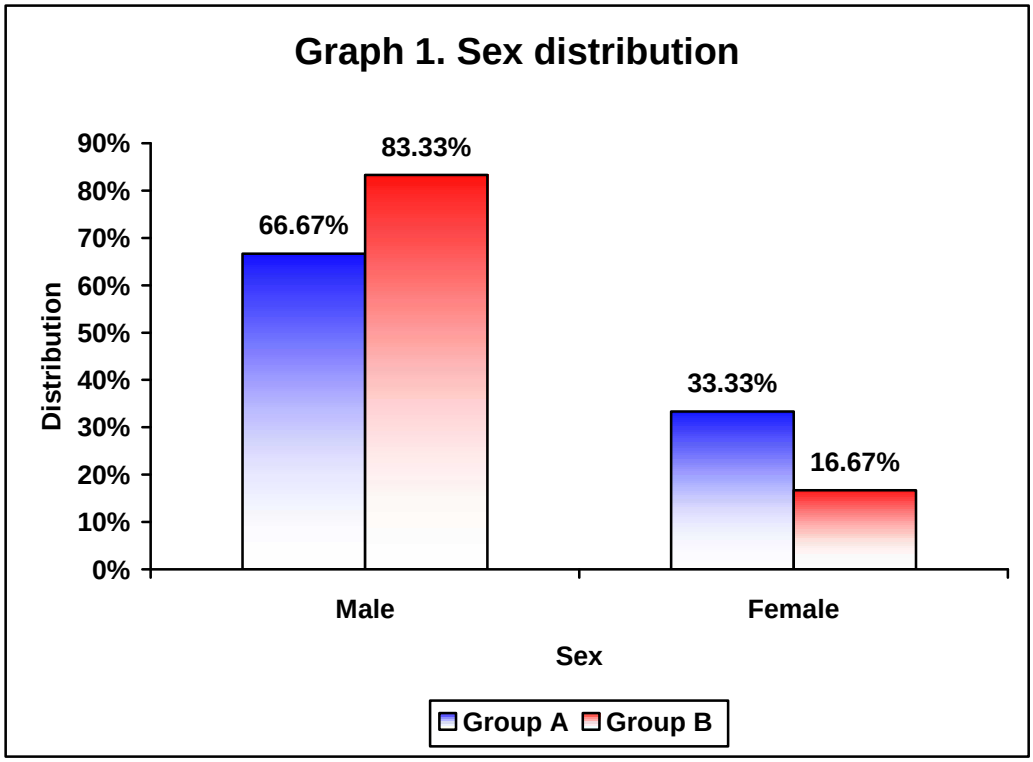
- Group A (n=30) – Patients in this group underwent dressing with topical insulin (Purified human biosynthetic neutral plain insulin).
- Group B (n=30) – Patients in this group underwent dressing with normal saline.

Data obtained was tabulated on Microsoft excel spreadsheet and analysis was done. The final results were tabulated as below.

Table 1. Sex distribution

Sex	Group A (Insulin) (n=30)		Group B (Normal saline) (n=30)	
	Number	**Percent**	**Number**	**Percent**
Male	20	66.67	25	83.33
Female	10	33.33	5	16.67
Total	**30**	**100.00**	**30**	**100.00**

x^2 = 2.41 **dF = 1** **p = 0.121**

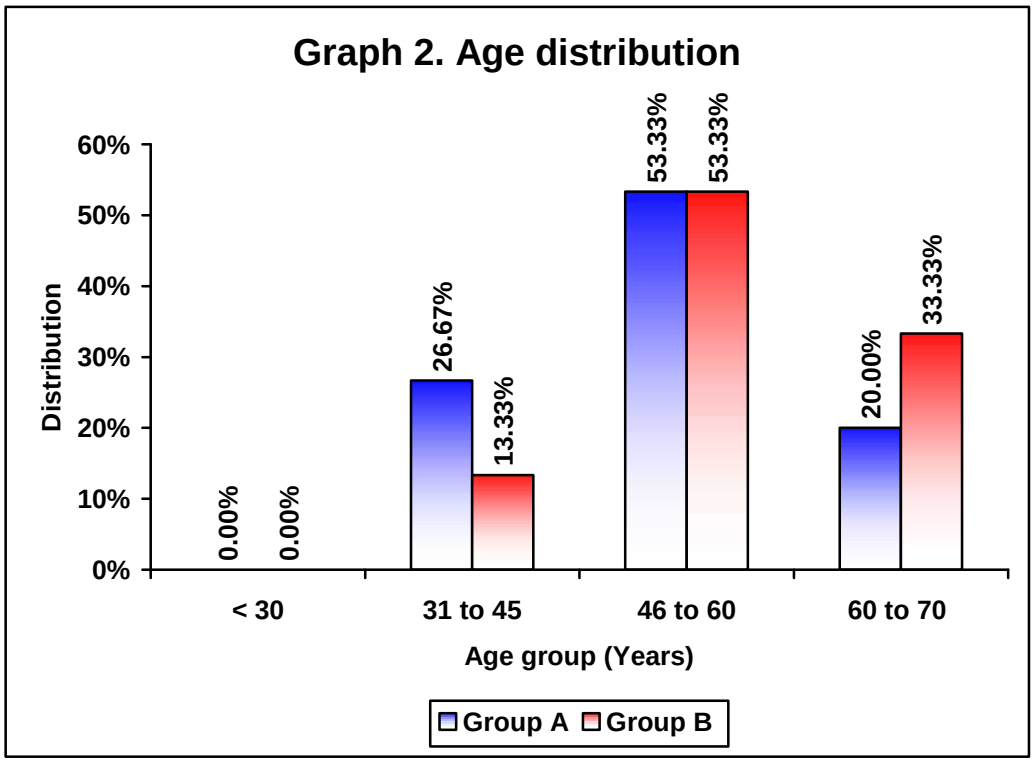


In this study majority of the patients were males in both the groups (66.67% in group A and 83.33% in group B) with male to female ratio of 2:1 in group A and 4:1 in group B.

Table 2. Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
< 30	0	0.00	0	0.00
31 to 45	8	26.67	4	13.33
46 to 60	16	53.33	16	53.33
60 to 70	6	20.00	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

x^2 = 2.33 **dF = 2** **p = 0.311**

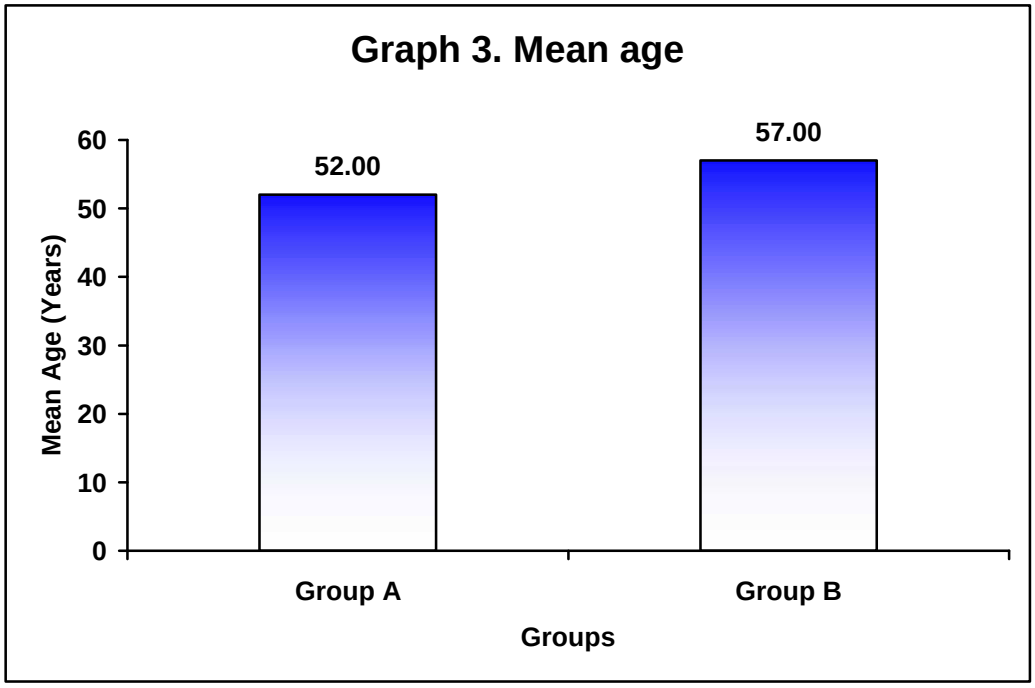


In this study most of the patients (55.33%) were aged between 46 to 60 years in both the groups.

Table 3. Mean age

Variable (Years)	Group A (n=30)	Group B (n=30)
Mean	52.00	57.00
SD	11.00	9.80

p = 0.100

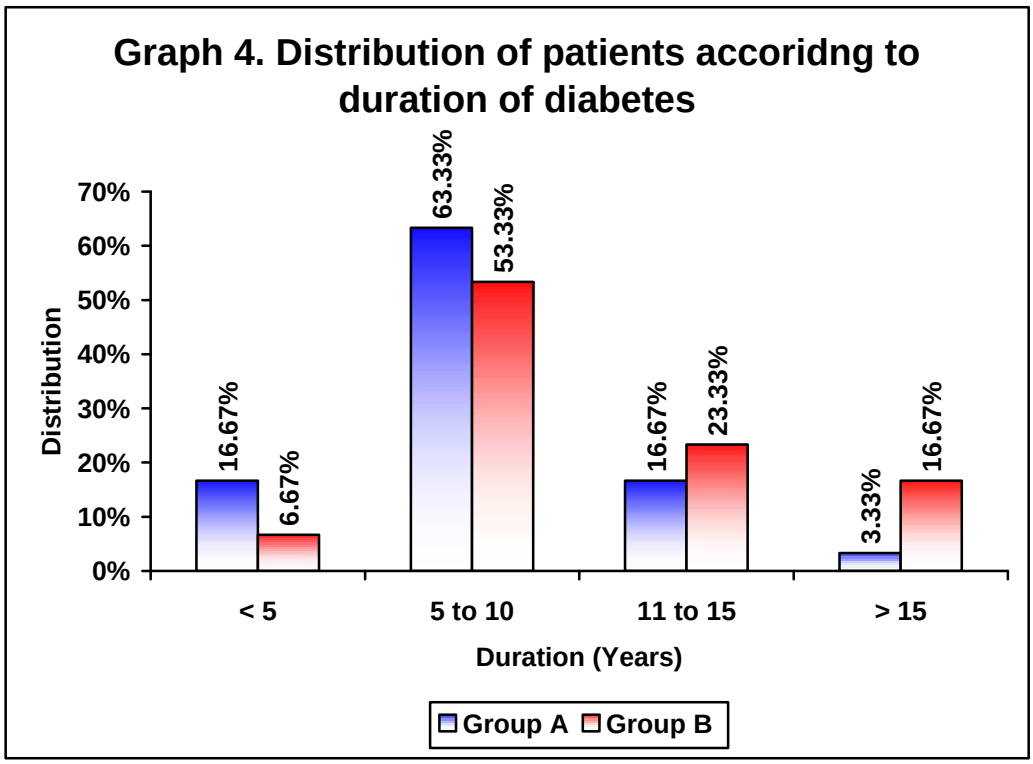


The mean age in group A was 52.00 ± 11.00 years and in group B it was 57.00 ± 9.80 years. The mean age was comparable in both the groups (p=1.000).

Table 4. Distribution of patients according to duration of diabetes

Duration (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
< 5	5	16.67	2	6.67
5 to 10	19	63.33	16	53.33
11 to 15	5	16.67	7	23.33
> 15	1	3.33	5	16.67
Total	**30**	**100.00**	**30**	**100.00**

x^2 = 4.54 **dF = 3** **p = 0.208**

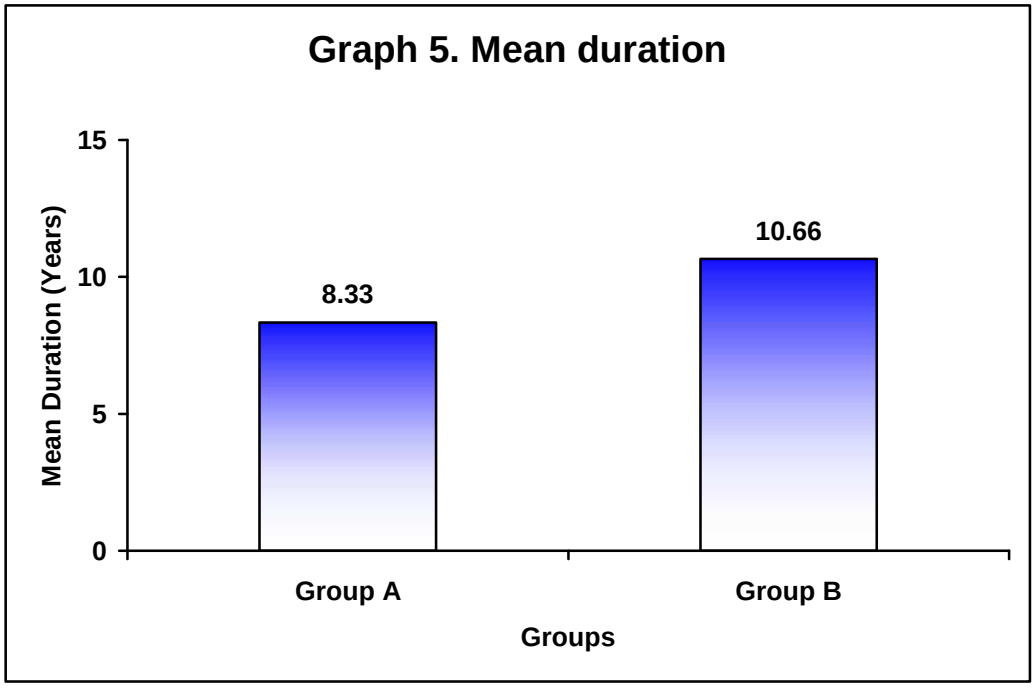


In this study most of the patients in both the groups (63.33% in group A and 53.33% in group B) had duration of diabetes between 5 to 10 years. The duration of diabetes comparable in both the groups (p=0.208)

Table 5. Mean duration

Variable (Years)	Group A (n=30)	Group B (n=30)
Mean	8.33	10.66
SD	3.44	5.40

p = 0.051

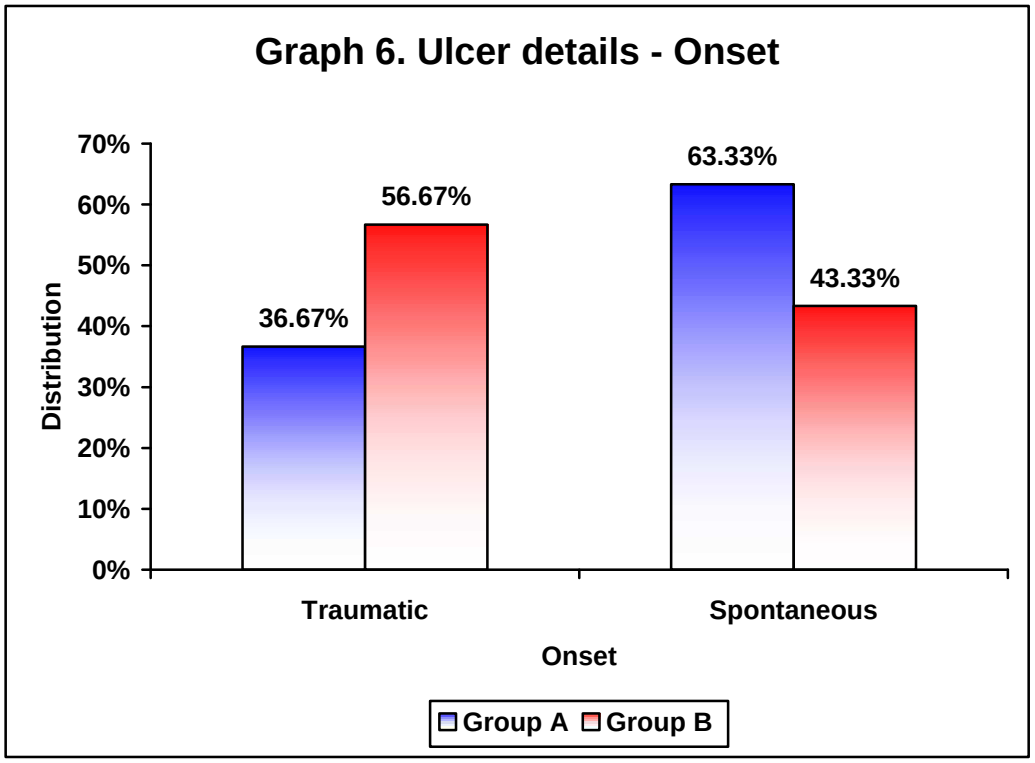


The mean duration of diabetes in group A was 8.33 ± 3.44 years and in group B 10.66 ± 5.40 years suggesting the mean duration of diabetes was comparable in both the groups (p=0.051)

Table 6. Ulcer details – Onset

Onset	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
Traumatic	11	36.67	17	56.67
Spontaneous	19	63.33	13	43.33
Total	**30**	**100.00**	**30**	**100.00**

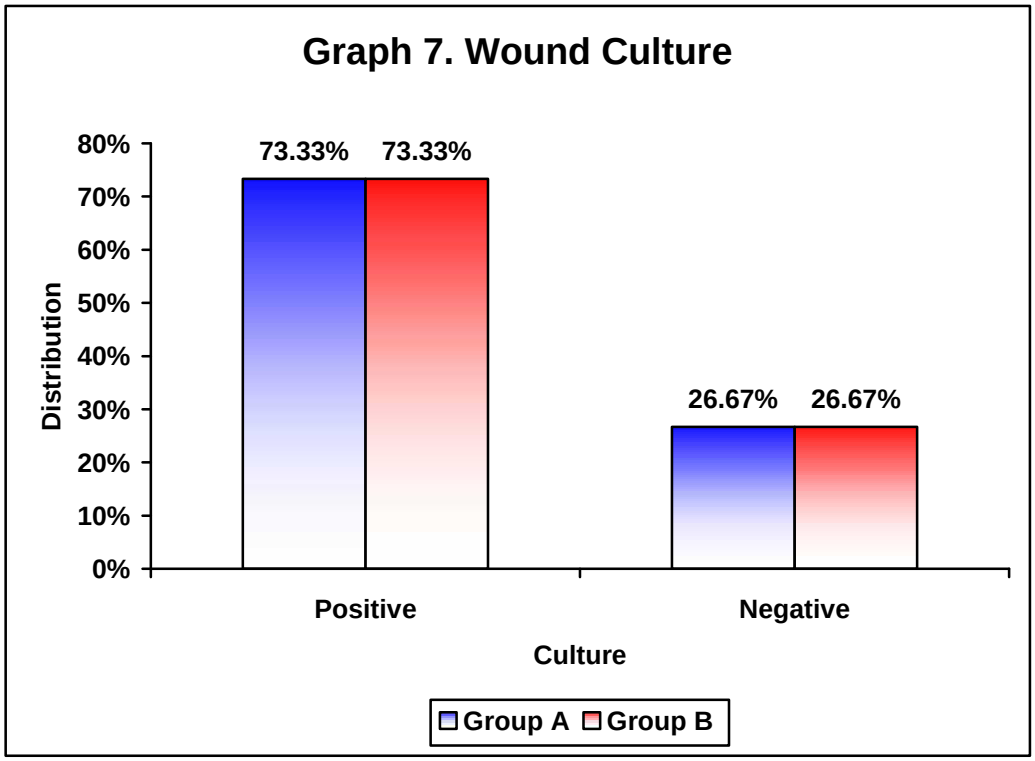
x^2 = 2.41 **dF = 1** **p = 0.121**



In the present study, 63.33% patients had spontaneous onset of ulcer in group A compared to 56.67% with traumatic onset in group B. However the onset of ulcer was comparable in both the groups (p=0.121)

Table 7. Wound culture

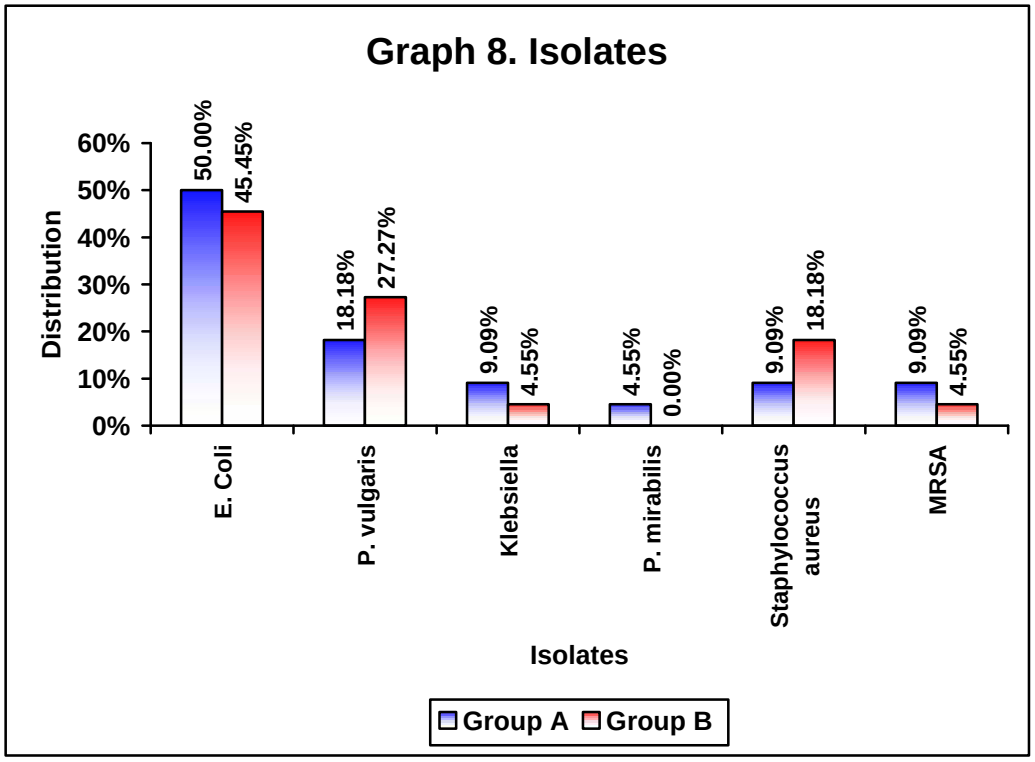
Culture	Group A (n=30)		Group B (n=30)	
	Number	**Percent**	**Number**	**Percent**
Positive	22	73.33	22	73.33
Negative	8	26.67	8	26.67
Total	**30**	**100.00**	**30**	**100.00**



In the present study wound culture was positive in 73.33% of patients each in both the groups.

Table 8. Isolates

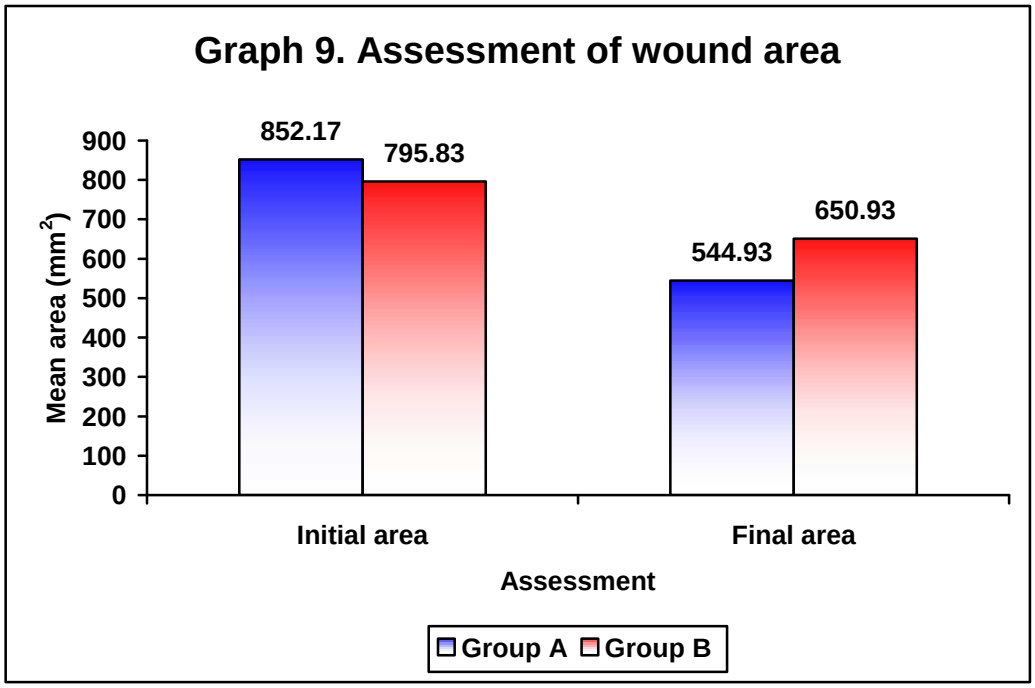
Isolates	Group A (n=22)		Group B (n=22)	
	Number	**Percent**	**Number**	**Percent**
E. Coli	11	50.00	10	45.45
P. vulgaris	4	18.18	6	27.27
Klebsiella	2	9.09	1	4.55
P. mirabilis	1	4.55	0	0.00
Staphylococcus aureus	2	9.09	4	18.18
MRSA	2	9.09	1	4.55
Total	**22**	**100.00**	**22**	**100.00**



In this study the most common organism was E. Coli in both the groups (50% in group A and 45.45% in group B).

Table 9. Assessment of wound area

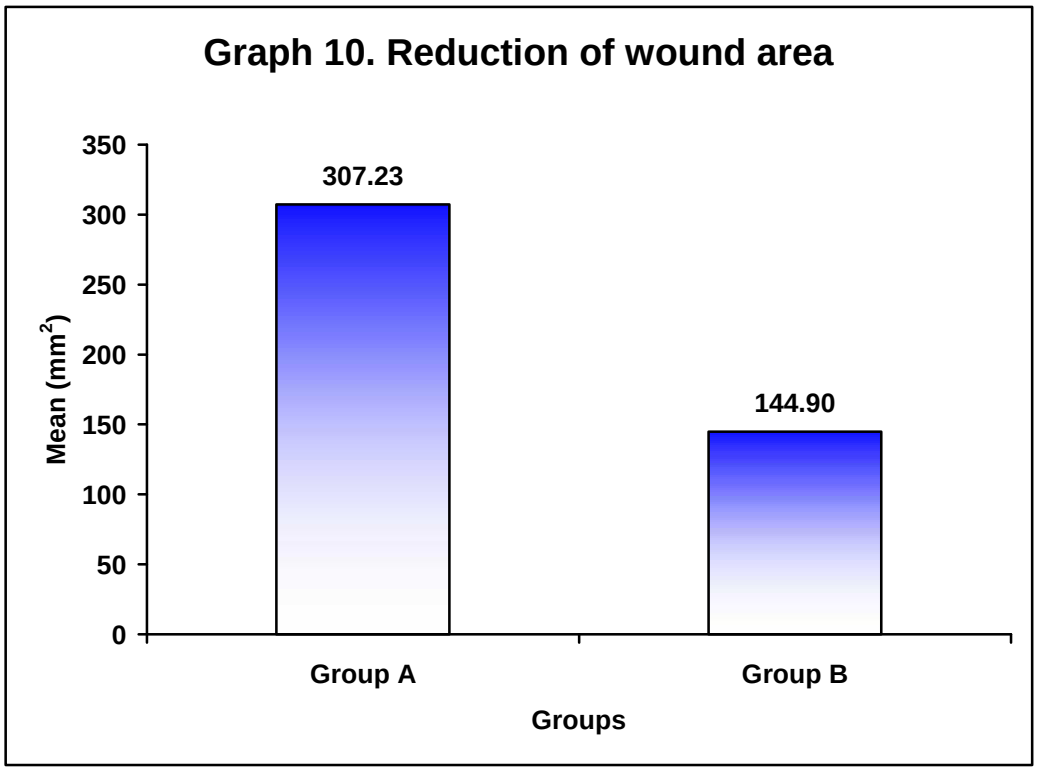
Assessment	Group A (n=30)		Group B (n=30)		p' value
	Mean	SD	Mean	SD	
Initial area (mm^2)	852.17	412.93	795.83	360.28	0.575
Final area (mm^2)	544.93	255.44	650.93	306.99	0.151

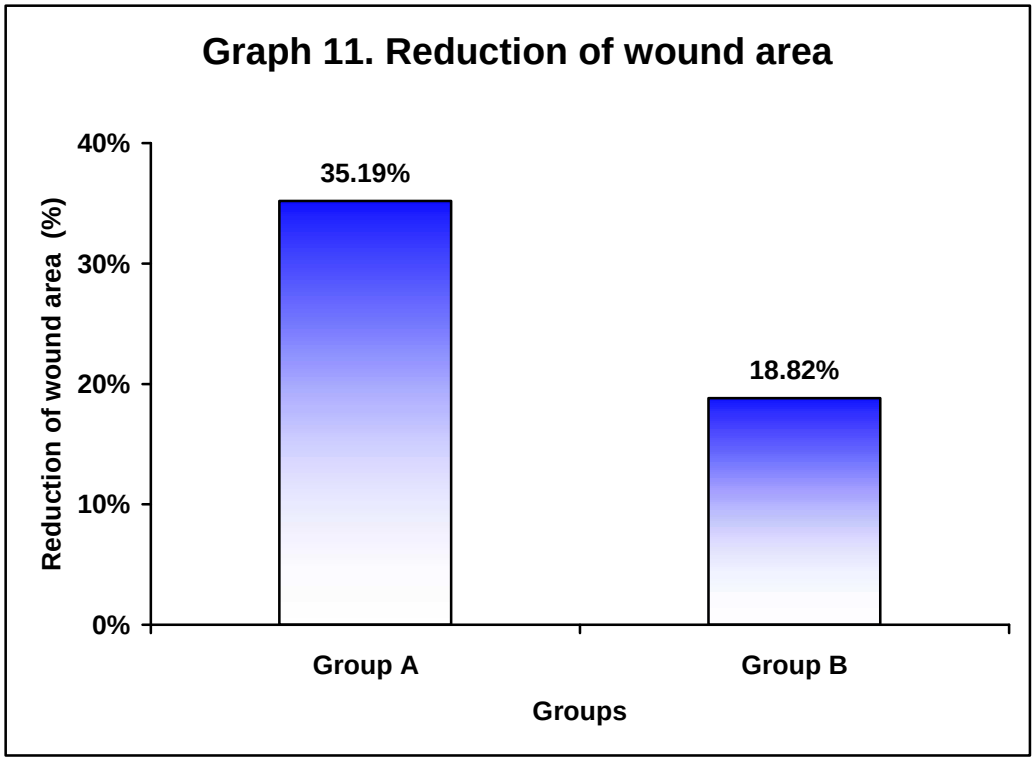


In the present study the mean initial ulcer area in group A was 852.17 ± 412.93 mm^2 in group A which reduced to 544.93 ± 255.44 mm^2. Similarly in group B the mean initial ulcer area in group B was 795.83 ± 360.28 mm^2 which reduced to 650.93 ± 306.99 mm^2.

Table 10. Reduction of wound area

Assessment	Group A (n=30)		Group B (n=30)		p' value
	Mean	SD	Mean	SD	
Reduction in area (mm^2)	307.23	169.87	144.9	64.45	<0.001
Percentage reduction (%)	35.19	6.84	18.82	4.06	<0.001



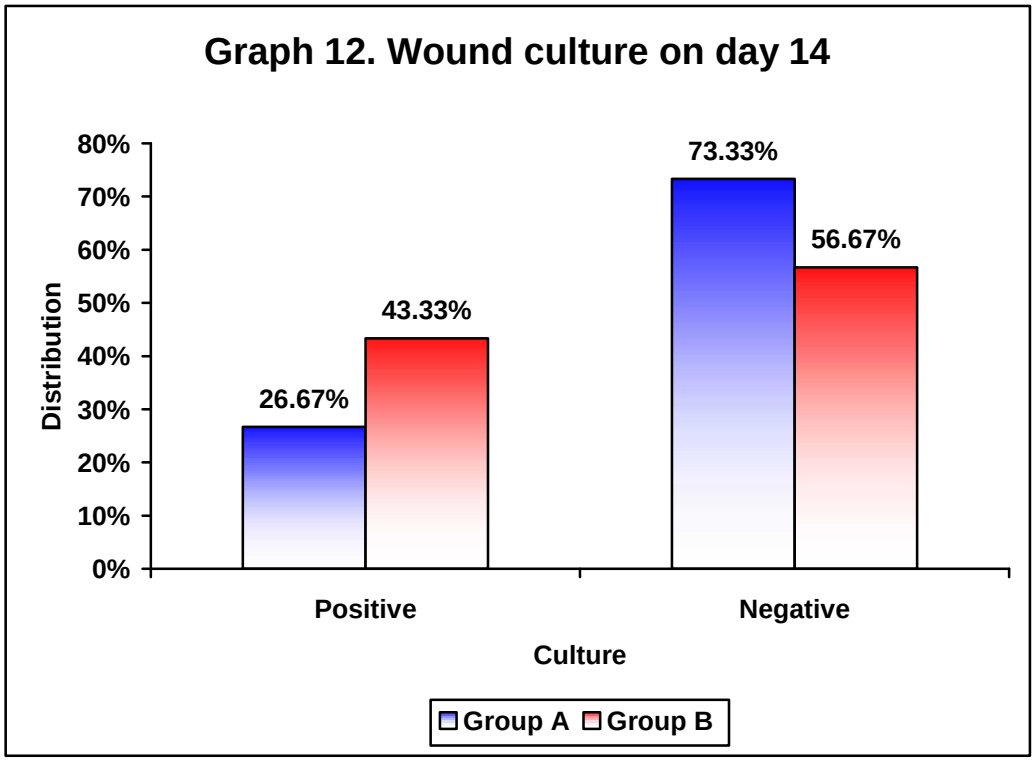


In this study among patients with group A significant reduction of mean ulcer area was observed (307.23 ± 169.87 mm^2) with higher mean percentage reduction (35.19 ± 19.00 percent) whereas in group B the mean percentage reduction was significantly less (18.82 ± 4.06 percent) with less reduction of mean final ulcer area (149.90 ± 64.45 mm^2). The difference between the percentage reduction and reduction of final ulcer area was statistically significant ($p<0.001$)

Table 11. Wound culture on day 14

Culture	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
Positive	8	26.67	13	43.33
Negative	22	73.33	17	56.67
Total	**30**	**100.00**	**30**	**100.00**

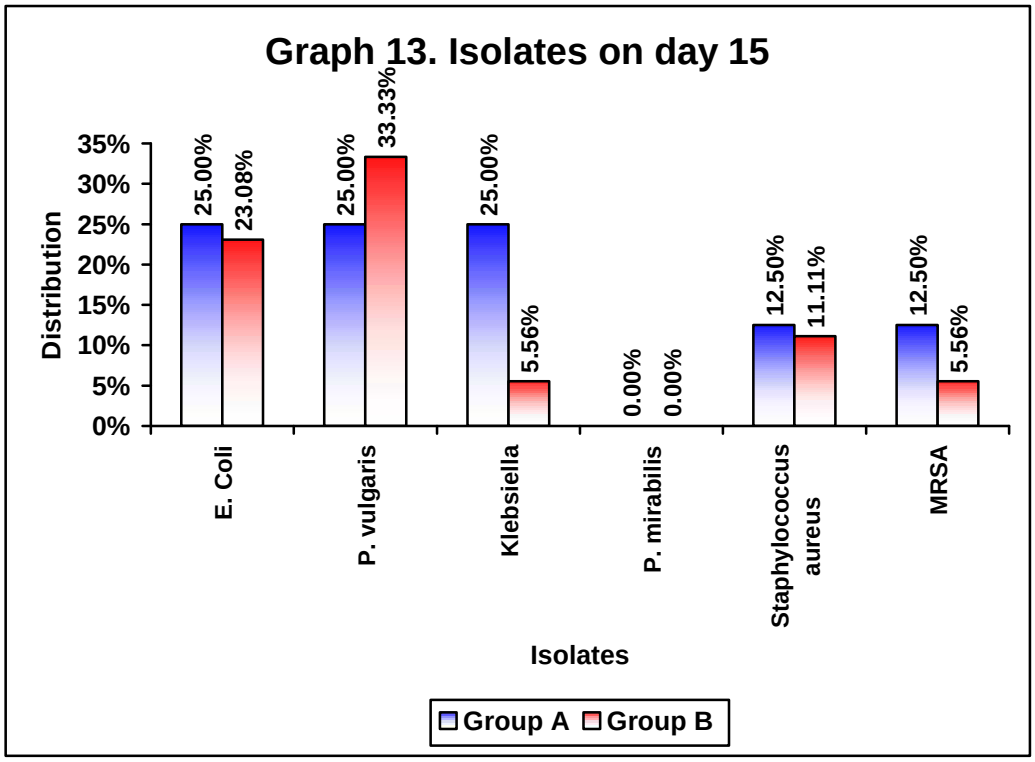
x^2 = 1.83 dF = 1 p = 0.176



In the present study, the wound culture on day 14 was negative in 73.33% patients in group A compared 56.67% in group B. However no statistically significant difference was observed between the two groups (p=0.176).

Table 12. Isolates on day 15

Isolates	Group A (n=8)		Group B (n=13)	
	Number	**Percent**	**Number**	**Percent**
E. Coli	2	25.00	3	23.08
P. vulgaris	2	25.00	6	33.33
Klebsiella	2	25.00	1	5.56
P. mirabilis	0	0.00	0	0.00
Staphylococcus aureus	1	12.50	2	11.11
MRSA	1	12.50	1	5.56
Total	**8**	**100.00**	**13**	**78.63**



In the present study, the most common isolate on day 14 was P. vulgaris in group B (33.33%) and in group A it was E. Coli and P.vulgaris (25%).

Chapter 6

Discussion

DISCUSSION

Diabetic foot ulcers are common and estimated to affect 15% of all diabetic individual during their lifetime. Patient suffering from diabetic ulcer often require hospitalization. One of the major causes of non-healing of ulcer in diabetes is infection. It is caused by a variety of micro-organism. Most common are *Staphylococcus aureus* and *Pseudomonas aeroginosa* which invade the wound and multiply, producing harmful toxic substances, causing destruction of tissue and disturbance in wound healing.[5]

The management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear,[7,8] daily saline or similar dressings to provide a moist wound environment,[9] debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present,[10,11] optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings.[11,12]

The present study was undertaken to compare the effect of topical insulin and normal saline dressing in healing of diabetic foot ulcers.

The present one year hospital based randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 60 patients with diabetic foot ulcers were studied. Based on the envelop method, patients were divided into two groups of 30 patients each that is

group A (Patients in this group underwent dressing with topical insulin) and group B (Patients in this group underwent dressing with normal saline).

In this males (66.67% in group A and 83.33% in group B) outnumbered females in both the groups. The male to female ratio was 2:1 in group A and 4:1 in group B (p=0.121). Most of the patients (55.33%) were aged between 46 to 60 years in both the groups. The mean age in group A was 52.00 ± 11.00 years and in group B it was 57.00 ± 9.80 years (p=1.000) suggesting the demographic characteristics of the study population were comparable in both the groups.

In this study most of the patients in both the groups (63.33% in group A and 53.33% in group B) had duration of diabetes between 5 to 10 years (p=0.208). The mean duration of diabetes in group A was 8.33 ± 3.44 years and in group B 10.66 ± 5.40 years (p=0.051). These findings suggest the characteristics of diabetic history was comparable in both the groups.

In the present study, 63.33% patients had spontaneous onset of ulcer in group A compared to 56.67% with traumatic onset in group B (p=0.121). The wound culture was positive in 73.33% of patients each in both the groups. The most common organism was E. Coli in both the groups (50% in group A and 45.45% in group B) suggesting the equal distribution of patients with regard to ulcer characteristics.

In the present study the mean initial ulcer area in group A was 852.17 ± 412.93 mm^2 in group A which reduced to 544.93 ± 255.44 mm^2. Similarly in group B the mean initial ulcer area in group B was 795.83 ± 360.28 mm^2 which

reduced to 650.93 ± 306.99 mm^2. However the mean ulcer area at beginning in the both the groups was comparable.

Among patients with group A significant reduction of mean ulcer area was observed in group A (307.23 ± 169.87 mm^2) with higher mean percentage reduction (35.19 ± 19.00 percent) whereas in group B the mean percentage reduction was significantly less (18.82 ± 4.06 percent) with less reduction of mean final ulcer area (149.90 ± 64.45 mm^2) The difference between the percentage reduction and reduction of final ulcer area was statistically significant ($p<0.001$) showing significantly favourable outcome in patients who underwent normal saline dressing.

There is scarcity of the literature showing the comparison of topical insulin and normal saline in diabetic foot ulcers.

It is known that insulin stimulates the growth and development of different cell types, and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts.[13-17] Previous data, although not well controlled, showed that topical insulin accelerates wound healing in the skin of diabetic rats and humans.[13,18-25]

A study[39] reported that, the insulin signaling pathways are upregulated in the wounded skin of normal rats, but in the wounded skin of diabetic animals these upregulations are blunted. However, when the wounded skin of diabetic rats were treated with a topical insulin cream, an acceleration of wound healing occurs, in association with a recovery in the proteins of the insulin signaling pathways.

A randomized, double-blind, placebo-controlled trial[25] was conducted to determine the safety and efficacy of topical insulin on healing in 45 patients (29 men, mean age for both groups 40.62 years, range 12 to 71 years) with noninfected acute and chronic extremity wounds. Patients were randomly assigned to twice-daily topical application (spray) of 1 cc saline 0.9% for each 10 cm^2 of wound with or without 10 units (0.1 cc) of insulin crystal. No patients developed signs or symptoms of hypoglycemia and glucose levels pre- and post-application did not differ significantly. Time to healing did not differ significantly between treatment groups. Healing rates were affected by baseline wound area, patient age, wound type (acute versus chronic), and treatment group. The mean rate of healing was 46.09 mm^2/day in the treatment and 32.24 mm^2/day in the control group (p=0.029), independent of baseline wound size. In this study, the topical application of insulin was safe and effective.

In the present study, the wound culture on day 14 was negative in 73.33% patients in group A compared 56.67% in group B. However no statistically significant difference was observed between the two groups (p=0.176). The most common isolate on day 14 was P. vulgaris in group B (33.33%) and in group A it was E. Coli and P.vulgaris (25%).

Literature demonstrates that, despite evidence of a significant role for topical insulin in the promotion of wound healing in several animal models,[18,84-88] there has been little work done in humans.[23] More research is needed to investigate a potential role for topical insulin in the management of wound healing.

Overall, in this study, topical insulin dressing provided favourable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing had positive role in reducing the infection if present.

Chapter 7

Conclusion

CONCLUSION

Based on the results of the present study it may be concluded that, topical insulin dressing provides favourable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing.

Chapter 8

Summary

SUMMARY

Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings. The present study was aimed to compare the effect of topical insulin and normal saline dressing in healing of diabetic foot ulcers.

The present one year hospital based randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 60 patients with diabetic foot ulcers were studied. Based on the envelop method, patients were divided into two groups of 30 patients each that is group A (Patients in this group underwent dressing with topical insulin) and group B (Patients in this group underwent dressing with normal saline).

In this males (66.67% in group A and 83.33% in group B) outnumbered females in both the groups. The male to female ratio was 2:1 in group A and 4:1 in group B (p=0.121). The mean age in group A was 52.00 ± 11.00 years and in group B it was 57.00 ± 9.80 years (p=1.000). The mean duration of diabetes in group A was 8.33 ± 3.44 years and in group B 10.66 ± 5.40 years (p=0.051). In the present study, 63.33% patients had spontaneous onset of ulcer in group A compared to 56.67% with traumatic onset in group B (p=0.121). The wound culture was positive in 73.33% of patients each in both the groups. The most common organism was E. Coli in both the groups (50% in group A and 45.45% in group B).

The mean initial ulcer area in group A was 852.17 ± 412.93 mm^2 in group A which reduced to 544.93 ± 255.44 mm^2. Similarly in group B the mean initial ulcer area in group B was 795.83 ± 360.28 mm^2 which reduced to 650.93 ± 306.99 mm^2. However the mean ulcer area at beginning in the both the groups was comparable. Among patients with group A significant reduction of mean ulcer area was observed in group A (307.23 ± 169.87 mm^2) with higher mean percentage reduction (35.19 ± 19.00 percent) whereas in group B the mean percentage reduction was significantly less (18.82 ± 4.06 percent) with less reduction of mean final ulcer area (149.90 ± 64.45 mm^2) The difference between the percentage reduction and reduction of final ulcer area was statistically significant ($p<0.001$) The wound culture on day 14 was negative in 73.33% patients in group A compared 56.67% in group B ($p=0.176$). The most common isolate on day 14 was P. vulgaris in group B (33.33%) and in group A it was E. Coli and P.vulgaris (25%).

Overall, topical insulin dressing provided favourable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing had positive role in reducing the infection if present.

Chapter 9

Bibliography

BIBLIOGRAPHY

1. Fauci AS, Kasper DS, Longo DL, Braunwald E, Hauser SL, Jameson JL, et al. Harrison's principles of internal medicine. United States; McGraw Hill: 2008.

2. American Diabetes Association. Clinical practice recommendations 2007. Diabetes Care 2007;30:S4.

3. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011.

4. American Diabetes Association Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004 Jan;27 Suppl 1:S5-S10.

5. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries. 2010; 30(2):75–9.

6. Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg. May 2004;187(5A):17S-24S.

7. Beuker BJ, van Deursen RW, Price P, Manning EA, van Baal JG, Harding KG. Plantar pressure in off-loading devices used in diabetic ulcer treatment. Wound Repair Regen. Nov-Dec 2005;13(6):537-42.

8. Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis. Aug 1 2004;39 Suppl 2:S100-3.

9. Edmonds M, Foster A. The use of antibiotics in the diabetic foot. Am J Surg. May 2004;187(5A):25S-28S.

10. O'Meara SM, Cullum NA, Majid M, Sheldon TA. Systematic review of antimicrobial agents used for chronic wounds. Br J Surg. Jan 2001;88(1):4-21.

11. Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, et al. Diabetic foot disorders: a clinical practice guideline. American College of Foot and Ankle Surgeons. J Foot Ankle Surg. 2000;39(5 suppl):S1–60.

12. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care: 7–8 April 1999, Boston, Massachusetts. Diabetes Care. 1999;22:1354–60.

13. Madibally SV, Solomon V, Mitchell RN, Van De Water L, Yarmush ML, et al. (2003) Influence of insulin therapy on burn wound healing in rats. J Surg Res 109: 92–100.

14. Benoliel AM, Kahn-Perles B, Imbert J, Verrando P (1997) Insulin stimulates haptotactic migration of human epidermal keratinocytes through activation of NF-kappa B transcription factor. J Cell Sci 110(Pt 17): 2089–2097.

15. Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008) Wound repair and regeneration. Nature 453: 314–321.

16. Brem H, Tomic-Canic M (2007) Cellular and molecular basis of wound healing in diabetes. J Clin Invest 117: 1219–1222.

17. Gallagher KA, Liu ZJ, Xiao M, Chen H, Goldstein LJ, et al. (2007) Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 alpha. J Clin Invest 117: 1249–1259.

18. Hanam SR, Singleton CE, Rudek W (1983) The effect of topical insulin on infected cutaneous ulcerations in diabetic and nondiabetic mice. J Foot Surg 22: 298–301.

19. Gerber RM, Van Ort SR (1979) Topical application of insulin in decubitus ulcers. Nurs Res 28: 16–19.

20. Apikoglu-Rabus S, Izzettin FV, Turan P, Ercan F (2009) Effect of topical insulin on cutaneous wound healing in rats with or without acute diabetes. Clin Exp Dermatol.

21. Belfield WO, Golinsky S, Compton MD (1970) The use of insulin in open-wound healing. Vet Med Small Anim Clin 65: 455–460.

22. Weringer EJ, Kelso JM, Tamai IY, Arquilla ER (1982) Effects of insulin on wound healing in diabetic mice. Acta Endocrinol (Copenh) 99: 101–108.

23. Greenway SE, Filler LE, Greenway FL (1999) Topical insulin in wound healing: a randomised, double-blind, placebo-controlled trial. J Wound Care 8: 526–528.

24. Wilson JM, Baines R, Babu ED, Kelley CJ (2008) A role for topical insulin in the management problematic surgical wounds. Ann R Coll Surg Engl 90: 160.

25. Rezvani O, Shabbak E, Aslani A, Bidar R, Jafari M, et al. (2009) A randomized, double-blind, placebo-controlled trial to determine the effects of topical insulin on wound healing. Ostomy Wound Manage 55: 22–28.

26. Anandi C, Alaguraja D, Natarajan V, Ramanathan M, Subramaniam CS, Thulasiram M, et al. Bacteriology of diabetic foot lesions. Ind J Med Microbiol 2004; 22 (3): 175-8

27. Von MJ, Minowski O. Diabetes Mellitus and pancreas extirpation. Arch Exper Path Pharm 1980; 26: 371-87.

28. St. Vincent Declaration. Diabetes care and research in Europe. Diabet Med 1990; 7: 360.

29. Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance. In: Gan D, editor. Diabetes Atlas. International Diabetes Federation. 3rd ed. Belgium: International Diabetes Federation; 2006 p. 15-103.

30. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27:1047-53.

31. Diabetes. Factsheet No. 312. Geneva: World Health Organization; 2012. Available from: URL: http://www.who.int/mediacentre/factsheets /fs312/en/ Access Date: 18.06.12

32. Mohan V, Pradeepa R. Epidemiology of diabetes in different regions of India. Health Administrator 2009;XXII(1&2):1-18.

33. Boden G. Fatty acids and insulin resistance. Diabetes Care. 1996; 19(4): 394-5.

34. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363 (9403): 157-63.

35. Boulton M, Marshall J. He-Ne laser stimulation of human fibroblast proliferation & attachment in vitro. Lasers in Life Sci 1986; 1: 125-34.

36. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004; 27: 553.

37. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med 2002; 137: 25.

38. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes prevention program research group: Reduction

in the incidence of type-2 diabetes with lifestyle intervention of metformin. N Engl J Med 2002; 346: 393-403.

39. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799.

40. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group Epidemiology of the diabetes interventions and complications research group: Effect of intensive therapy on the microvascular complications of type-I Diabetes mellitus. JAMA 2002; 287: 2563-9.

41. UK Prospective Diabetes Study (UKPDS) Group (UKPDS 33). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type-2 diabetes. Lancet 1998; 352: 837-53.

42. Young, MJ, Boulton, AJ, Macleod, AF, MacLeod AF, Williams DR, Sonksen PH. et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 36: 150.

43. Franklin, GM, Kahn, LB, Baxter, J, Marshall JA, Hamman RF. Sensory neuropathy in non - insulin- dependent diabetes mellitus: The San Luis Valley Diabetes Study. Am J Epidemiol 1990; 131: 633-43.

44. Fryberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Phys 2002; 66(9): 1655-62.

45. Bowler PG, Armstrong DG, Duerden BI. Wound microbiology and associated approaches to wound management. Clin Micro Rev 2001; 14: 244-69.

46. Krizek TJ, Robson MC. Evolution of quantitative bacteriology in wound management. Am J Surg 1975; 130(5): 579-84.

47. Stranding S. Grays Anatomy. 39th ed. Philadelphia; Churchill Livingstone; 2005.

48. Snell RS. Clinical anatomy. 7th ed. Baltimore; Lippincott Williams and Wilkins: 2004.

49. Duckworth WC, Fawcett J, Reddy S, Page JC. Insulin-degrading activity in wound fluid. J Clin Endocrinol Metab. 2004;89(2):847-51.

50. Arora S, Pomposelli F, LoGerfo FW, Veves A. Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. J Vasc Surg. Mar 2002;35(3):501-5.

51. Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet. May 3 2003;361(9368):1545-51.

52. Nielson DL, Ali Y, Diabetic Foot Infections J Am Podiatric Med Assoc 2009; 99 (5): 454-8.

53. Tomic-Canic M, Brem H. Gene array technology and pathogenesis of chronic wounds. Am J Surg. Jul 2004;188(1A Suppl):67-72.

54. Edelman D, Matchar DB. Clinical and radiographic findings that lead to intervention in the diabetic patients with foot ulcers: A nationawide survey of primary care physicians. Diabetes Care 1996; 19: 755-7.

55. Smith JMB, Payne JE, Berue TV. Diabetic foot lesions ofskin and soft tissue infections of surgical importance. Chapter 14. In: The surgeons Guide to Antimicrobial Chemotherapy 2002; 218-21.

56. Pittet D, Wyssa B, Herter-Clevel C, Kursteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively a retrospective cohort study with long term follow up. Arch Inter Med 1999; 159: 851-6.

57. Bailey TS, Yu HM, Rayfield EJ. Patterns of foot examination in a diabetic clinic Am J Med 1985; 78: 371-4.

58. Frykberg RG. Diabetic foot ulcers: current concepts. J Foot Ankle Surg 1998; 37: 440-6.

59. Abergel RP, Mecker CA, Lam TS, Dwyer RM, Lesavoy MA. Uitto J. Control of connective tissue metabolism by lasers: recent developments and future prospects. J Am Acad Dermatol 1984; 11: 1142-50.

60. Yu W, Naim JO, Lanzafame RJ. The effects of photo-irradiation on the secretion of TGF and PDGF from fibroblasts in vitro. Lasers Surg Med Suppl 1994; 6: 8.

61. Maiya GA, Kumar P, Rao L. Photo Medicine and Laser Surgery: Effect of Low Intensity Helium-Neon (He-Ne) Laser Irradiation on Diabetic Wound Healing Dynamics. Photomed Laser Surg 2005; 23(2): 187-90.

62. Pandit A, Godhi AS. A randomized control trial to test the effectiveness of low level laser therapy along with conventional therapy vs conventional therapy alone in type 2 diabetic foot ulcer healing – Dissertation. Bangalore, India: Rajiv Gandhi University of Health Sciences – Karnataka; 2006.

63. Effects of 810 nm laser irradiation on in vitro growth of bacteria: Comparison of continuous wave and frequency modulated light. Lasers Surg Med 2002; 31(5): 343-51.

64. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg 2006; 117(7 Suppl): 212S-38S.

65. Newman LG, Walker J, Palestro CJ. Unsuspected osteomyelitis in diabetic foot ulcers. JAMA 1991; 266: 1246-51.

66. Cutting K, Harding K. Criteria for identifying wound infection. J Wound Care 1994; 3(4): 198-201.

67. Young MJ, Veves A, Boulton AJM. The diabetic foot: aetiopathogenesis and management. Diabetes Metab Rev 1993; 9: 109-27.

68. Pecoraro RE, Reiber GE, Burges EM. Pathways to diabetic limb amputation: basis for prevention. N Engl J Med 1994; 331: 854-60.

69. Pecoraro RE, Reiber GE. Classification of wounds in diabetic amputees. Wounds 1990; 2: 65-73.

70. Jeffcoate WJ, Macfarlane RM, fletcher EM. The description and classification of diabetic foot lesions. Diabet Med 1993; 10; 676.

71. Armstrong DG, Lavery LA, Harklens LB. Validation of a diabetic wound classification system. The contribution of depth, infection and ischemia to risk of amputation. Diabetic care 1998; 21; 855-9.

72. Foster A, Edmonds ME. Simple staging system. A tool for diagnosis and management. The diabetic foot 2000; 3: 56-62.

73. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg 2006; 117(7 Suppl): 212S-38S.

74. Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D. Systematic reviews of wound care management: (2). Dressings and topical agents used in the healing of chronic wounds. Health Technol Assess. 1999;3(17 Pt 2):1-35.

75. Dyson M, Young S, Pendle CL, Webster DF, Lang SM. Comparison of the effects of moist and dry conditions on dermal repair. J Invest Dermatol 1988;91(5):434–9.

76. Adair HM. Epidermal repair in chronic venous ulcers. Br J Surg 1977;64(11):800–4.

77. Fivenson DP, Faria DT, Nickoloff BJ, Poverini PJ, Kunkel S, Burdick M, et al. Chemokine and inflammatory cytokine changes during chronic wound healing. Wound Repair Regen 1997;5:310–22.

78. Winter GD. Formation of the scab and the rate of epithelialisation of superficial wounds in the skin of the young domestic pig. Nature 1962; 193(4812):293–4.

79. Knighton DR, Silver IA, Hunt TK. Regulation of wound-healing angiogenesis-effect of oxygen gradients and inspired oxygen concentration.Surgery 1981;90(2):262–70.

80. Leveen HH. Chemical acidification of wounds. An adjuvant to healing and the unfavourable action on alkalinity and ammonia. Ann Surg 1973;178:745–53.

81. Varghese MC, Balin AK, Carter DM, Caldwell D. Local environment of chronic wounds under synthetic dressings. Arch Dermatol 1986;122(1):52–7.

82. Wound Healing. Available from: URL: http://www.lef.org/protocols /prtcls-txt/t-prtcl-111.html Access Date: 21.08.12

83. Steed DL. The role of growth factors in wound healing. Surg Clin North Am. 1997;77(3):575-86.

84. Zhang XJ, Chinkes DL, Irtun O, Wolfe RR. Anabolic action of insulin on skin wound protein is augmented by exogenous amino acids. Am J Physiol. 2002;282:E1308–15.

85. Liu Y, Zhang X, Zhang Z, Fang PY, Xu WS. [Effects of topical application of insulin on the wound healing in scalded rats] Zhonghua Shao Shang Za Zhi. 2004;20:98–101.

86. Liu Y, Zhang X, Zhang Z, Xu WS. The influence of topical application of insulin on the formation of basement membrane in scalded rats. Zhonghua Shao Shang Za Zhi. 2005;21:445–7.

87. Zhang XJ, Chinkes DL, Sadagopa Ramanujam VM, Wolfe RR. Local injection of insulin-zinc stimulates DNA synthesis in skin donor site wound. Wound Repair Regen. 2007;15:258–65.

88. Zhang XJ, Wu X, Wolf SE, Hawkins HK, Chinkes DL, Wolfe RR. Local insulin-zinc injection accelerates skin donor site wound healing. J Surg Res. 2007;142:90–6.

Annexures

Annexure I

ANNEXURE I – CONSENT FORM

INFORMED CONSENT

Mr / Mrs / Miss _____ we are requesting you to enrol yourself in study entitled, "**COMPARATIVE STUDY OF EFFECT OF TOPICAL INSULIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A HOSPITAL BASED ONE YEAR RANDOMIZED CONTROLLED TRIAL"** is being conducted by Dr. **** *****, Post Graduate in Surgery at Jawaharlal Nehru Medical College Belgaum, Karnataka. Under guidance of Dr. ***** ***** Professor, Department of Surgery, Jawaharlal Nehru Medical College, Belgaum, under KLE University, Belgaum.

Respected Sir/Madam, we request you to enrol yourself to participate in our study as you are eligible for participating in this study. During the study you will be asked some questions regarding your present complaints and your are suppose to answer to the best of your knowledge.

Your participation in research is voluntary. If you decide to participate you are free to withdraw at any time. The purpose of research is to evaluate the safety and efficacy of topical insulin in patients with acute and chronic wounds.

Procedure involved

If you agree to enrol yourself in my study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly. You will be randomly allocated

either into Group A or Group B. Initially wound is assessed and if required debridement is done and will be dressed with either topical insulin or with normal saline daily (Both are the standard procedures for wound dressing). Wound size assessed at the end of every week. Wound is observed for granulation tissue quality, discharge and control of infection at the end of each week and noted.

Benefits and Risks

The benefits of taking part in this research are you will have early wound healing. The no observable risks associated with this study except that you will have hypergranulation.

Voluntary participation / Withdrawal

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

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 you will remain 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 at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. There is compensation or payment for such medical treatment by law.

Questions/Contact details

If you have any queries, in future or in case of study related injury or illness, you may contact. **** ******. at Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum Phone Number ***** ***** or on ***** ******.

If you have any queries about your rights as a study subject, you may call Principal and Chairman, J. N. Medical College Institutional Ethical Committee for Human Subjects Research, Ph. ***** ****** at J. N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, Mr./Mrs. _____

voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

Subject Name: _____

Signature of the participant _____ Date _____
Or Left thumb print

Witness name: _____

Signature: _____ Date _____

Investigator's name: _____

Signature: _____ Date _____

Place: _____

Annexures

Annexure II

ANNEXURE II – PROFORMA

"COMPARATIVE STUDY OF EFFECT OF TOPICAL INSULIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A HOSPITAL BASED ONE YEAR RANDOMIZED CONTROLLED TRIAL"

Investigator: **Dr. ****** ******.**
Post Graduate Student,
Department of Surgery,
J. N. Medical College, Belgaum

Name of the Guide: **Dr. ****** *******

PATIENT IDENTIFICATION DATA

Group	:	Case No.	:
IP No	:	DOA	:
Name	:	DOS	:
Sex	:	DOD	:
Age	:	Occupation	:
Address	:		

CHIEF COMPLAINTS

MEDICAL HISTORY

Peripheral neuropathy	:
Nephropathy	:
Retinopathy	:
Peripheral vascular disease	:
Cardiovascular disease	:

DIABETIC STATUS

Type :

Duration :

Medication

Oral hypoglyecemics :

Insulin :

Complications

Neuropathy :

Vasculopathy :

ULCER DETAILS

Mode of onset

Traumatic :

Spontaneous :

Pressure :

Others :

Duration :

Progress :

WOUND OBSERVATION

Site :

Size :

Shape :

Edge :

Margin :

Floor :

Base :

Discharge :

Surrounding skin :

Contraction :

NEUROLOGICAL EXAMINATION

VASCULAR EXAMINATION

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

FOOT DEFORMITIES PRESENT

Toe deformity :

Bunion :

Charcots foot :

Foot drop :

AMPUTATION

Any amputation done :

If yes, Date :

Side :

Level :

Cause :

INVESTIGATIONS

CBC :

FBS : Date: Time:

Blood urea :

Serum creatinine :

Urine

Routine :

Microscopy :

X-ray foot

AP view :

Lateral view :

Tissue culture / sensitivity

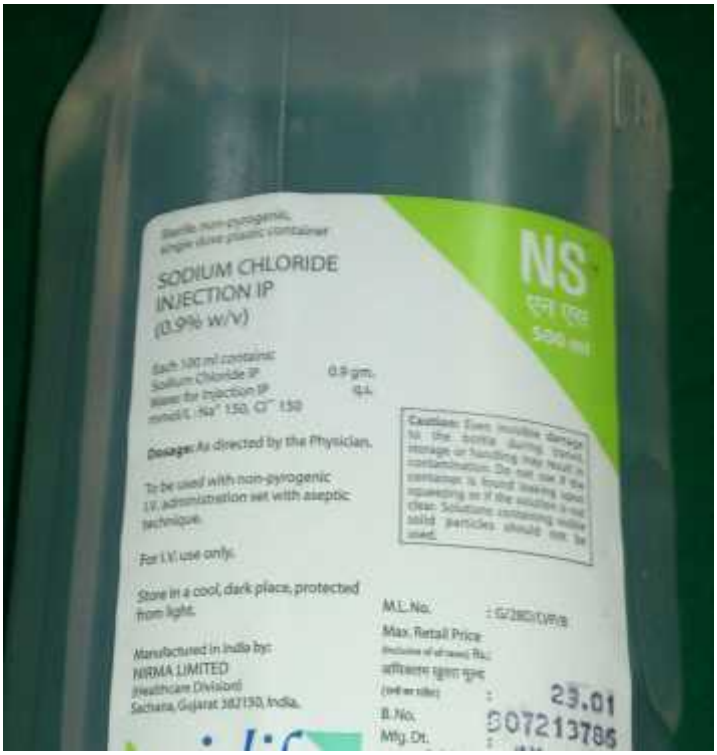
Before dressing :

After dressing :

Annexures

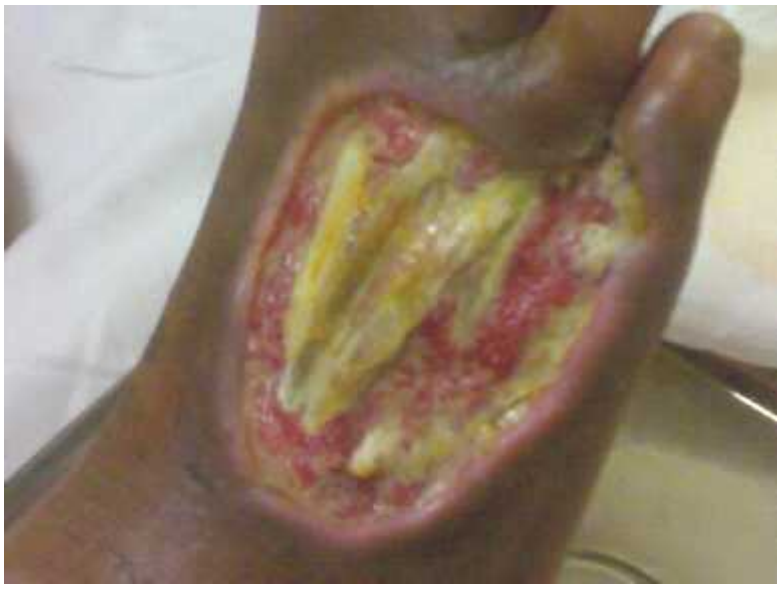
Annexure III

ANNEXURE III – PHOTOGRAPHS

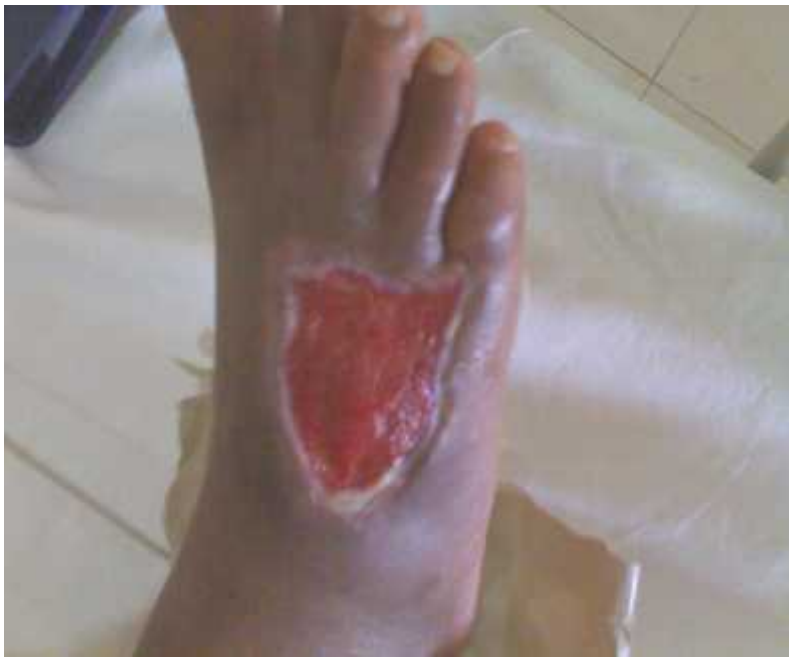


Photograph 1. Normal saline

Photograph 2. Syringe filled with insulin



Photographs 3. Ulcer size on day one in group A



Photographs 4. Ulcer size on day 14 in group A

Annexures

Annexure IV

ANNEXURE IV – MASTER CHART

-	- Negative
+	- Positive
B	- Bilateral
DA	- Dorsal Aspect
DR	- Dorsum
F	- Female
I	- Insulin
KL	- Klebsiella
LLA	- Lateral Aspect Of Left Foot
L	- Left
M	- Male
Mm	- Millimeter
MRSA	- Methicillin-resistant Staphylococcus aureus
NP	- Neuropathy
O	- Oral
PM	- Proteus Mirabilis
PS	- Pseudomonas
PTV	- Proteus vulgaris
R	- Right
SP	- Spontaneous
S	- Sole of Foot
STPH	- Staphylococcus aureus
TR	- Traumatic
VP	- Vasculopathy

ANNEXURE IV - MASTER CHART - GROUP A (TOPICAL INSULIN)

Serial number	In Patient Number	Sex	Age (Years)	DM status			Ulcer details						Vascular exam				Investigations					Final ulcer area	Change in ulcer area	Percentage reduction
																		Tissue culture						
																		Before		After				
				Type	Duration (Years)	Medication	Onset	Site	Lenth	Breadth	Area (mm2)	Discharge	Popliteal a.	Anterior tibial	Posterior tibial	Dorsalis pedis	FBS (mg/dL)	Sensitivity	Organism	Sensitivity	Organism			
1	428326	M	65	2	12	O	SP	L DR	6.7	3.2	838	+	B	B	B	B	138	+	PS	-	-	570	268	31.98
2	428427	M	75	2	6	O	SP	L DR	8.4	4.2	1166	+	B	B	B	B	134	-	-	-	-	785	381	32.68
3	451588	F	60	2	9	O	SP	L LA	9.8	6.8	642	+	B	B	B	B	122	+	PTV	-	-	400	242	37.69
4	449444	M	30	2	10	O	TR	L DR	5.8	4.2	1228	+	B	B	B	B	170	+	PTV	+	PTV	875	353	28.75
5	448462	F	39	2	12	O	SP	L DR	8.8	4.2	696	+	B	B	B	B	120	+	KL	+	KL	470	226	32.47
6	448357	M	53	2	8	O	SP	R DR	7.2	5.1	1548	+	B	B	B	B	138	+	PS	-	-	1085	463	29.91
7	444285	M	37	2	4	O	TR	R S	6.1	3.2	874	+	B	B	B	B	160	+	MRSA	-	-	580	294	33.64
8	443189	M	43	2	3	O	TR	R LA	2.2	1.1	350	+	B	B	B	B	138	+	STPH	-	-	215	135	38.57
9	441273	M	46	2	4	O	TR	L S	6.2	3.1	1248	+	B	B	B	B	154	+	PS	-	-	790	458	36.70
10	441273	M	46	2	7	O	SP	L DR	5.8	2.4	502	+	B	B	B	B	138	+	PS	-	-	317	185	36.85
11	437023	F	50	2	7	O	SP	L DR	4.7	3.2	459	+	B	B	B	B	174	+	PM	-	-	283	176	38.34
12	416061	F	44	2	8	O	SP	R DR	9.2	4.8	550	+	B	B	B	B	172	-	-	-	-	345	205	37.27
13	442214	M	69	2	10	O	SP	L DR	8.1	3.2	452	+	B	B	B	B	142	+	PS	-	-	385	67	14.82
14	436915	F	63	2	8	O	SP	L DR	8.2	3.4	390	+	B	B	B	B	128	-	-	-	-	255	135	34.62
15	441131	F	68	2	3	I	TR	L DR	6.8	7.2	335	+	B	B	B	B	184	+	PTV	-	-	210	125	37.31
16	448592	M	60	2	8	O	SP	L LA	11	7.2	500	+	B	B	B	B	154	-	-	-	-	335	165	33.00
17	447343	M	56	2	12	O	SP	R DR	5.2	3.4	417	+	B	B	B	B	190	+	PTV	+	PTV	270	147	35.25
18	446253	M	60	2	8	O	SP	L DR	9.4	5.4	396	+	B	B	B	B	170	+	KL	+	KL	345	51	12.88
19	445225	F	50	2	2	O	SP	R DR	7.2	4.1	320	+	B	B	B	B	149	+	PS	-	-	190	130	40.63
20	446217	M	49	2	10	O	SP	R DA	8.2	4.5	495	+	B	B	B	B	203	+	PS	+	PS	315	180	36.36
21	445218	M	49	2	8	O	TR	R S	8.2	2.4	1250	+	B	B	B	B	182	+	MRSA	+	MRSA	750	500	40.00
22	444211	M	40	2	14	O	TR	L LA	6.7	3.3	950	+	B	B	B	B	178	+	STPH	+	STPH	595	355	37.37
23	444083	M	50	2	6	O	TR	RS	7.2	4.1	895	+	B	B	B	B	146	+	PS	-	-	540	355	39.66
24	441273	F	46	2	7	O,I	TR	RS	7.1	4.1	1020	+	B	B	B	B	138	+	PS	-	-	635	385	37.75
25	444091	F	52	2	10	O	TR	LS	6.9	3.1	1365	+	B	B	B	B	166	+	PS	-	-	800	565	41.39
26	442214	M	69	2	9	O	SP	L DR	6.4	4	1425	+	B	B	B	B	180	+	PS	+	PS	945	480	33.68
27	416362	F	59	2	7	O	SP	LS	5.3	2.4	1628	+	B	B	B	B	194	-	-	-	-	909	719	44.16
28	415397	M	45	2	12	O	SP	R DR	11	5.6	1224	+	B	B	B	B	168	-	-	-	-	705	519	42.40
29	418112	M	60	2	18	O	SP	LS	8.2	4.6	1320	+	B	B	B	B	154	-	-	-	-	812	508	38.48
30	417088	M	41	2	8	O	TR	LS	9.2	6.3	1082	+	B	B	B	B	146	-	-	-	-	637	445	41.13

ANNEXURE IV - MASTER CHART - GROUP B (NORMAL SALINE)

Serial number	In Patient Number	Sex	Age (Years)	DM status			Ulcer details						Vascular exam				Investigations					Final ulcer area	Change in ulcer area	Percentage reduction
																		Tissue culture						
																		Before		After				
				Type	Duration (Years)	Medication	Onset	Site	Lenth	Breadth	Area (mm2)	Discharge	Popliteal a.	Anterior tibial	Posterior tibial	Dorsalis pedis	FBS (mg/dL)	Sensitivity	Organism	Sensitivity	Organism			
1	416092	M	71	2	18	O	TR	LS	6.4	3.2	931	+	B	B	B	B	162	-	-	-	-	730	201	21.59
2	412455	M	75	2	14	O	TR	RS	8.2	3.2	1024	+	B	B	B	B	148	+	STPH	-	-	885	139	13.57
3	418165	M	54	2	8	O	TR	LS	8.4	4.2	905	+	B	B	B	B	202	+	STPH	-	-	725	180	19.89
4	424475	M	61	2	12	O	TR	RS	8.4	3.1	1493	+	B	B	B	B	186	-	-	-	-	1319	174	11.65
5	437863	M	57	2	6	O	TR	LS	7.3	3.4	753	+	B	B	B	B	186	+	PS	-	-	647	106	14.08
6	412392	M	75	2	18	O	TR	R DR	6.2	2.4	1590	+	B	B	B	B	148	-	-	-	-	1271	319	20.06
7	424817	M	48	2	9	O	SP	R DR	9.1	4.3	1475	+	B	B	B	B	178	+	PTV	+	PTV	1179	296	20.07
8	409926	M	62	2	14	O	TR	R DR	8.2	5.1	714	+	B	B	B	B	184	+	PTV	+	PTV	615	99	13.87
9	437019	F	47	2	7	O	SP	R LA	7.4	3.2	498	+	B	B	B	B	173	-	-	-	-	375	123	24.70
10	412381	M	62	2	12	O	SP	R LA	7.1	4.2	300	+	B	B	B	B	174	-	-	-	-	225	75	25.00
11	413468	M	41	2	8	O	SP	L DR	6.1	2.8	695	+	B	B	B	B	148	+	PS	+	PS	590	105	15.11
12	439016	M	52	2	6	O	SP	L DR	6.2	4.1	713	+	B	B	B	B	188	+	PS	+	PS	565	148	20.76
13	436915	F	63	2	12	O	TR	LS	6.8	3.2	575	+	B	B	B	B	168	+	PS	-	-	476	99	17.22
14	412731	M	58	2	8	O	TR	LS	7.3	3.4	512	+	B	B	B	B	186	+	PS	-	-	395	117	22.85
15	418579	F	60	2	22	O	TR	R LA	6.4	3.2	450	+	B	B	B	B	186	+	STPH	+	STPH	390	60	13.33
16	399714	M	58	2	9	O	SP	R DR	7.3	4.2	386	+	B	B	B	B	152	+	PS	-	-	315	71	18.39
17	422787	M	38	2	4	O	TR	RS	4.4	3.2	430	+	B	B	B	B	174	+	MRSA	+	MRSA	330	100	23.26
18	405045	M	40	2	8	O	SP	R DA	8.2	4.5	375	+	B	B	B	B	174	+	PTV	+	PTV	285	90	24.00
19	418068	M	54	2	6	O	SP	L DR	9.2	4.5	356	+	B	B	B	B	174	+	KL	+	KL	280	76	21.35
20	413457	M	53	2	7	O	TR	R DR	5.4	3.2	410	+	B	B	B	B	194	+	PTV	+	PTV	335	75	18.29
21	405879	M	70	2	24	O	SP	L LA	10	5.4	925	+	B	B	B	B	184	-	-	-	-	700	225	24.32
22	435688	M	42	2	3	O	SP	R DR	6.1	4.2	840	+	B	B	B	B	124	-	-	-	-	685	155	18.45
23	439898	M	70	2	12	O	TR	R DR	8.2	5	575	+	B	B	B	B	164	+	PTV	+	PTV	480	95	16.52
24	439016	M	52	2	8	O	TR	L DR	9.1	4.2	735	+	B	B	B	B	148	+	PTV	+	PTV	620	115	15.65
25	439833	M	52	2	8	O	SP	R LA	8.1	4.2	1225	+	B	B	B	B	170	-	-	-	-	1060	165	13.47
26	405156	M	52	2	6	O	SP	L DR	6.2	4.1	1385	+	B	B	B	B	188	+	PS	+	PS	1190	195	14.08
27	412632	F	63	2	12	O	TR	LS	6.8	3.2	975	+	B	B	B	B	168	+	PS	-	-	802	173	17.74
28	412286	M	58	2	8	O	TR	LS	7.3	3.4	988	+	B	B	B	B	186	+	PS	-	-	780	208	21.05
29	409821	F	60	2	22	O	TR	R LA	6.4	3.2	798	+	B	B	B	B	186	+	STPH	+	STPH	594	204	25.56
30	430129	M	58	2	9	O	SP	R DR	7.3	4.2	844	+	B	B	B	B	152	+	PS	-	-	685	159	18.84