"A COMPARATIVE STUDY OF PLATELET RICH PLASMA DRESSING VS NORMAL SALINE DRESSING IN THE MANAGEMENT OF DIABETIC FOOT ULCER''

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

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IN

GENERAL SURGERY

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LIST OF ABBREVATIONS

GF : Growth Factor

IL : Interleukin

TNF : Tumor Necrosis Factor

TGF : Transforming Growth Factor

VEGF : Vascular Endothelial Growth Factor

EGF : Epidermal Growth Factor

PDGF : Platelet Derived Growth Factor

NO : Nitric Oxide

DM : Diabetes Mellitus

PRP : Platelet Rich Plasma

DFU : Diabetic Foot Ulcer

OHA : Oral Hypoglycemic Agents

ECM : Extracellular Membrane

HbA1c : Glycated Hemoglobin

ICAM : Intra Cellular Adhesion Molecules

IGF : Insulin like Growth Factor

PMN : Poly Morphonuclear Neutrophil

KGF : Keratinocyte Growth Factor

MMP : Matrix Metallo Proteinase

TIMP : Tissue Inhibitor Metallo Proteinase

PEDCS: Pittsburg Epidemiology of Diabetes Complication Study

PF : Platelet Factor

ABSTRACT

Background: Platelet rich plasma (PRP) is an autologous platelet rich concentrate prepared from patients own blood with growth factor upto 8 times that of normal serum. PRP has chemotactic and mitogenic property and serves as growth factor agonist.

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Objectives:

1. To evaluate the efficacy of platelet rich plasma dressing in the management of diabetic foot ulcers in study group.

2. To evaluate the efficacy of Normal saline dressing in management of diabetic ulcers in control group.

3. Comparing effectiveness of study and control groups in terms of decrease in the size of ulcer and duration of ulcer healing in the management of diabetic foot ulcers

Methods: The study is estimated to include diabetic foot ulcer patients satisfying inclusion criteria who are admitted in surgical wards of RLJH and RC.

A complete detailed history, as per standard proforma will be obtained and documented. All patients will undergo clinical examination with relevant investigations after obtaining an informed consent. Patients are divided into 2 groups using even-odd method to include similar type of cases in both groups, where even group is study group and odd group is control group.

Results: The study sample included 90 patients with diabetic foot ulcers admitted in surgical wards of R L Jalappa and diabetic foot ulcer was commonest among 5^{th} and 6^{th} decade of life, males were more commonly affected than females, trauma was most cause of ulcer and most common on plantar aspect than on dorsal aspect of foot and ulcer on dorsal surface heals faster than on plantar surface and lesser the wagner grade better the healing rate and patients on insulin shows better reduction in ulcer size and over all PRP dressing group showed higher rate of ulcer size reduction than those on saline dressing.

Conclusion:

1. The vulnerable age group for Diabetes is in 5^{th} and 6^{th} decade of life.
2. Male population is affected from diabetes and its complications are more compared to female population.
3. Foot ulcers following trauma is more common than spontaneous onset.
4. Ulcers on the sole of the foot is common than on the dorsal aspect.
5. Healing of ulcers with Wagner grade 1> grade 2> grade 3.
6. The patients who are treated with insulin has good glycemic control and shows good results in healing when compared to those on OHA.
7. The diabetic ulcer in the study group treated with PRP dressing contracted in wound size more than in the control group (38.19% vs 19.63% with p value < 0.001 which is statistically significant).
8. This indicates that PRP dressing is an effective method to facilitate wound contraction in diabetic patients with foot ulcer.

9. PRP dressing is found to be more effective, cost efficient and safe promoter of ulcer wound healing and can be used as an adjunct to saline dressings for enhanced healing of diabetic wounds.

Keywords: PRP, Wagner grade, plantar, trauma

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INTRODUCTION

Diabetes mellitus is defined by the WHO as a disorder of metabolism characterized by hyperglycemia with disturbance of carbohydrates, lipoproteins and amino acids metabolism which results from defects in secretion of insulin, insulin action or both.[1]

Diabetic foot ulcer a major complication and concern of diabetes mellitus, it affects about 15% of population with diabetes. Studies have shown that up to 88% of all lower leg amputation are due to diabetic foot ulcer. Prevalence of diabetes is rapidly rising all over the world at an alarming rate. According to, the World Health Organization, at least 171 million people in globe have diabetes the figure is sooner to double by 2030.[2]

Diabetes mellitus causes 2 major vascular complications i.e micro and macro vascular complications. Micro vascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy). Macro vascular complications include cardiovascular disease, stroke and peripheral vascular disease. Peripheral vascular disease may lead to bruises or injuries that do not heal, gangrene and ultimately amputation.[3]

Conventional treatments like dressings, debridement of the wound and even skin grafting cannot provide a satisfactory healing since these were not able to provide necessary growth factors that can augment the healing process.[4]

Autologous platelet–rich plasma (PRP) is an expensive methods used in treating non-healing ulcers as it provides growth factors which enhance healing. PRP functions as a tissue sealant and drug delivery system, with the platelets initiating wound repair by releasing locally acting growth factors via α-granules degranulation.[5]

OBJECTIVES

AIM OF STUDY

1. To evaluate the efficacy of platelet rich plasma dressings in the treatment of diabetic foot ulcers in study group.

2. To evaluate the efficacy of Normal saline dressing in the treatment of diabetic foot ulcers in control group.

3. Comparing the effectiveness of study and control groups in terms of decrease in the size of ulcer and duration of ulcer healing in the treatment of diabetic foot ulcers.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORICAL

Diabetes is characterized by the too great emptying of urine found in antiquity through Egyptian manuscripts dating back to 1500 B.C.[6]

Ancient Indian physicians termed it as madhumeha (honey urine) because it attracted ants. The ancient Indian surgeon Charaka and the physician Sushruta (400-500A.D.) were able to identify 2 types of diabetes mellitus, later to named it as Type 1 and Type 2 diabetes mellitus.[7,8]

The comprehensive descriptions was first given in the first century A.D. by Aretaeus, the Cappadocian, who described the word diabetes

(greek, ‘’sipho’’) and stated “ no essential part of drink is absorbed by body while great masses of the flesh are liquefied into urine”.[9]

Avicenna (980-1037A.D.) a great Persian physician, in the canon of medicine not only pointed out to abnormal appetite and observed diabetic gangrene in patients but also formulated a mixtures of seeds(lupin, fenugreek, zedoary) as a remedy for it.[10]

The term mellitus (Latin, “sweet like honey’’) was first coined by a British surgeon–General, John Rollo in 1798, to distinguish diabetes mellitus from the diabetes insipidus in which the urine was tasteless.[11]

Grant Banting and Herbert best together proved that diabetes in dogs is reversible by administering them an extract from the pancreatic islets of Langerhans

from a healthy dog and thereby confirming a definitive endocrine role of pancreas in 1921. In view of this finding, Banting′s birthday which is on November 14 is observed as World Diabetes Day.[12]

Ancient Egyptian physicians treatment for open wounds is documented in papyruses dating back to 1400 B.C. They would apply a paste of honey, grease and lint into open wounds to remove skin and pus to encourage wound healing.[13]

Recorded history of wound care goes back to 2100 BC. where ″three healing gestures ″were engraved into the famous Sumerian clay tablet .Those were washing the wound with hot water and beer, making plasters from mixtures of ointments, herbs and oils and bandaging of wound. Ancient slaves and herbs are very bactericidal.[14]

A mixture containing of one-third honey and two-third grease (butter) decreased the count of staphylococcus and Escherichia coli within 24 hours. Greek physicians would cover their patients wounds with a variety of slaves diluted in wine and made from combinations of salts (copper acetate , copper oxide, lead oxide),vinegar, nuts, flowers, grease and fragrance (myrth or frankincense – bactericidal and fragrant).Wine (which has an alcohol content of 9.8%) is more bactericidal than 10% alcohol.[15]

One of the first written reports of maggot therapy is credited to Ambroise Pare. He noted the beneficial effects of maggots in the wounds of soldiers in 1557.[16]

In 1908, llya Metchnikoff (1845-1916) won the Nobel prize for his discovery of phagocytosis and the theory that purpose of inflammation was to bring phagocytic cells to the injured area to engulf bacteria.[17]

Cytokines and growth factors were first described about 50 years ago. In the 1950s, endogenous pyrogen (which we know as interleukin-1) nerve growth factor and interferon were described.[18]

For an efficient wound healing, a multidisciplinary approach is needed like involving off-loading of the pressure points, regular dressing and wound debridement whenever needed, control of gangrene or sepsis, appropriate antibiotic based on culture, negative- pressure wound therapy, and skin grafting when applicable, while glycemic control is of utmost importance in treating a diabetic foot ulcer.

Apart from the above mentioned treatment, the growth factors (GFs) were used as adjunct to enhance tissue remodelling and augment ulcer healing has been extensively studied in the literature. Their use lies on their contributing factor in the biological events that take place during the process of healing.[19]

SKIN

The largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital functions, including protection against external physical, chemical and biological agents in prevention of excess water loss from the body and a role in thermoregulation.[20]

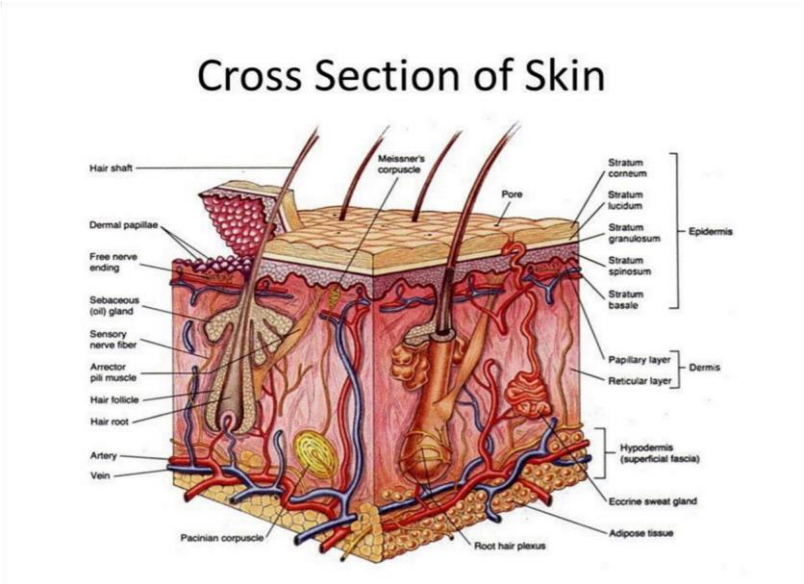
The skin is composed of three layers: the epidermis, the dermis and subcutaneous tissue. The outer most level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin a long thread like protein with a protective role.

The layers of the epidermis are

- Stratum basale (basal or germinativum cell layer)
- Stratum spinosum (spinous or prickle cell layer)
- Stratum granulosum (granular cell layer)
- Stratum corneum (horny layer)
- Stratum lucidum is a thin layer of translucent cells seen in thick epidermis.

The dermis, is a fundamentally made up of the fibrillar structural protein known as collagen.[105] The integrity of the dermis is maintained by a supporting matrix containing ground substance and two types of protein fibres: collagen, which has great tensile strength and forms the major constituent of the dermis and elastin.[21]

Figure 1: Anatomy of Skin



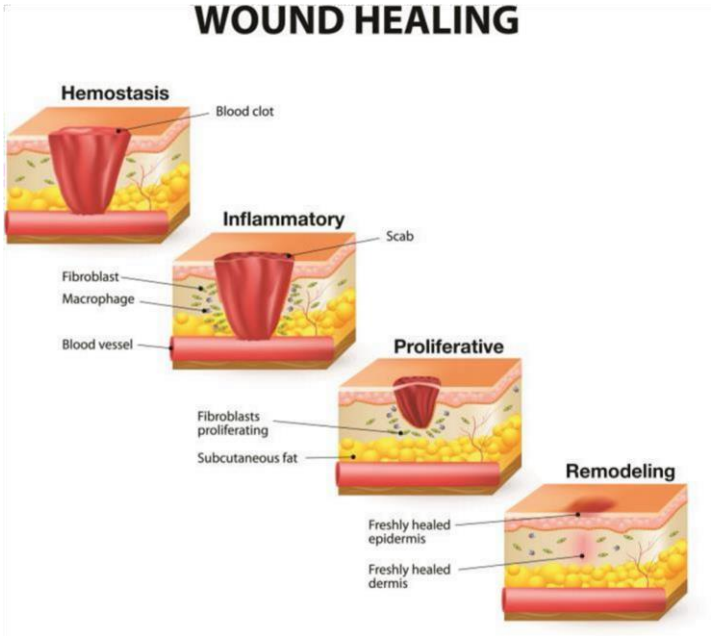
WOUND HEALING PHASES

A wound comprises a break in continuity of epithelium and is characterized by disruption of structure and functions of underlying tissues.

As noted by John Hunter (1728-1793), a keen observer of biologic phenomena, "the injury alone has in all cases a tendency to produce the disposition and the means of a cure."[22] The phases of wound healing are:

1. Inflammation
2. Proliferation
3. Maturation
4. Remodeling

Figure 2: Phases of wound healing



TYPES OF WOUND HEALING

Primary Healing (First intention)

Healing by primary intention is seen in clean incised wound or surgical wound. Wound edges are approximated with sutures. There is more epithelial regeneration than fibrosis. Wound heals rapidly with complete closure. Scar will be linear, smooth and supple.

Secondary Healing

Healing by secondary intention is seen in wounds with extensive soft tissue loss like in major trauma, burns and wound with sepsis. It heals slowly with fibrosis. It leads to a wide scar, often hypertrophied and contraction occurs. It usually causes disability.

Re-epithelialisation occurs from remaining dermal elements or wound margins.

Healing by Third Intention (tertiary Wound Healing or Delayed Primary Closure)

After wound debridement and control of local infection, wound is closed with sutures or covered using skin graft. Contaminated primary or mixed wounds heal by tertiary intention.

Figure 3: Types of Wound Healing

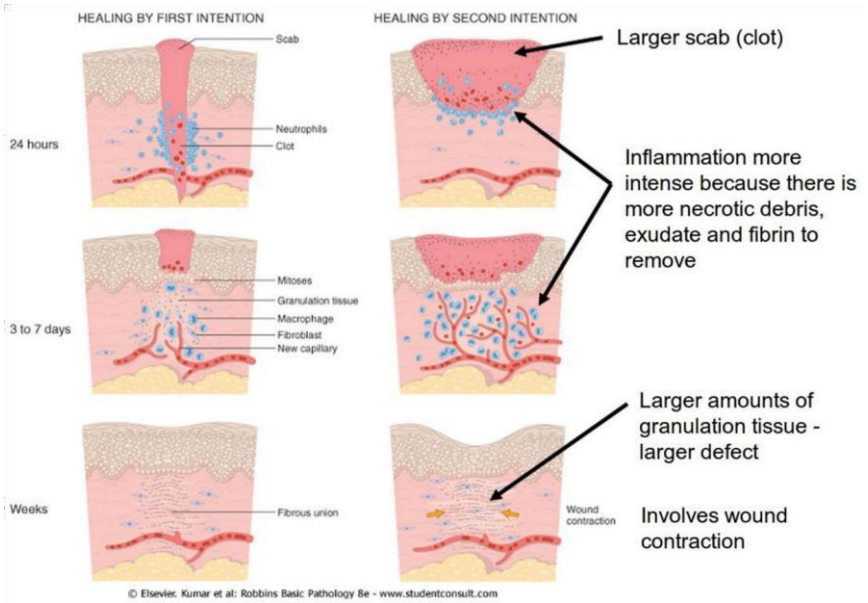
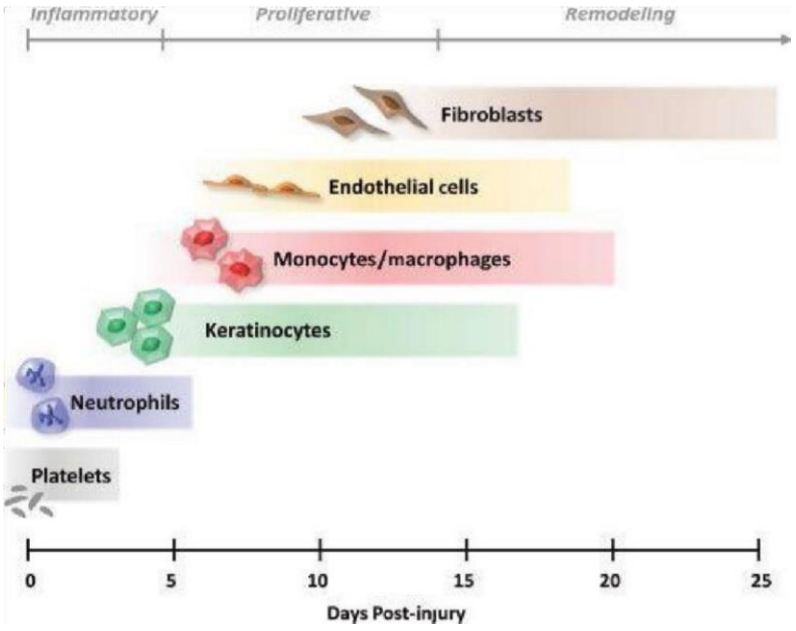


Figure 4: Duration of Wound Healing



All three phases occur simultaneously and the phases may overlap with their individual processes. All wounds need to progress through their series of cellular and biochemical events that characterizes the phases of healing for successful re-establishment of tissue integrity.

Hemostasis and Inflammation

Hemostasis is the first step and foundation for any healing process. Inflammation results in vasodilation and increased vascular permeability. However, the first action the body takes immediately after wounding is to control bleeding. The injured blood vessel vasoconstricts and the endothelium and nearby platelets activate the intrinsic part of the coagulation cascade. The clot that forms is made of collagen, platelets, thrombin and fibronectin and these factors release cytokines and growth factors that initiate the inflammatory response.[23]

The fibrin clot acts as a scaffold for invading cells, such as neutrophils, monocytes, fibroblasts and endothelial cells to use. The clot also serves to concentrate the elaborated cytokines and growth factors.[24]

After the fibrin clots forms, another mechanism is activated as part of the body's defense system- fibrinolytic system – in which the fibrin clot starts to break down. This process prevents clot extension and dissolves the fibrin clot to allow case of further cell migration into the wound space.[25]

Chemotaxis and Activation

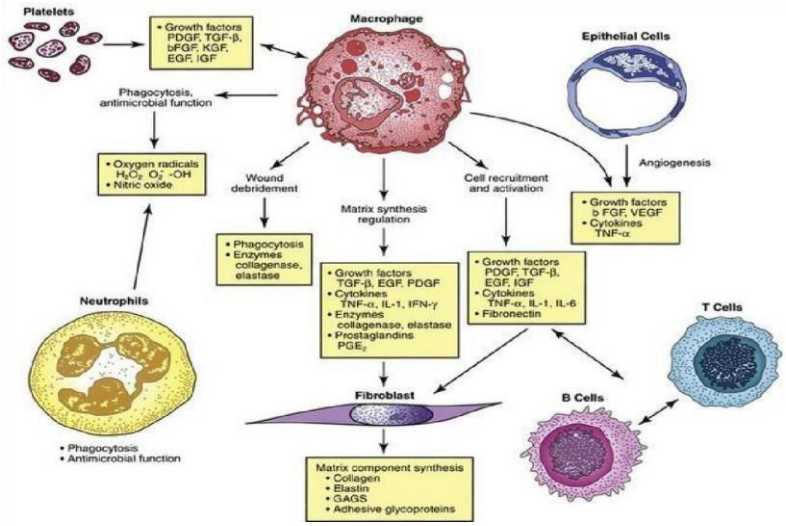
Immediately as the clot is formed, cellular signals are activated which results in a neutrophil response and as the inflammatory mediators accumulate, prostaglandins are elaborated and the nearby blood vessels vasodialate to allow for the increased cellular traffic as neutrophils are drawn into the injured area by interleukin (IL) – 1, tumor necrosis factor (TNF- alpha), transforming growth factor (TGF-Beta), PF4 and bacterial products.[26,27]

An activated macrophage will mediate angiogenesis [by synthesizing vascular endothelial growth factor (VEGF), fibroblast growth factor, and TNF-alpha] and fibroplasia [by synthesizing TGF-beta, epidermal growth factor (EGF), platelet derived growth factor(PDGF), IL-1 and TNF- alpha] and synthesize nitric oxide (NO) (from activation of inducible nitric oxide synthase by IL-1 and TNF alpha).[28]

Neutrophils enter into wound site and begin clearing it of invading bacteria and cellular debris. The neutrophil releases caustic proteolytic enzymes that will digest bacteria and nonviable tissue. The neutrophil has several different types of proteases grouped by their preferred target proteins, amino acids, or the metal ion within the enzyme.

Serine proteases have broad specificity (e.g., elastase), whereas metalloproteinase (which contains a zinc ion) specifically digests collagen. Both types of proteases will destroy the preexisting extracellular matrix in the wound area.

Figure 5: Interacting of cellular and Humoral factors in wound healing[23]



Macrophages do not possess myeloperoxidase but do continue in pathogen killing by generating NO. The macrophages iNOS is stimulated to synthesize very large quantities of NO by TNF and IL-1 that react with peroxide ion oxygen radicals to yield an even more toxic peroxy nitrite and hydroxyl radicals.[29]

The macrophage's most pivotal function is activation and recruitment of other cells via mediators such as cytokines and growth factors, and is directed by cell-cell interaction and intercellular adhesion molecules (ICAM)

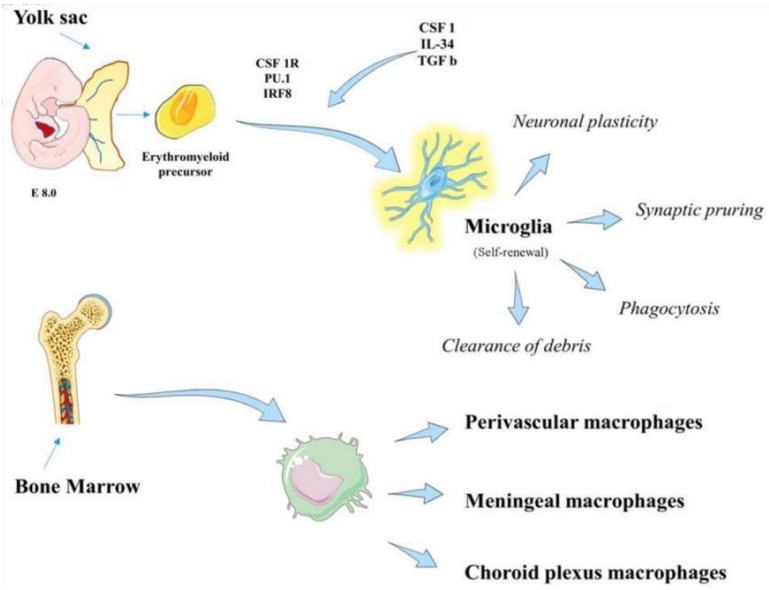
Macrophages also play a significant role in regulating angiogenesis and matrix deposition and remodeling.

Table 1: Macrophage activities during wound healing[30,31]

ACTIVITY	MEDIATORS
Phagocytosis	Reactive oxygen species Nitric oxide
Debridement	Collagenase, Elastase
Cell recruitment and activation	Growth factors: PDGF,TGF-β,EGF,IGF Cytokines: TNF-α,IL-1,IL-6 Fibronectin
Matrix synthesis	Growth factors: TGF-β,EGF,PDGF Cytokines: TNF-α,IL-1,IFN-γ Enzymes: Arginase, collagenase Prostaglandins Nitric oxide
Angiogenesis	Growth factors: EGF, VEGF Cytokines : TNF-α Nitric oxide

Macrophage secrete numerous inflammatory mediators. IL-1 a proinflammatory cytokine, an acute-phase response cytokine. This endogenous pyrogen causes lymphocyte activation and stimulation of the hypothalamus, thereby inducing the febrile response.

Figure 6: Role of Macrophage



It also directly effects hemostasis by inducing the release of vasodilators and stimulating coagulation. Its effect is further amplified as endothelial cells produce it in presence of TNF-α and endotoxin.

IL-1 has numerous effects such as enhancement of collagenase production, stimulation of cartilage degradation and bone reabsorption, activation of neutrophils, regulation of adhesion molecules and promotion of chemotaxis.

Table 2: Major cytokines involved in wound healing[32]

Cytokine	Cell source	Biological activity
Pro -inflammatory Cytokines		
Tumor necrosis factor(TNF-a)	Macrophages	• Increase PMN margination and cytotoxicity • Increase MMP synthesis
Interleukin-1 (IL-1)	Macrophages, keratinocytes	• Increase fibroblast and keratinocyte chemotaxis • Increase MMP synthesis
Interleukin-6(IL-6)	Macrophages, keratinocytes, PMNs	• Increase fibroblast proliferation
Interleukin-8(IL-8)	Macrophages, fibroblasts	• Increase Macrophages and PMN chemotaxis • Increase Collagen synthesis
Interleukin-γ	Macrophages, T lymphocytes	• Increase Macrophage and PMN activation • Decrease Collagen synthesis • Increase MMP synthesis

Anti - inflammatory cytokines		
Interleukin-4 (IL-4)	T-Lymphocytes, basophil, mast cells	• Decrease TNF-α,IL1, IL-6 • Decrease macrophage and PMN activation
Interleukin-10(IL-10)	T-Lymphocytes, macrophages, keratinocytes	• Decrease TNF-α, IL-1, IL-6 synthesis • Decrease macrophage and activation

Proliferative phase

Epithelial cells located on the skin edge begin proliferating and sending out projections to reestablish a protective barrier against fluid losses and further bacterial invasion. The stimulus for epithelial proliferation and chemotaxis is EGF and TGF-β produced by activated platelets and macrophages (fibroblasts do not appear to synthesize TGFβ).[33,34]

Epithelization begins shortly after wounding and is first stimulated by inflammatory cytokines (IL-1and TNF-α up regulate KGF gene expression in fibroblasts). In turn, fibroblasts synthesize and secrete keratinocyte growth factor

KGF-1 , KGF-2 and IL-6 which simulate neighboring keratinocytes to migrate in the wound area, proliferate and differentiate in the epidermis.[35,36]

The most important positive regulators of angiogenesis are VEGF-A and fibroblast growth factor 2.

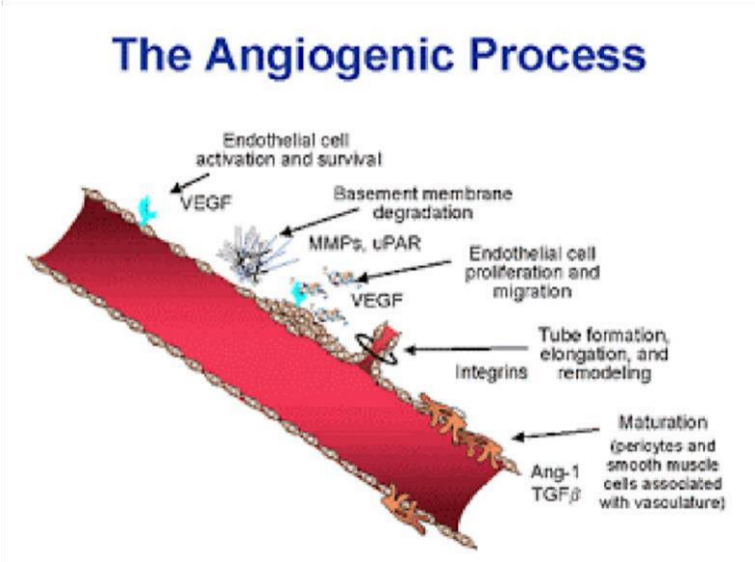
About 4 days after injury, the granulation tissue replaces the provisional ECM. This change in morphology is further attributed by recruitment of fibroblasts, collagen (produced by fibroblasts) and blood vessels. Granulation tissue contains macrophages which produces various growth factors and cytokines, bridges the inflammatory and proliferative phase and thus aids wound healing. The collagen – based ECM produced by fibroblasts replaces the provisional fibrin-based matrix. They also help in re-approximation of wound edges. Since the provisional cellular matrix relatively lacks progenitor cells, the process of migration, proliferation and ECM production are of crucial importance in regeneration of functional dermis.[37]

Angiogenesis can also occurs due to the recruitment of bone marrow derived endothelial progenitor cells, although the magnitude of this contribution is less, at least in non –ischemic wounds (in which the concentration of oxygen is normal).[38]

Angiogenesis – 'process by which damaged blood vessels are replaced by "sprouts" from intact capillaries in the local vicinity of the wound. Increase in lactate or decrease in pH and low oxygen tension, as a result of local tissue injury due to low tissue perfusion also stimulates angiogenesis'.[39]

Angiogenesis is further promoted by various growth factors and cytokines, produced during the inflammatory phase of wound healing. VEGF, FGF, angiopoietin and TGF-β,[121] proteoglycans, MMPs play a very significant role.[40,41,42]

figure 7 : Process of Angiogenesis



In humans, it seems that KGF-2 is most importance for directing this process.[36]

Endothelial cells and fibroblasts are the predominant cells proliferating during this phase. Endothelial cells located at intact venules are seduced by VEGF (secreted predominantly by keratinocytes on the wound edge, but also by macrophages, fibroblasts, platelets and other endothelial cells) to begin forming new capillary tubes. Recall that keratinocytes can be stimulated to express VEGF by IL-1, TNF-α, TGF-1 and KGF. NO is made by endothelial cells (from endothelial nitric oxide synthase eNOS) in response to hypoxia and this stimulates more VEGF production. The

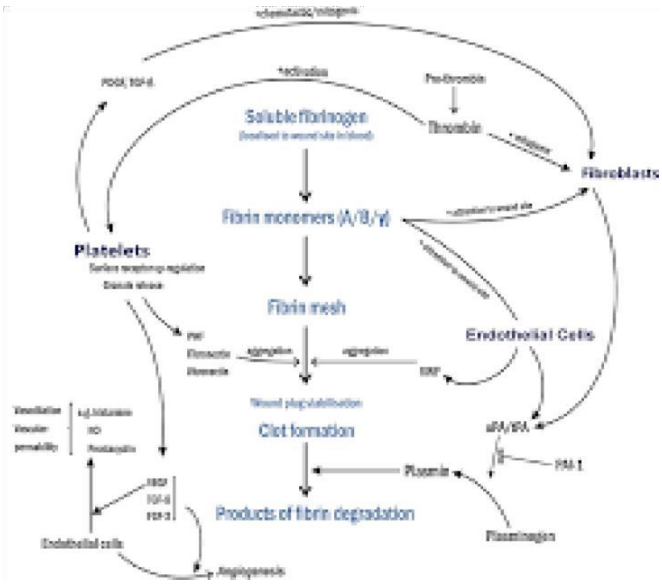
increased concentration of NO also protect the new tissue from the toxic effects of ischemia and reperfusion injury and cause endothelium to vasodilate.[28]

Fibroblasts migrate into the wound site from the surrounding tissue, become activated and begin synthesizing collagen and proliferate. PDGF and EGF are the main signals to fibroblasts and are derived from platelets and macrophages. The process involving fibroblasts and the ECM they synthesize is known as fibroplasia. It is influenced by numerous bioactive molecules secreted by various cell types present in the wound bed during healing.[43]

Growth factors (especially PDGF-BB, FGF-2 and TGF-b) interacting with Fibronectin, fibrinogen chains (Aa1, Aa2 and Bb) and factor 2 in the early hemostatic clot stimulate fibroblasts to proliferate and express specific integrin receptors.[44]

This facilitates fibroblast migration along provisional ECM fibrils into the wound space.[44]

Figure 8: The mechanism of clot formation and angiogenesis



PDGF expression by fibroblasts is amplified by autocrine and paracrine signaling. Fibroblasts already located in the wound site (termed “wound fibroblasts”) begin synthesizing collagen and transform into myofibroblasts for wound contraction (induced by macrophage –secreted TGF-β1). They have less proliferation compared with the fibroblasts coming in from the wound periphery. In response to PDGF, fibroblasts begin synthesizing a provisional matrix composed of collagens type 3, glycosaminoglycans and fibronectin.[45]

Integrins are a matrix component that serves to another cells to the provisional matrix and is upregulated by TNF-α.[46]

In a normal incisional wound, TGF-β peaks around day 7 to 14 and directs extracellular matrix production and a decrease in its degradation . TGF-β causes fibroblasts to synthesize type 1 collagen, decrease production of MMP, enhance production of tissue inhibitors of metalloproteinase and increase production of cell adhesion proteins. The signal to turn off activity seems to come from interferon-inducible protein (IP-10), which inhibits EGF-induced fibroblast motility and thereby limits fibroblast recruitment, interferons themselves and PF4, which has a negative mitogenic effect on fibroblasts.[29,13]

Larger wounds healing by secondary intention are by cytokine TGF-β, which causes wound contracture (transforming “wound fibroblasts” into myofibroblasts) and epithelialization.[46]

Maturation and Remodeling Phase of Wound Healing

This phase comprises of

1. Wound contraction
2. Epithelialization

Wound Contraction

Wound contraction is a process by which wound heals in a centripetal manner.

- Wound contraction is one function of granulation tissue which is critical for repair.
- The events starts from injury to fibroplasias, occurs in almost all wounds.
- In humans, the wound contraction is less because in most parts of the body the skin is somewhat firmly attached to subcutaneous tissue but it can occurs in areas like back of neck and buttocks.

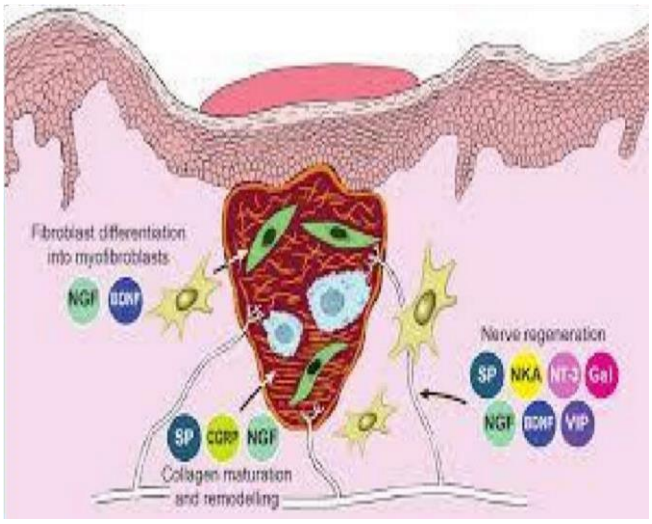
Wound contraction is not materially affected by size or shape of the wound but perhaps by the length of the wound perimeter.

Mechanism of wound contraction

The mechanism of wound contraction is disputable and debatable. Many theories like pull theory, push theory picture frame theory etc have been proposed but none of them appears to be satisfactory. Wound contraction can be both beneficial or detrimental. Wound contraction can lead to distortion, disfigurement and impairment of function.

Wound contraction begins approximately 4 to 5 days after initial injury and continues for about two weeks, depending on wound healing environment. Contraction, cell-directed process requires cell division. In an un sutured wound, wound edges approximate at the rate of 0.6 to 0.75mm /day. This process coincides in time with phenotypic morphogenesis of fibroblasts into myofibroblasts. About 4 to 6 days later myofibroblasts appear due to elevated levels of actin filaments, as demonstrated by electron microscopy.[47,48]

Figure 9: Differentiation of fibroblasts into myofibroblasts resulting in wound contraction



PDGF and TGF aids the phenotypic "switching" of fibroblasts to myofibroblasts. NGF up-regulates the production of actin in myofibroblasts contributing to wound contraction. Presence of IL8 delays wound contraction by prolonging the inflammatory processes.[30]

The increase in wound strength and decrease in wound thickness over time is attributed primarily to remodeling of the collagen based ECM. This process of remodeling represents a balance between collagen production, collagen breakdown , and collagen remodeling. Collagen synthesis increases until about day 21 post wounding and then declines.[47,49]

Collagen synthesis caeses by autoregulatory mechanism. The growth factors interferon and TNF stimulate fibroblasts to decrease collagen synthesis. On day 21, the wound strength is only roughly 20% though the collagen content is peak. At 6 weeks post wounding, the site has approximately 80 to 90% of its long term strength. Long term strength never reaches baseline and achieves only approximately 80% of baseline by 6 months post wounding. Collagen breakdown and collagen rearrangement occur during 3 to 6 weeks and increase wound strength.[47,49]

Collagen breakdown is attributed by increased mRNA level of MMP-2, TIMP-2 and MMP-7 during the early phases of ECM remodeling. Conversely, expression of MMP -1 and MMP-9 and TIMP-1 mRNA levels decreases prior to ECM remodeling. This regulation is mediated by TGF-β, PDGF, IL-1 and cyt6.

As collagen production decreases and collagen breakdown increases, ECM remodeling occurs, overtime. The proportion of type 1 collagen increases with a corresponding decrease in the proportion of type 3 collagen, proteoglycans and water. The processes that underline ECM remodeling are most active during the first 6 months post wounding, less so the subsequent 6 months, and minimally (although not zero) thereafter.[49]

As scars mature, they become less red. Young wounds are characterized by granulation tissue with high level of capillary density, mature wounds are less vascular. Antiangiogenic mediators, including thrombospondin 1 play a role in this change.[50,51,52]

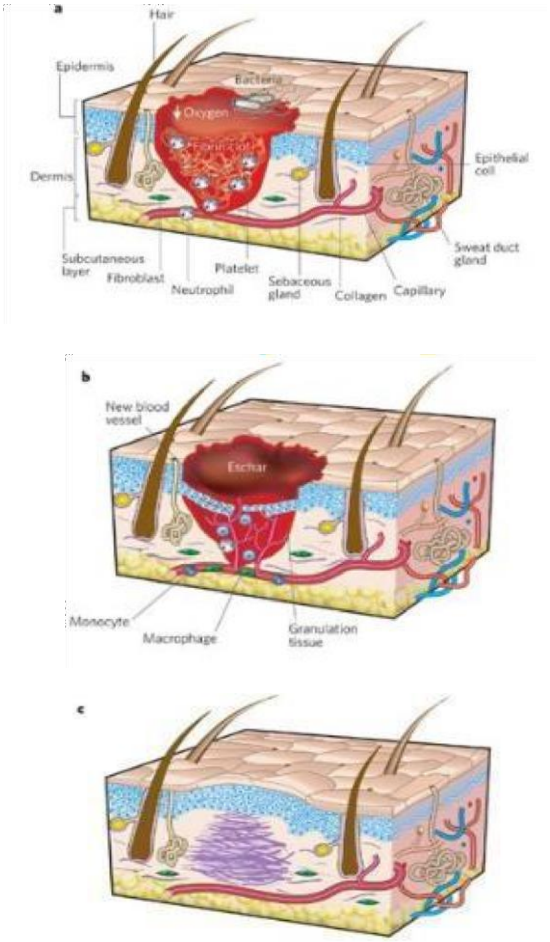
Although apoptosis contributing to loss of fibroblasts, the precise molecular regulatory mechanism are yet to be determined.[53,54,55]

The absence of appendages like missing hair follicles are seen with mature scars. It is due to the inability of scar tissue to reproduce a suitable appendage –specific niche that contributes to the absence of the appendages in mature scars.[56,57,58]

Epithelialization

While tissue integrity and strength are being re-established, the external barrier must also be restored. This process is characterized primarily by proliferation and migration of squamous cells are adjacent to wound.

Figure 10: Regeneration of Epithelium



The processes begins within 1 day of injury and is seen as thickening of the epidermis at the wound edge. Marginal basal cells at the edge of the wound lose their firm attachment to the underlying dermis, enlarge and begin to migrate across the surface of the provisional matrix. Fixed basal cells in a zone near the cut edge undergo a series of rapid mitotic division and these cells appear to migrate by moving over one another in a leapfrog fashion until the defect is covered.[59]

Once the defect is bridged, the migrating epithelial cells lose their flattened appearance, become more columnar in shape and increase their mitotic capacity and layering of the epithelial surface is re-established and the surface layer eventually keratinizes.[60]

Re-epithelialization is complete in less than 48 hours in the case of approximated incised wounds, but may take substantially larger in the case of larger wounds, where there is a significant epidermal/dermal defect.

If only the epithelium and superficial dermis are damaged, such as occurs in split –thickness skin graft donor sites or in superficial second-degree burns, then repair consists primarily of re-epithelialization with no fibroplasia and granulation tissue formation.

The stimuli for re-epithelialization remain incompletely explained; However, some authors explains it has the process of combination of a loss of contact inhibition exposure to constituents of the extracellular matrix, particularly fibronectin; and cytokines produced by immune mononuclear cells.

In particular EGF, TGF-β , basic fibroblast growth factor (bFGF), PDGF, and IGF-1 have been shown to promote epithelialization.

HYPERTENSION

Definition

It is as a systolic blood pressure of 140mm Hg or more or a diastolic blood pressure of 90mm Hg or more taking antihypertensive medication.

Classification

The classification of BP (mm Hg) for population aged 18 years or older is as follows[61]

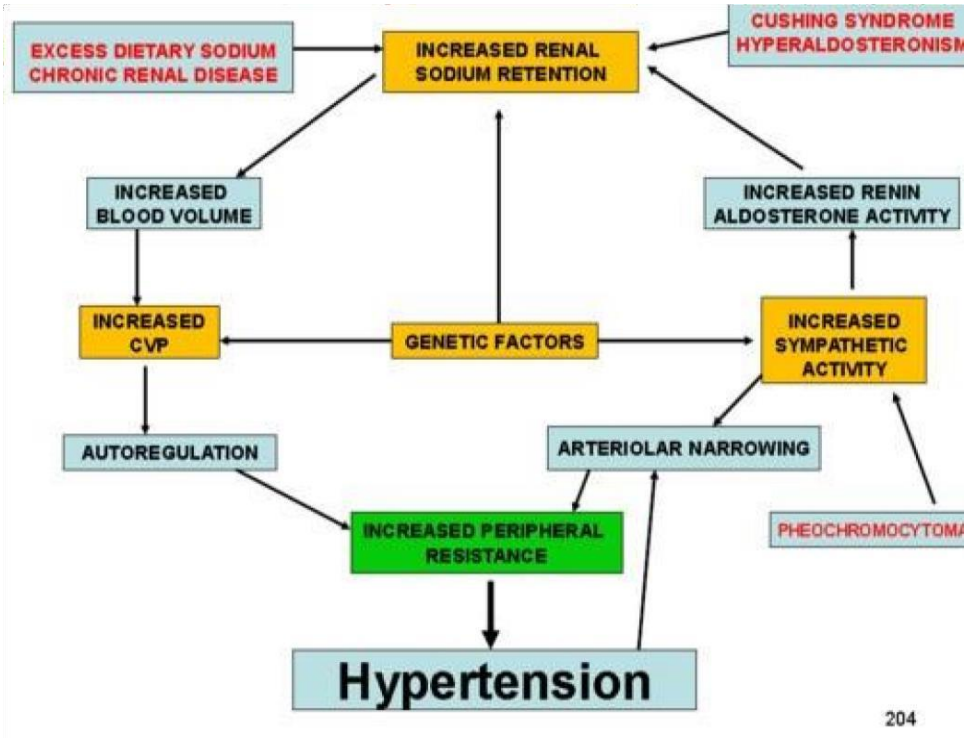
1. Normal: systolic lower than 120mm Hg, diastolic lower than 80 mm Hg
2. Prehypertension: systolic 120-139 mm Hg, diastolic 80-89 mm Hg
3. Stage 1: systolic 140-159 mm Hg, diastolic 90-99 mm Hg
4. Stage 2: systolic 160mm Hg or greater, diastolic 100 mm Hg or greater

The classification mentioned above considers on the average of 2 and more reading taken at each of 2 or more visits after initial screenings. Normal BP with respect to cardiovascular risk is less than 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.[61,62]

Complication of Hypertension with respect to Diabetes Mellitus[63]

There is a large amount of overlap seen between the complication of diabetes and hypertension; these complications are grouped into macrovascular and microvascular disorders. Large and medium sized vessels complications include coronary artery disease, myocardial infarction, congestive heart failure, stroke and peripheral vascular disease.

Figure 11: Etiopathogenesis of Hypertension



Diabetes Mellitus

Diabetes is defined as chronic hyperglycemia with disturbance of carbohydrate, fatty acids, and amino acids metabolism resulting from defects in insulin action and secretion or both.

Classification of diabetes mellitus based etiology[64]

I. Type 1 Diabetes

a. Immune mediated

b. Idiopathic

II. Type 2 Diabetes

III. Other Specific types:

1. Genetic defects of β-cell function

- Chromosome 12- HNF-1α
- Chromosome 7 glucokinase

2. Genetic defects in insulin action

- Type 1 insulin resistance
- Leprachaunism

3. Diseases of exocrine pancreas

    - Acute/chronic Pancreatitis
    - Trauma/pancreatectomy

4. Endocrinopathies

    - Acromegaly
    - Cushing's syndrome

5. Drug or chemical induced

    - Glucocorticoids
    - Thyroid hormone

6. Infections

- Congenital rubella
- Cytomegalovirus

7. Other forms of immune related disease

    - "Stiff –man syndrome''
    - Antibodies against Insulin receptor

8. Other genetic disorders related to diabetes

    - Down's syndrome
    - Klinefelter's syndrome

IV. Gestational diabetes mellitus (GDM)

TYPE 1: Diabetes Mellitus

This is due to primarily to β-cell destruction in which insulin is must for survival. It is due to the presence of anti–GAD, anti-islet cells and anti insulin antibodies, this shows the auto antibody processes that have led to destruction of β-cell.[65,66]

TYPE 2: Diabetes Mellitus

Type two diabetes mellitus is the most common form. Resistance to insulin receptors and abnormal insulin secretion are central to the development of type 2 DM. Patients diagnosed with type two diabetes usually have resistance to insulin and relative, rather than absolute insulin deficiency and progressive β-cell failure with increasing duration of diabetes.[64]

The risk of type two diabetes increases with age, obesity, physical inactivity and family history of diabetes. This disorder can occur at any age and is now seen in children and adolescents.[67]

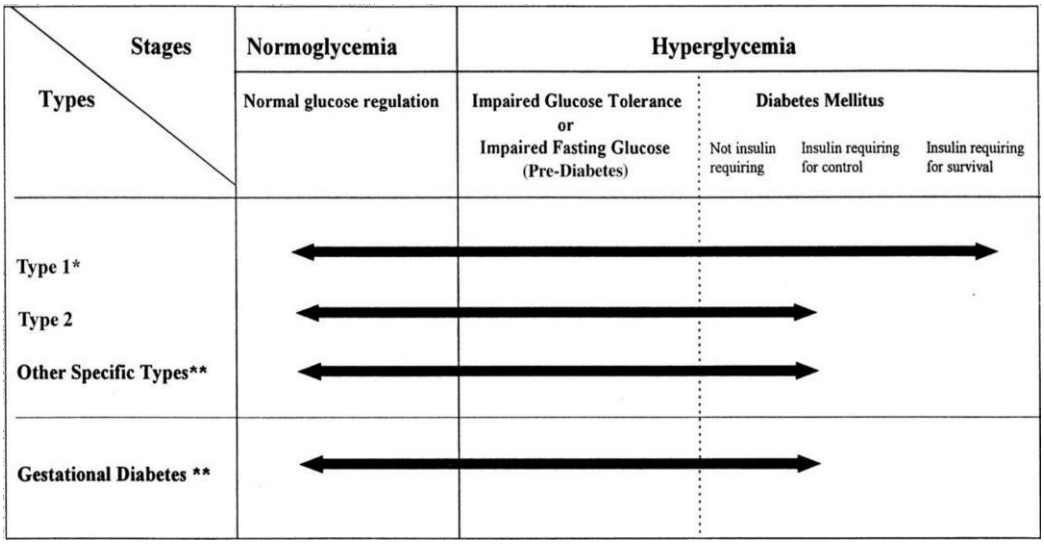
Impaired Glucose tolerance

Defined as two hours values in the OGTT between 140 and 199mg/d1 (7.8 and 11.0mmol/L). Glucose tolerance is above the conventional normal range but lower than the level significant of diabetes. Persons with IGT have a more risk of acquiring diabetes mellitus and arterial disease. Impaired Glucose Tolerance is more frequent in obese persons and often seen with hyperinsulinemia and resistance to insulin.[68]

Impaired Fasting glucose

It is fasting plasma sugars concentrations of 100-125mg/dL (5.6 to <6.9 mmo1/L). IFG is a stage of altered sugar metabolism with fasting glucose levels were above normal diagnostic value but below the level diagnostic for diabetes.

Figure 12: The degree of hyperglycemia in each diabetic type



HbAlc

Glycated hemoglobin (hemoglobin Alc, HbAlc, Alc, or Hblc; Hblc or HGBa1C) is a form of Hb which is measured primarily to identify the 3 month average plasma sugar concentration. The test is limited to a 3 month average because the lifespan of a RBC is four months (120 days), but RBCs donot all undergo lysis at the same time, so HbAlc is taken as a limited measure of three months. It is derived in a nonenzymatic glycation pathway

by Hb's exposure to plasma sugars. It is a measure of the β-N-1-D fructosyl component of Hb.[69,70]

Figure 13: Relationship of HbAlc to risk of micro-vascular complications.

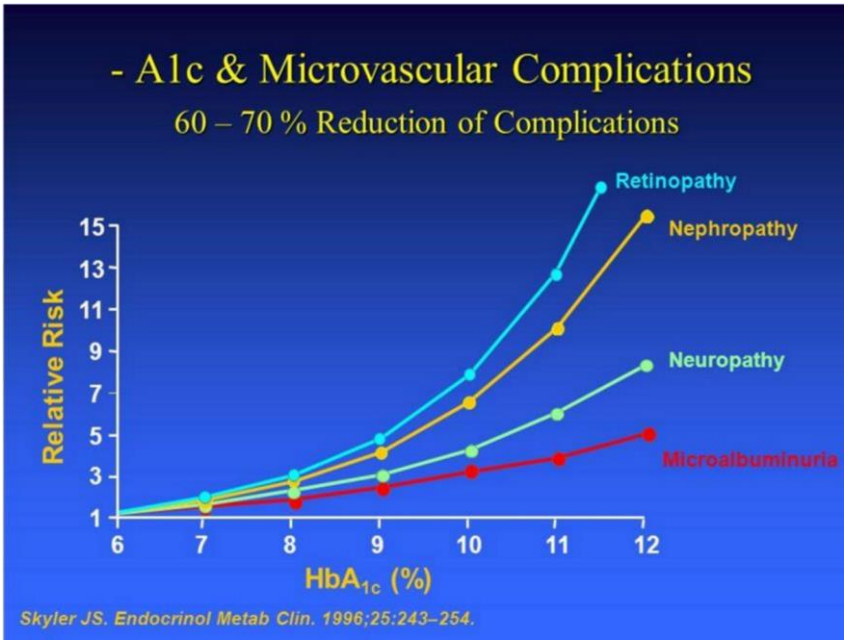


Table3: Diagnostic criteria for diagnosing diabetes

Variables	**Prediabetic**	**Diabetic**
HbAlc	5.7-6.4	≥6.5
Plasma fasting sugar level	100-125mg/dl	≥126mg/dl
OGTT	140-199mg/dl	≥200mg/dl
Random plasma glucose		≥200mg/dl

CAUSES OF DIABETIC FOOT ULCER[71]

Recent articles have indicated many causative factors associated with the development of DFU.

These factors are as follows

- Duration of diabetes mellitus longer than 10 years
- Advanced age of patients
- High body mass index
- Comorbidities like peripheral neuropathy, peripheral vascular disease
- Glycated hemoglobin level (HbAlc)
- Foot deformity
- High plantar pressure
- Infections
- Inappropriate foot self -care habits.
- Male gender

Although the literature has identified a number of diabetes related risk factors that contribute to lower extremity ulceration and amputation, to date most DFU has been caused by ischemic, neuropathic or combined neuro-ischemic abnormalities. Pure ischemic ulcers probably represent only 10% of DFU, ninety percent are due to neuropathy, alone or with ischemia.

Metabolic disturbance such as the glycation of proteins, including hemoglobin, albumin, collagen and fibrin. Glycated proteins and the cross

linked advanced glycation end products they form, appear to contribute to both the micro-vascular and macro-vascular derangements of diabetes.

Figure 14: The risk factors for diabetes foot ulcer

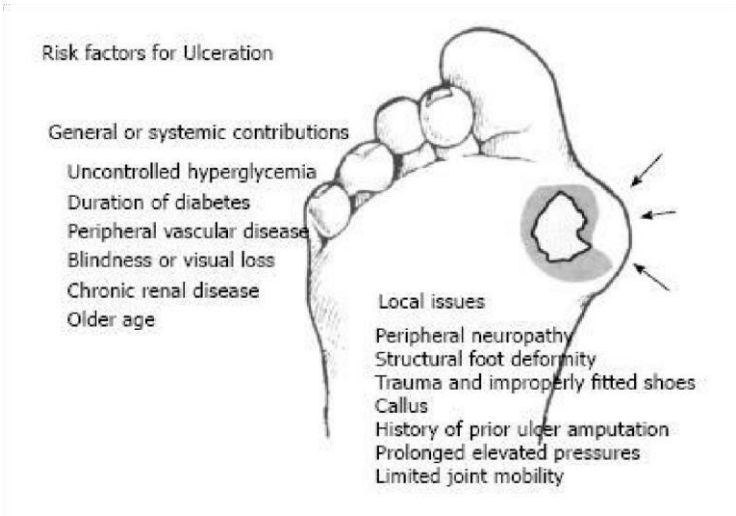
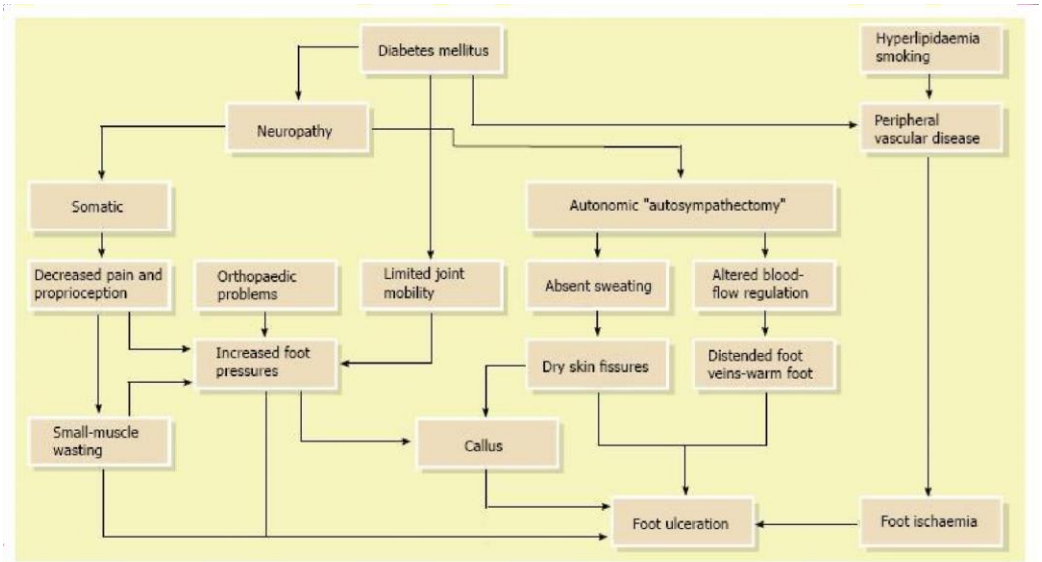


Figure 15: Etiology of diabetic foot ulcer[18]



Neuropathy

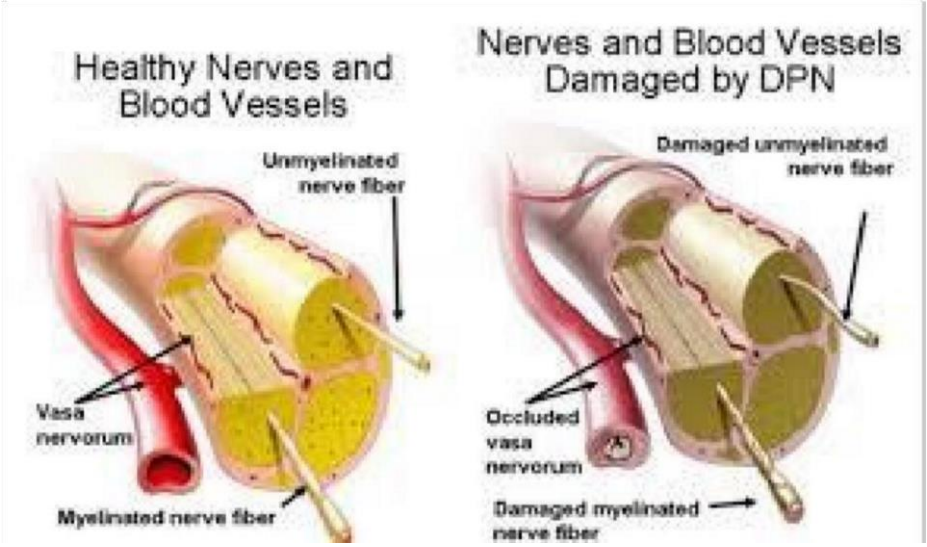
Diabetes affects sensory, motor and autonomic nervous system functions in diabetics with sensory neuropathy, pins and needle sensation which is the primary natural warning system that alerts the body to take action and seek medical care is defective.

Sensory neuropathy contributes to an inability to perceive the injury to the foot due to what is commonly referred to as loss of protective sensation (LOPS). LOPS represents a level of sensory loss where patients can injure themselves without recognizing the injury.[72]

Motor neuropathy contributes to wasting of the intrinsic muscles of the foot muscle imbalance; structural foot deformity, such as claw toes and subluxated metatarsophalangeal joints and limited joint mobility.

Autonomic neuropathy causes shunting of blood and loss of sweat and oil gland function, which leads to dry, scaly skin that can easily develop cracks and fissures. The combined effect of these neuropathies results in a foot with structural deformity and biochemical faults; dry, poorly hydrated integument; and an inability to respond to pain and repetitive injury.[73]

Figure 16: Diabetic Neuropathy



Diabetic neuropathy can cause a number of serious complications, including:

1. Loss of a limb
2. Charcot joint
3. Urinary tract infections and urinary incontinence
4. Hypoglycemia unawareness
5. Low blood pressure
6. Digestive problems
7. Sexual dysfunction
8. Increased or decreased sweating

Peripheral Arterial Disease

Peripheral arterial disorder (PAD) in patients with disease is characterized by many occlusive plagues of small and medium sized arteries of the infra popliteal vessels. PAD puts the patient with diabetes at greater risk for foot ulcers, infections and amputations.

Hypothesis attempts to discuss the micro vascular changes that occur in diabetes. One theory proposes that increased micro vascular pressure and flow results in direct injury to the endothelial cells of vessels, which causes the release of extravascular matrix proteins. This leads to micro-vascular sclerosis and thickening of capillary basement membrane.

Increased capillary fragility also leads to micro hemorrhage, which could be the reason that infection spreads through the planes within the tissues in diabetics.[73,74]

LoGerfo and colleagues stated that no microcirculatory occlusive process in diabetes; rather, they suggests some other indirect physiologic abnormality occurs. Altered micro-vascular blood flow is a complication of diabetic autonomic neuropathy that causes a shunting of blood away from the skin, making it prone to ulceration and impairing the healing process.[75,76,77]

Any theory of small vessel involvement in the process of diabetic ulceration and healing must include both the direct effects of glycosylation and local inflammation and the indirect effect of alteration of micro-vascular hemodynamics associated with autonomic dysfunction.

Table 4: Risk factors predisposing to the non-healing of diabetic foot ulcers[78]

Local	systematic
Infection/tissue maceration /foreign bodies/smoking/ischemia	Chronic disease
Local cancer	Nutritional/anemia
Venous insufficiency	Congenital healing problem e.g. epidermolysis bullosa
Pressure sore	Alcoholism/steroid /cytotoxic /therapy
Toxins/radiation/iatrogenic measures	Ageing/cancer/uremia

Pathogenesis of diabetic foot ulcers

In diabetic patient, foot is the crossroad for many pathological processes, in which almost all contents of the lower extremities are involved; from skin, subcutaneous tissue, muscles, bones and joints, to blood vessels and nerves. An understanding of these processes is necessary for the development and application of management and preventative strategies.

The development pathway towards ulceration is multifactorial. A critical triad of neuropathy, minor foot trauma and foot deformity is responsible for over 50% of diabetic foot ulcers. In addition, other risk factors like uneven plantar pressures, joint rigidities and impaired wound healing ability are all contributing factors.

Apart from obvious clinical predisposing risk factors, recent studies have revealed that very complex mechanism are involved at the tissue molecular level, which prevent normal healing processes.[79]

Many chemo-cytokines are involved, including[80,81,82,83,84]

1. Matrix metalloproteinases
2. Serine proteinases
3. Integrins
4. Chemokines
5. Replicative cell senescence
6. Growth factors
7. Adult stem cells

Diabetic patients with tissue injury initially display impairment in the immune system response with reduced chemotactic effects to bring inflammatory cells and mediators to the damaged tissues, thus, slowing down healing and increases the incidence of bacterial infection.[83,84,85]

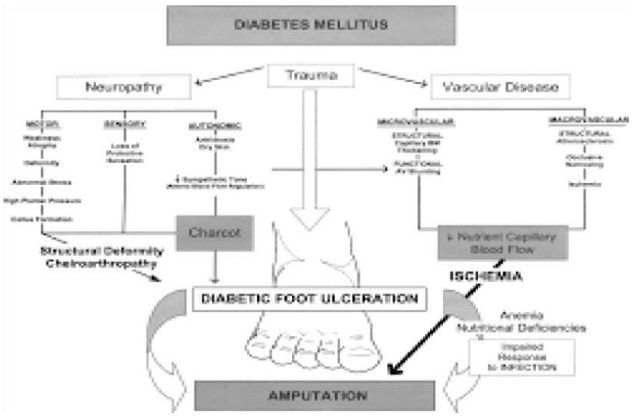
Following this initial period, when the inflammatory response is eventually established, the process switches to an exacerbation of inflammation and proteolysis.[81]

The prolonged exposure to hyperglycemia also generates glycation of proteins and disturbances of cell responses, thus, hindering the mechanism of fibrosis and tissue repair.[86,87,88,89,90,91]

Recent molecular studies on chronic diabetic ulcers indicated that more specific processes may be involved. Example, it is found that leucocytes are prevented from ready entry and accumulation in the ulcers, which therefore, fail to achieve normal healing.[92,93,94]

Other studies on specific properties of fibroblasts in the patients with chronic diabetic ulcers showed that these cells were different from those taken from patients without chronic ulcers in which the high molecular weight hyaluronic acid in pericellular matrix was much more concentrated. The unique property of fibroblasts might predispose these patients to chronic ulcer formation.[95,96,97,98,99,100]

Figure 17: Various pathways and contributing factors leading to diabetic foot complications



Types of ulcers

Clinicians have tried to classify diabetic foot ulcers into different categories and grades. The university of Texas system grades ulcers by depth and then stages them by the presence or absence of infection and ischemia, excluding grade of neuropathy. The international group working on diabetic foot proposes the PEDCS classification grades for the ulcers on the basis of perfusion, extent, depth, infection and sensation.[101,102]

This looks good but it is too complicated. The size, area, depth (SAD) classification attempts to simplify the categories. Alternatively the six grade Wagner–Meggitt classification looks at the depth of ulcers and the existence of tissue gangrene.[103,104]

Of these classification the most practical system to help with the prediction of healing and the possibility of amputation is probably the simpler, Wagner-Meggitt classification. For grade 2 through 6, the overall chance of local or major amputation is estimated to be around 60%.[105,106,107]

Table5: Classification by ulcer depth and gangrene tissues (Wagner-Meggitt)[103,104]

Grade 1	Partial skin thickness
Grade 2	Full skin thickness
Grade 3	Underlying tissues(fascia, ligaments, tendons)
Grade 4	3+ abscess or osteomyelitis
Grade 5	4+ necrotic tissues
Grade 6	Gangrenous tissue found

Infection and Ulcers

Infection is usually the consequences rather than the cause of diabetic foot ulcers. Infected chronic ulcers may be classified as mild to moderate or severe, when osteomyelitis is involved.[108]

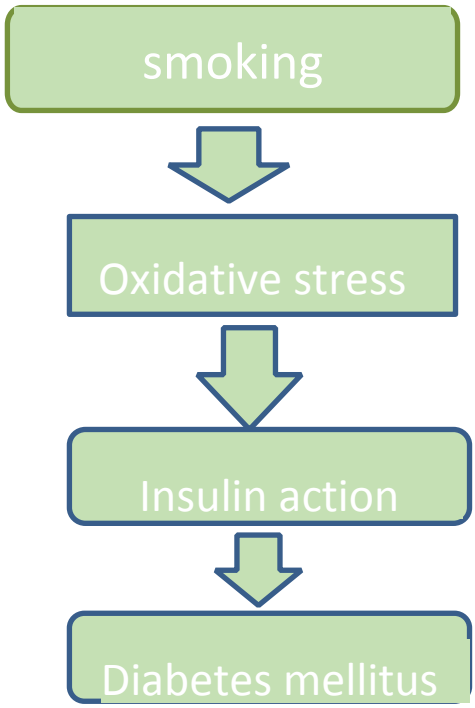
Gram-positive organisms account for major infections, whereas the prevalence of methicillin resistant staphylococcus aureus has become prevalent in recent years. Although gram-positive organisms are overwhelming in chronic diabetic ulcers, the polymicrobial nature of bacterial growth should not be ignored in the management planning, especially in developing countries. 64 chronic ulcers are frequently coexisting with fungal infections of the foot and it has been said that bacterial infection could be predisposed by fungal infection.[109]

Type two diabetes mellitus and Smoking

Smoking is the modifiable risk factors chronic diseases, such as cardiovascular disease (CVD), cancer, chronic obstructive lung disease, asthma and diabetes.

The adverse effects of smoking on diabetes mellitus are not only diabetic macro-vascular complications but the causal nature of smoking with diabetes and the progression of small-vessels complications are to be explored.[110]

Figure 18: Smoking and diabetes



There is much results that smoking increases the risk of diabetes and its complications.[111]

The exact cause for increases in the risk of diabetes and deterioration of glucose metabolism has not been fully explained, but the available data shows that insulin resistance is increased in smokers.

The smoking reduced insulin mediated glucose uptake by 10% to 40% in men who smoked compared with non –smoking men. In type 2 diabetic subjects, insulin and C-peptide responses to oral glucose load were significantly higher in smokers than non-smokers and the insulin resistance, as determined by the euglycemic clamp technique. Thus smoking induces resistance to insulin action in patients with type two diabetes, as well as in normal subjects.[112]

In addition to this, smoking also showed dyslipidemia prone to atherosclerosis. Smokers had higher fasting triglycerides and lower high density lipoprotein cholesterol levels and an increased proportion of small dense low density lipoprotein particles. Fibrinogen levels and plasminogen activator inhibitor 1 activity were also elevated in smokers.[113]

There has been studies which indicates the negative effects of smoking on wound healing.[114,115,116]

Smoking and diabetic micro-vascular complications

The smoking effects on micro-vascular diabetes complications vary across reports. Generally, smoking has an adverse effect on diabetic nephropathy, but the influence of smoking independently with glucose control, on retinopathy and neuropathy are unclear.

Smoking and Neuropathy

There are few studies about smoking and neuropathy. Smoking may effect diabetic neuropathy in different manner according to diabetic type. In type 2 patients, smoking was not a risk factor if the patient has polyneuropathy or sensory neuropathy as diagnosed by symptom and sign. There was no relationship between current or previous levels of smoking and the severity and duration of chronic painful neuropathy. But in the study by Tamer et al. while smoking was not associated with neuropathic complaints, using electromyography supported neuropathy examination there were significant relationships with smoking, as well as HbAlc. Therefore, lot of research are required to evaluate the association between smoking and neuropathy.[117,118].

Smoking and Macro-vascular complications

Smoking is a significant risk factor for all cause mortality, and for mortality due to Cerebral Venous Disease and CHD in diabetes. Smokers die on average 8 to 10 years younger than non-smokers, as age is entered into most multi-regression analysis.

Management of Diabetic Foot Ulcer

Diabetic foot ulcer is the most common complication of diabetes,that usually responds poorly, and leads to lower limb amputation.

Early effective management of DFU as follows:

- Education

- Blood sugar control
- Wound debridement
- Advanced dressing
- Offloading
- Advance therapies
- In some cases surgery

These advices reduces the grades of complications, and can improve overall quality of life of patients especially by using a multidisciplinary team approach.

In total, it is estimated that 15% of patients with diabetes will suffer from DFU during their lifetime. Although accurate figures are difficult to obtain for the prevalence of DFU, the prevalence of this complication ranges from 4% to 27%.[119,120]

To date, DFU is considered as a major source of morbidity and a leading cause of hospitalization in patients with diabetes. It is estimated that approximately 20% of hospital admissions among patients with DM are result of DFU[121,1,122].

Diabetes can lead to infection, gangrene, amputation and even death if necessary care is not provided. Once DFU has developed, there is an increased risk of ulcer progression to wet gangrene which leads to amputation. The rate of lower limb amputation in patients with DM is 15 times more than patients without diabetes. It is estimated that approximately 50%-70% of all lower limb amputations are mainly due to DFU[119,121]

It is reported that every 30 second one leg is amputated due to DFU worldwide.[120]

EDUCATION

Up to 50% of DFU cases are prevented by effective education. In fact, educating patients on foot self management is considered the cornerstone to prevent DFU. Currently, a wide range and combinations of patient educational interventions have been evaluated for the prevention of DFU such as [120,123,124]

- Brief education
- Intensive education including demonstration
- Hands on teaching

DFU patients are educated about need for foot care, including the need for[125]

- Self-inspection
- Monitoring foot temperature
- Appropriate daily foot hygiene
- Proper foot wear
- Blood sugar control

Blood sugar control

The patients with foot ulcers, sugar control is the most important metabolic factor. In fact, it is reported inadequate control of blood sugar is the primary cause of DFU. The best indicator of diabetic control over a period of time is HbAlc level.[126,127]

Glycated hemoglobin

This test measures the average blood sugar concentration over a 90-d span of the average red blood cell in peripheral circulation. The higher the HbA1C level, the more glycosylation of hemoglobin in red blood cells will result. The blood glucose level > 11.1mmol/L (equivalent to > 310 mg/mL or an HbA1C level of > 12) is associated with[127]

1. Decreased neutrophil function

2. Decreased leukocyte chemotaxis.

3. Suppressing inflammatory responses

4. Decreasing host response to an infection

In addition, it is indicated that a 1% mean reduction in Hb1C results in 25% reduction in micro vascular complications, including neuropathy. Investigations have found that poor glucose control accelerated the manifestation of Peripheral Arterial Disease (PAD).

For every 1% increase HbA1C, there is an increase of 25% -28% in the relative risk of PAD, this is a primary cause of DFU.[128,129]

Debridement

Debridement is the excision of necrotic and aged tissues, foreign and infected materials from a wound, which is considered as the initial and most important therapeutic step to wound healing and a decrease in the possibility of limb

amputations DFU patients. Debridement seems to decrease bacterial counts and stimulates production of local growth factors. This method also reduces pressure, evaluates the wound bed, and facilitates wound drainage.[129,130,131]

There are different kinds of debridement including surgical, enzymatic, autolytic, mechanical and biological.

Table 6: Different kinds of debridement for patients with diabetic foot ulcer[132]

Method	Advantage	Disadvantage
Surgical	Cost effective	Requires a certain amount of skill to prevent enlarging the wound
Mechanical	Allows removal of hardened necrosis	It is not discriminating and may remove granulating tissue
Enzymatic	They can be applied directly into the necrotic area	Streptokinase can be systematically absorbed and is therefore contraindicated in patients at risk of an myocardial infarction and its expensive
Autolytic	It's cost-effective It is suitable for an extremely painful wound	It's time consuming and may require an equivocal time for treatment
Biological	They discriminate between the necrotic and granulating tissue	There may be a objection to use this treatment by patients and doctors and it is expensive

Among these methods, surgical debridement is more effective in DFU healing. The method of debridement depends on characteristics, preferences and practitioner level of expertise.[130]

OFFLOADING

The use of offloading techniques, commonly known as pressure modulation, is considered the most important component for the treatment of neuropathic ulcers in patients with diabetes.[133]

The common offloading techniques in practice are:

1. Total contact cast-TCC
2. Removable cast walker –RCW
3. Instant total contact cast-iTCC

TCC is minimally padded and molded carefully to the shape of the foot with a heel for walking. The most effective offloading device for the management of neuropathic DFU is total contact casts (TCC).

RCW is cast –like device that is easily removable to allow for selfinspection of the wound and application of topical therapies that require frequent administration.

iTCC, which involves simply wrapping a RCW with a single layer of cohesive bandage, Elastoplast or casting tape, is another offloading technique that is shown to be more effective than TCC and RCW.[134]

Table 7: Common offloading techniques

Casting techniques	**Footwear related techniques**	**Surgical offloading techniques**	**Other techniques**
TCC	Shoes or half shoes	Achilles tendon lengthening	Bed rest
RCW	Sandals	Liquid silicone injections tissue augmentation	Crutches canes wheelchairs
iTCC	Insoles	Callus debridement	Bracing
Scotch –cast boots	In-shoe orthoses	Metatarsal head resection osteotomy Arthroplasty Osectomy Exostectomy	Felted from padding plugs
Windowed casts	shocks	External fixation	

Figure 19: Total contact cast (TCC) for patients with diabetic foot ulcer

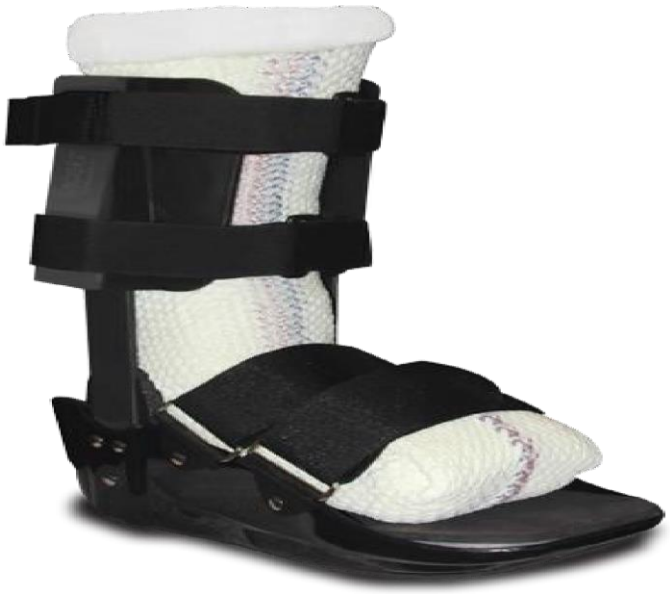


Figure 20: Removable cast walker(RCW) for patients with diabetic foot ulcer

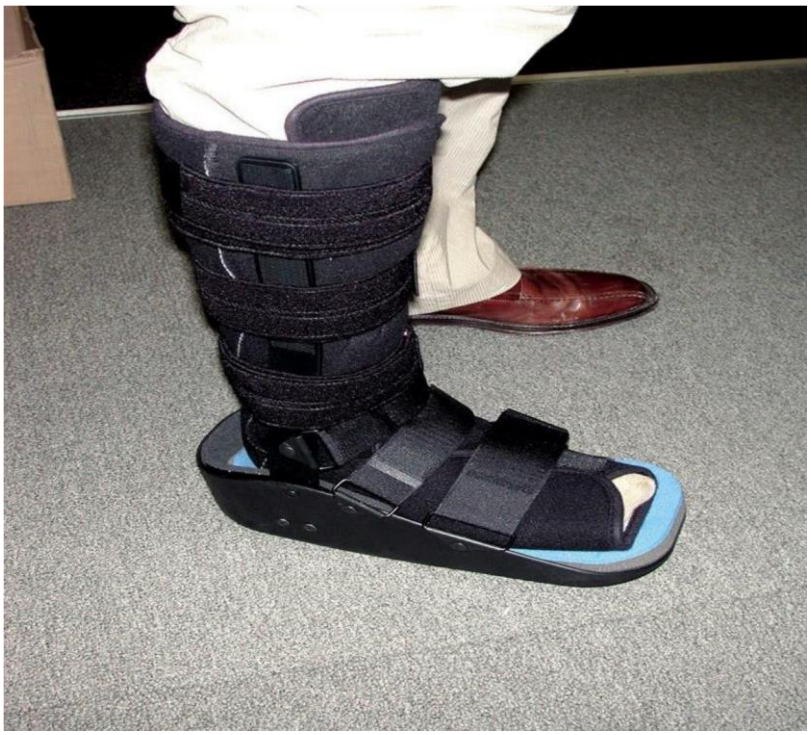
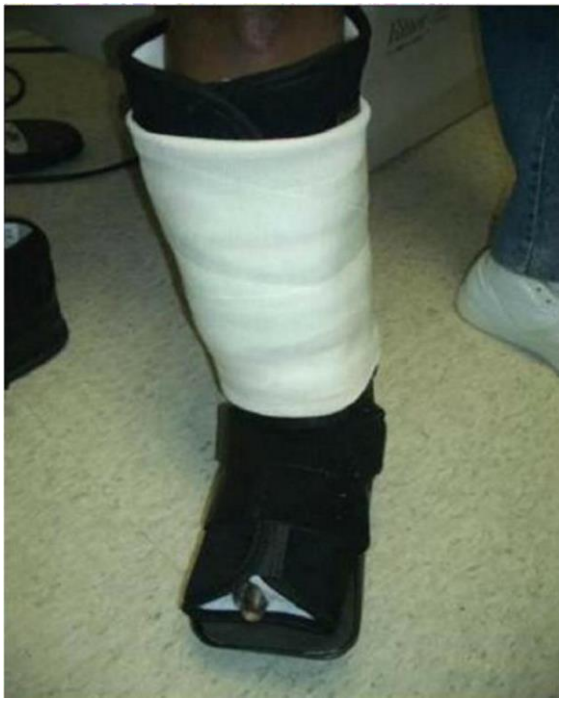


Figure 21: Instant total contact cast (iTCC) for patients with diabetic foot ulcers



ADVANCED DRESSING

Ideally, dressing should confer

1. Moisture balance
2. Protease sequestration
3. Growth factor stimulation
4. Antimicrobial activity
5. Oxygen permeability
6. Capacity to promote autolytic debridement which facilitates the generation of granulation tissues and the re-epithelialization process.

It should have a prolonged time of action, high efficiency and improved sustained drug release in the case of medicated therapies. Hence, no single dressing fulfills all the requirements of a diabetic patient with a foot ulcer.[135]

The choice of dressing is largely determined by[136]

1. The causes of DFU
2. Wound location
3. Depth
4. Amount of scar or slough
5. Exudates
6. Condition of wound margins
7. Presence of infection and pain, need for adhesiveness
8. Conformability of the dressing

Figure 22: Classification of advanced dressing types in diabetic foot ulcer treatment[135]

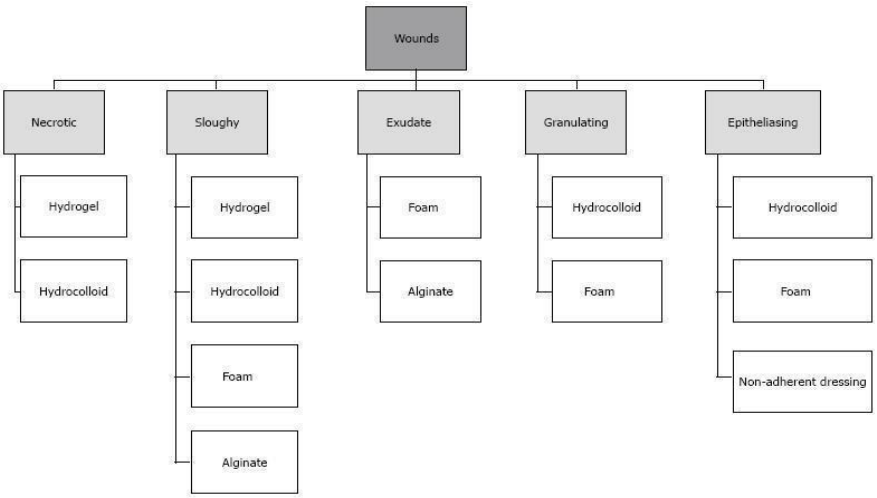


Figure 23: Hydrocolloid dressing

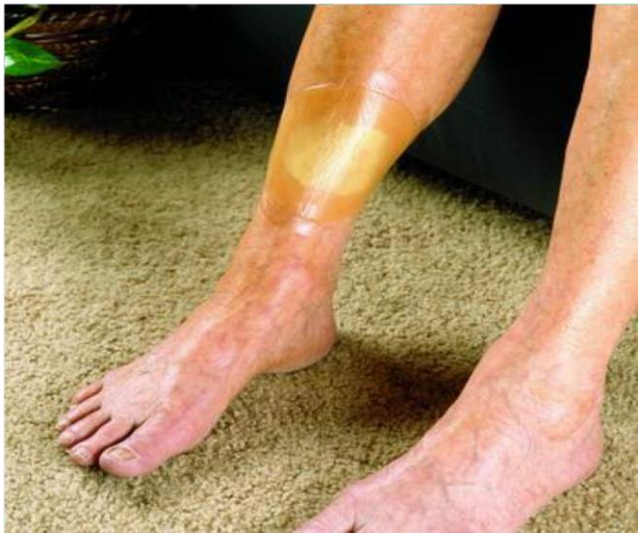


Table 8: Advanced dressing in diabetic foot ulcer

Type	Advantage	Disadvantage
Hydrocolloids	Absorbent Can be left for several days Aid autolysis	Concerns about use for infected wounds May cause maceration Unpleasant odor
Hydrogels	Absorbent Donate liquid Aid autolysis	Concerns about use for infected wounds May cause maceration using for highly exudative wounds
Foams	Highly absorbent and protective Manipulate easily Can be left up to seven days	Occasional dermatitis with adhesive Bulky May macerate surrounding skin

Films	Cheap Manipulate easily Permeable to water vapor and oxygen but not to water micro organisms	May need wetting before removal Aren't suitable for infected wounds Nonabsorbent If fluid collects under film it must be drained or the film replaced
Alginates	Bacteriostatic, hemostatic Highly absorbent Useful in cavities	May need wetting before removal
Silver impregnated	Antiseptic, absorbent Reduce odor Improved pain-related symptoms Decrease wound exudates	• High cost

SURGERY

Diabetic foot surgery plays an essential role in the prevention and management of DFU, and has been on the increase over the past 2 decades. Although surgical interventions for patients with DFU are not without risk, the selective correction of persistent foot ulcers can improve outcomes.[137]

In general, surgery for DFU healing includes

1. Vascular foot surgery
2. Nonvascular foot surgery
3. Amputation

Vascular foot surgery such as bypass grafts from femoral to pedal arteries and peripheral angioplasty to improve blood flow for an ischemic foot have been developed in recent past.

Nonvascular foot surgery is divided into[138]

1. Elective
2. Prophylactic
3. Curative
4. Emergent surgeries that aim to correct deformities that increase plantar pressure.

Table 9: Different types of nonvascular diabetic foot surgery[139]

Type	Explanation
Elective	Relieve the pain associated with particular deformities such as hammertoes, bunions, and bone spurs in patients without peripheral sensory neuropathy and at low risk for ulceration
Prophylactic	Prevent ulceration from occurring or recurring in patients with peripheral neuropathy and those with past history of ulceration (but without active ulceration)
Curative	To effect healing of non-healing ulcer or a chronically recurring ulcer when offloading and standard wound care techniques are not effective. These include multiple surgical procedure aimed at removing areas of chronically increased pressure and procedures for resecting infected bone or joints as an alternative to the partial foot amputation
Emergent	These are done to arrest or limit progression of acute infection

Indications for an amputation include[140]

1. The removal of infected or gangrenous tissues
2. Control of infection
3. Creation of a functional foot or stump that can accommodate footwear or prosthesis

ADVANCED THERAPIES

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) has shown excellent results in the management of serious cases of DFU, which are not responding to other therapeutic methods.[141,142,143,144]

HBOT involves intermittent administration of 100% oxygen, usually in daily sessions. During each session, patients breathed pure oxygen at 1.4-3.0 absolute atmospheres during 3 periods of 30 min (overall 90 min) intercalated by 5 min intervals in a hyperbaric chamber[145,141,146].

Some studies have reported that HBOT[147,148,149,150]

1. Improved wound tissue hypoxia
2. Enhanced perfusion
3. Reduced edema
4. Down regulated inflammatory cytokines
5. Promoted fibroblast proliferation
6. Collagen production

7. Angiogenesis
8. Stimulated vasculogenic stem cell mobilization from bone marrow

Figure24: Hyperbaric oxygen chamber

Electrical stimulation[151]

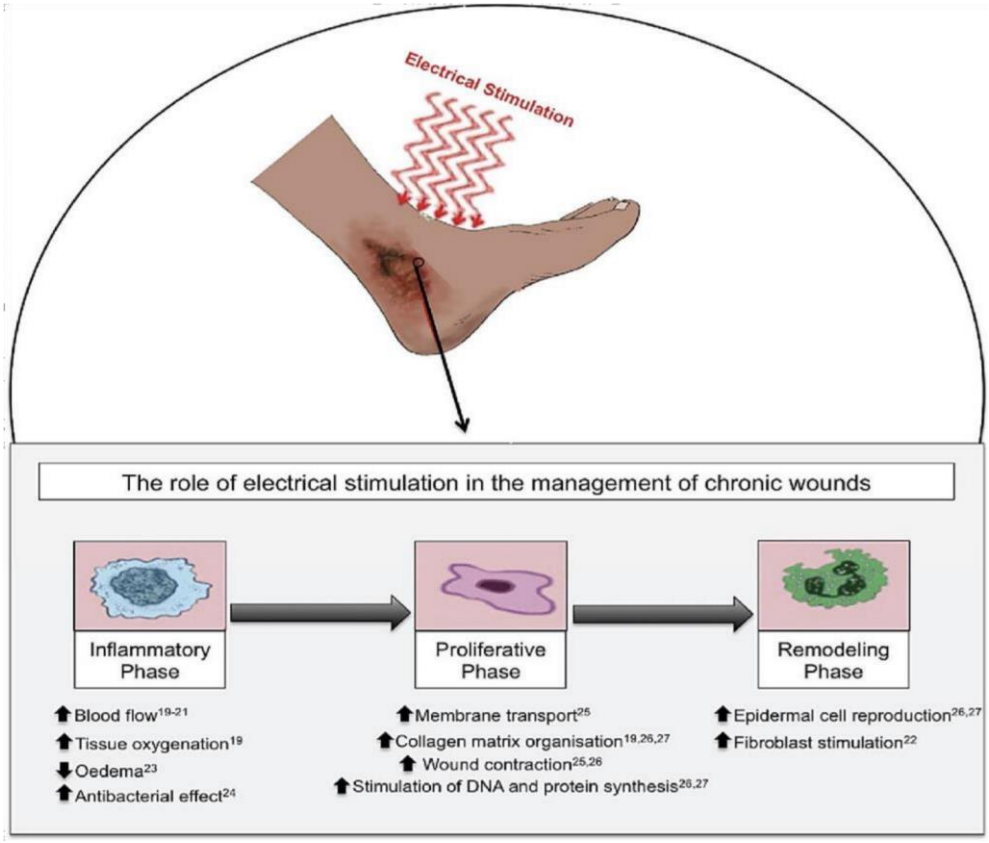
Electrical stimulation (ES) is a perfect adjunctive therapy for DFU healing. Presently, there is substantial body of work which is supporting the effectiveness of ES for DFU healing.

It is suggested that ES could improve common deficiencies which are associated with faulty wound healing in DFU, such as

1. Poor blood flow
2. Infection
3. Deficient cellular responses

This therapy is a safe, inexpensive and a simple intervention to improve wound healings in patients with DFU.

Figure 25: Role of electrical stimulation in chronic wounds



Negative pressure wound therapy

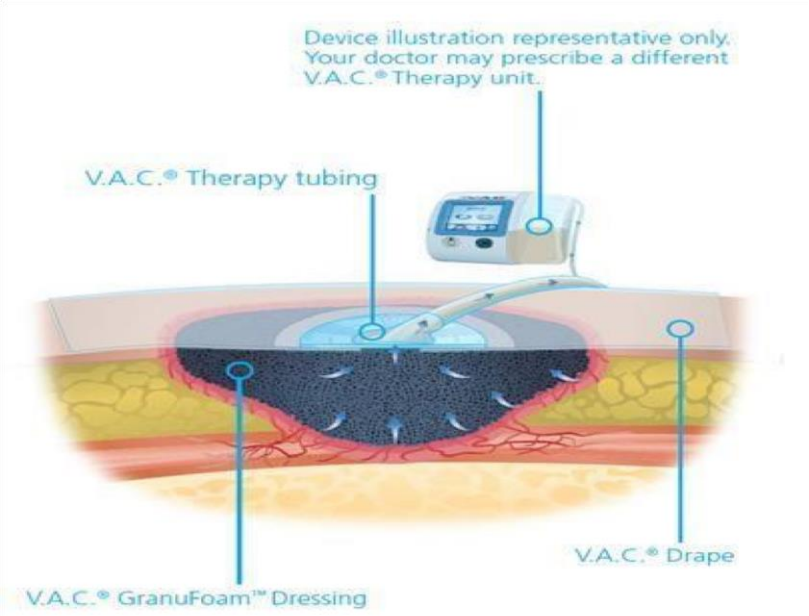
Negative pressure wound therapy (NPWT) is a noninvasive wound closure system that uses controlled, localized negative pressure to help heal chronic and acute wounds. This system uses latex-free and sterile polyurethane or polyvinyl alcohol foam dressing that is fitted at the bedside to the appropriate size for every wound and then covered with an adhesive drape to create an airtight seal. Most commonly, 80-

125 mmHg of negative pressure is used, either continuously or in cycles. The fluid suctioned from the wound is collected into a container in the control unit.

It seems that NPTW[152,153,154]

1. Removes edema and chronic exudate
2. Reduces bacterial colonization
3. Increases cellular proliferation
4. Improves wound oxygen due to applied mechanical force

Figure 26: Schematic drawing of the negative pressure wound treatment[155]



Bio-Engineered Skin

Bio-engineered skin (BES) has been used during the past as newer therapeutic method to treat DFU. This method replaces the degraded and destructive milieu of extra cellular matrix (ECM) with the introduction of a new ground substance matrix with cellular components to start a new healing trajectory.[156]

BES product cells are seeded into the scaffolds and cultured in vitro. In vitro incubation establishes the cells and allows the cell-secreted Extra Cellular Matrix to accumulate scaffold. The cells within live cell scaffolds are believed to accelerate DFU healing by actively secreting growth factors during the repair process.[156]

In addition, it seems that BES can provide the cellular substrate and molecular components necessary to increase healing process and angiogenesis. They act as biologic dressings and as delivery systems for growth factors and ECM components through the activity of fibroblasts in the dermal elements. Despite the advantages of BES, they cannot be used in isolation to treat DFU. Peripheral ischemia, which is one of the pathological characteristics of DFU, is a critical contributing factor that effects BES transplantation.[157]

Table 10: Brief description of commonly used bioengineered tissue products

Type	Uses
Apligraf	It‟s used for full-thickness neuropathic DFU of greater than 3 week duration, resistant to standard therapy (also without tendon, muscle, capsule or Bone exposure) and is contraindicated in infected ulcers
Dermagraft	It's used for DFU of greater than 6 week duration, full thickness in depth but without tendon, muscle ,joint or bone exposure and is contraindicated is infected ulcers
Oasis	It's used for full-thickness DFU

Growth factors

DFU has demonstrated the benefits from growth factors (GFs) such as [158]

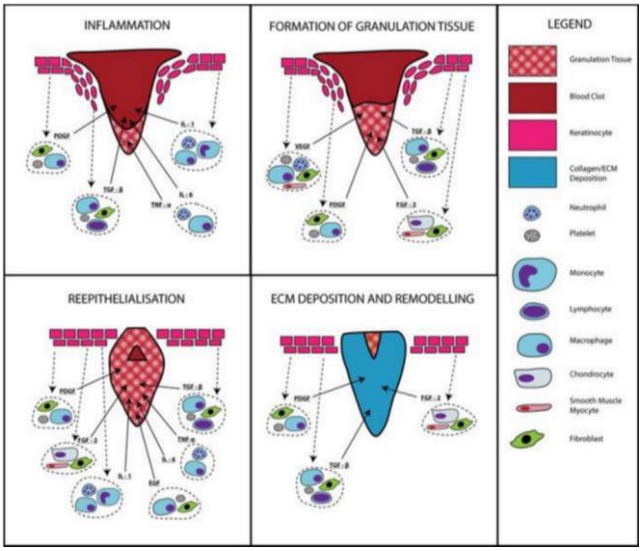
1. Platelet derived growth factor(PDGF)
2. Fibroblast growth factor
3. Vascular endothelial growth factor
4. Insulin-like growth factors(IGF1,IGF2)
5. Epidermal growth factor
6. Transforming growth factor β

Among the aforementioned GFs, only recombinant human PDGF (rhPDGF) (Becaplermin), is a hydrogel that contains 0.01% of PDGF-BB (rhPDGF-BB), has demonstrated increased healing rates.

GFs is used to[84,151]

1. Stimulate chemotaxis
2. Mitogenesis of neutrophils, fibroblast, monocytes and other components that form the molecular basis of healing of wound
3. Infiltrating fibroblasts

Figure 27: Growth factors role in wound healing



Platelet Rich Plasma

PRP is referred as a plasma fraction of autologous blood having concentration of the platelets above baseline.[159,123]

PRP or platelet-enriched plasma, platelet-rich concentrate, autologous platelet gel and platelet releasate.[145]

Platelet releasates have been used to treat wounds since 1985[51]. PRP serves as a growth factor agonist and has chemotactic and mitogenic property[123,160,161,162].

It is used in treatment of chronic skin and soft tissue ulcerations, other areas where PRP is used include periodontal and oral surgery, maxillofacial surgery[39,163,164,166,165,167,168]

Orthopedic and trauma surgery, cosmetic and plastic surgery, spinal surgery, heart bypass surgery and burns[39,129,139,166,169,170,171,172,173].

Mechanism of action of Platelet Rich Plasma

PRP functions by activation of platelets, which contains numerous granules with in it and activation of which causes release of the agents and help in wound healing and via α-granules.[162,174,175]

The proteins contained in α-granules of platelets include PDGF (isomers are PDGF-AA, BB and AB), transforming growth factor-β (TGF-β) PF4,IL-1,platelet derived angiogenesis factor(PDAF), vascular endothelial growth factor(VEGF), epidermal growth factor (EGF), platelet derived endothelial growth factor (PDEGF) , epithelial cell growth factor(ECGF), insulin like growth factor (IGF),osteocalcin(Oc), Osteonectin(On),fibrinogen(Ff), vitronectin(Vn).[161,166,167,172,173,175,176,177,178,179,180181,172]

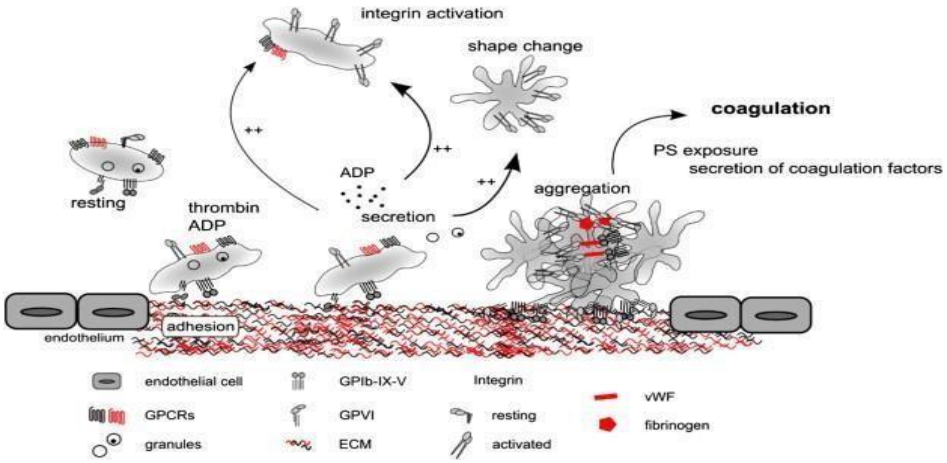
PRP also play a role in host defense mechanism at the wound site by producing signaling proteins that attract macrophages, PRP also may contain a small number of

Leukocytes that synthesize interleukins as a part of a non-specific immune response. Previous studies of PRP have demonstrated antimicrobial activity against Escherichia coli, Staphylococcus aureus, including methicillin-resistant staphylococcus aureus, Candida albicans and Cryptococcus neoformans.[165,169,172,182,183]

Platelet activation cascade

Under physiological conditions, platelets circulate in close proximately to the vascular walls[184], but are protected from untimely activation by the healthy endothelial monolayer which provides a natural "barrier" to thrombosis, as well as by the release of inhibitory mediators such as nitric oxide and PG12 from the intact endothelium. Platelets become activated when the continuity of the endothelial layer is disrupted and the underlying sub endothelial matrix is exposed, or if inflammation perturbs the endothelium. Platelet receptors then interact with collagen and Von Willebrand factor among others, which capture the platelets and induce activation signals. The initial events following platelet activation are summarized as follows.[184]

Figure 28: Activation cascade of platelet leading to the platelet plug information[183]

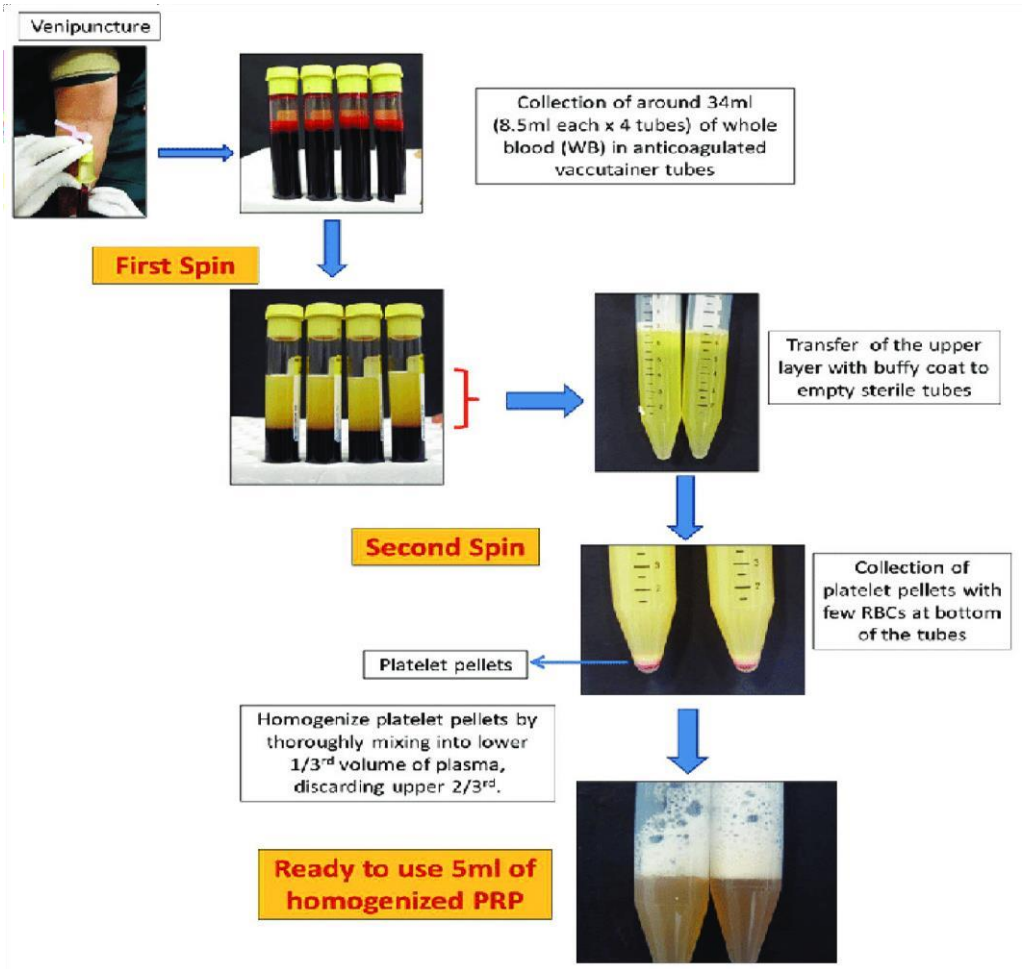


Preparation of PRP[185,186]

PRP is prepared by a process known as differential centrifugation. In differential centrifugation, acceleration force is adjusted to sediment certain cellular constituents based on different specific gravity.

There are many ways of preparing PRP. It is of two types mainly by the PRP method and by the buffy-coat method.

Figure29: Preparation of PRP



There is no debut on whether platelets must be activated previously or not before their application and with which agonist. Some authors activate platelets with thrombin or calcium, whereas others apply platelets without being previously activated arguing that better results are obtained.

PRP method

- Obtain blood by venipuncture in acid citrate dextrose tubes.
- Do not clot the blood at any time before or during platelet separation.
- Centrifuge the blood using a ‘’soft’’ spin.
- Transfer the plasma containing platelet into other sterile tube(without anticoagulant)
- Centrifuge tube at a higher speed (a hard spin) to obtain a platelet concentrate.
- The lower one-third is PRP and upper two- third is Platelet–Poor Plasma(PPP). At the bottom of the tube, platelet pellets are formed.
- Remove PPP and suspend the platelet pellets in a minimum quantity of plasma (2-4mL) by gently shaking the tube.

Buffy coat method

1. Whole Blood should be stored at 20 to 24^{o}C before centrifugation.
2. Centrifuge whole blood at a high speed.
3. 3 layers are formed because of its density: the lower layer consisting of RBCs, the middle layer has platelets and WBCs and the upper PPP layer.
4. Remove supernatant plasma from the top of the container.

5. Transfer the buffy-coat layer to the another sterile tube.
6. Centrifuge to separate WBCs or use leukocyte filtration filter.

Commercially available PRP kits

PRP devices can be usually divided into

1. Lower (2.5-3 times baseline concentration)
2. Higher (5-9 times baseline concentration) systems.

The lower concentration systems include Arthrex ACP, Cascade PRP therapy and PRGF by biotech institute Vitoria, Spain. The high-yielding devices include Biomet GPS II and III, Harvest smartPRep 2, Arterio Cyte Medtronic Magellan.

Side effects of PRP

It is an autologous preparation, PRP is inherently safe and therefore it is free from transmissible diseases such as HIV, Hepatitis etc. During the preparation of PRP calcium chloride and bovine thrombin are used.

The use of bovine thrombin can cause development of auto antibodies to the clotting factors V, XI and thrombin this results in the risk of life threatening coagulopathies. Bovine thrombin preparation contains factor V, which can result in the stimulation of immune mechanism when given with a new protein.

METHODOLOGY

MATERIALS AND METHODS

The study titled "**A COMPARATIVE STUDY OF PLATELET RICH PLASMA DRESSING VS NORMAL SALINE DRESSINGS IN THE MANAGEMENT OF DIABETIC FOOT ULCER**" was carried out in department of surgery in R.L. JALAPPA HOSPITAL, TAMAKA, KOLAR

1. **Study design**: prospective Comparative study

2. **Period of study**: Dec 2017- June 2019

3. **Study group**: The study included 90 patients with diabetic foot ulcer admitted in wards or attending the outpatient departments who met the inclusion criteria

4. **Sample size**

- Total patients : 90
- Study group : 45
- Control group : 45

Inclusion criteria:

1. Patients with type 2 diabetes mellitus with diabetic foot ulcers of Wagner's grade 1 and 2.

Exclusion criteria:

1. Patients with uncontrolled diabetes i.e, HbA1c level more than 10.
2. Patients with peripheral vascular disorders and Chronic Venous Insufficiency.

Our study was carried out at RL Jalappa hospital and Research Institute, tamaka, olar, for a study period - 1and half year. In our study 90 patients with diabetic foot ulcer were included. The included patients were randomized into study and control group for our study using an open label randomization method. The history was taken and data was carefully entered in to the pretested and predesigned proforma.

Patients who are included in the study were informed about the necessary of study and an informed consent was obtained. Among the 90 patients in the study, 45 patients underwent treatment with conventional normal saline dressing and were assigned to control group, remaining 45 patients underwent PRP dressing and were assigned to group study.

Routine blood investigation was done and culture from the ulcer site was taken for both the groups, both group patients are strictly monitored and treated to obtain glycaemic control. If the obtained culture grows any organism, appropriate antibiotic were started as per the culture sensitivity report for both the groups. The antibiotics were administered for recommended days and if needed. Ulcer is monitored closely and debridement of the wound is undertaken whenever necessary, X-ray foot was taken for both the group patients and any bone involvement is ruled out.

The ulcer size is measured at the presentation and total initial area is calculated and recorded. The size of the ulcer is again measured after respective treatment for each group was carried out for 30 days. The final area of the ulcer is calculated and recorded .for control group the dressing is changed on daily basis, whereas for the study group, the dressing is changed once in 5 days. The results are then calculated using student t-test.

DRESSING TECHNIQUE

For control Group-saline dressing:

After thorough debridement and cleaning of the wound with normal saline, a saline soaked gauze piece are placed over the ulcer and then covered with pad and roller bandage. Patient are advised to take appropriate care of the wound dressing.

For study group –PRP dressing:

3.8w/v% sodium citrate is drawn in a10ml vacuum tube, sodium.

Citrate is used to bind with free calcium ions to prevent blood clotting.

9ml of patient's blood I withdrawn using a 18G needle to limit irritation and trauma to platelet, so that they would remain in intact state.

We use PRP method to obtain platelet rich plasma.

In First spin the tube is spun at 250G for ten min. three layers are formed due to difference in density of blood components. The top layer is platelet poor plasma, the middle layer contains platelet and leukocytes and deep layer contains Red blood

cells, Middle layer and top layer are collected by gentle aspiration with pipette and transformed to new sterile centrifuge tube.

During the second spin the tube is spun at 500G for 10min, the top two thirds of the portion accepted as PPP are removed. Remaining part is considered PRP and is obtained for transfer onto wound site.

The platelet rich site plasma is then applied over the ulcer area and covered with gauze and dressing done with pad and roller bandage. Patient are advised to take appropriate are of the wound dressing.

In both groups, dressing is changed, daily morning dressing change for control group and once in 5 days for study group. The ulcer is closely monitored and whenever debridement is needed, it is done and respective dressing applied. The initial area and final area of the ulcer size is measured and values recorded in chart for statistical analysis.

After recording the values in study and control group, we calculate the % of reduction in ulcer size after 30 days using the below formula for each patient in both groups

Percentage of wound contraction $= \frac{(initial\ wound\ area - final\ wound\ area)}{(initial\ wound\ area\ )} \times 100$

The values are noted in the chart for statistical analysis.

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data. Continuous data was represented as mean and SD. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and line.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

RESULTS

Table11: Distribution of age

		Sex			
		Female		Male	
		Count	%	Count	%
Age Group	30 - 40 Years	1	5.3%	12	16.9%
	41 - 50 Years	7	36.8%	20	28.2%
	51 - 60 Years	7	36.8%	17	23.9%
	61 - 70 Years	2	10.5%	16	22.5%
	> 70 Years	2	10.5%	6	8.5%
	Total	19	100.0%	71	100.0%

$\chi 2 = 3.870$, df $= 4$, $p = 0.424$

In the study, majority of population were in age group of 40 to 60 years (51 patients) and followed by 7th decade (18 patients). Least common occurrence of diabetic foot ulcers were in age group of more than 70 years (8 patients).

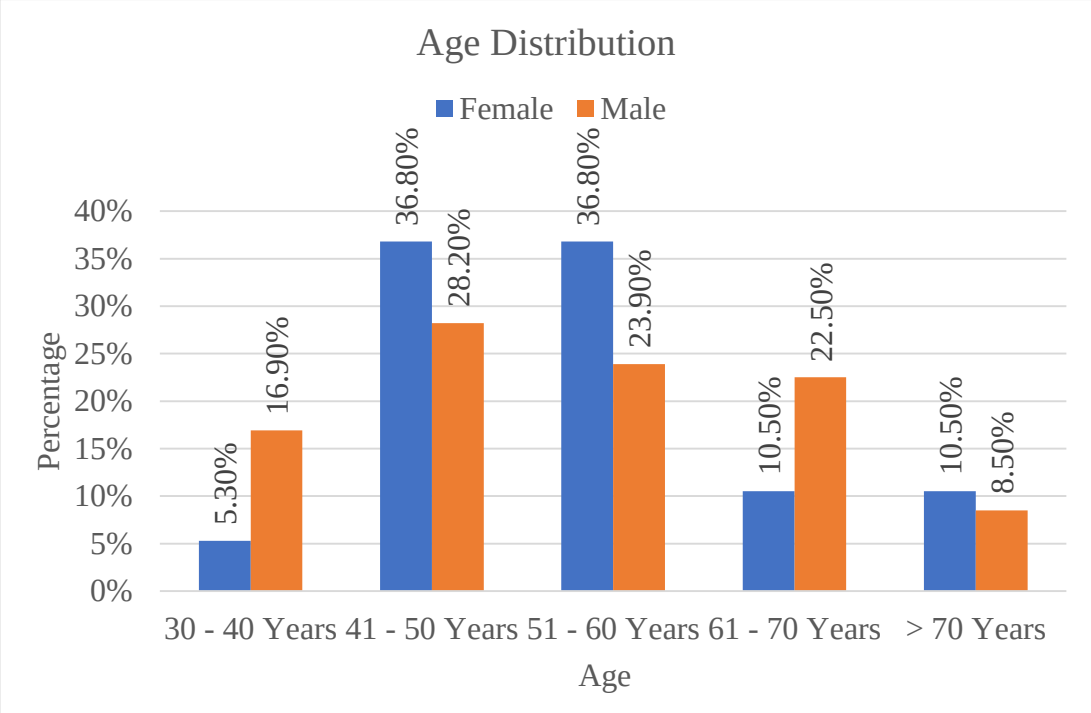


Chart 1 : Bar Diagram Showing Age distribution

Table 12: Age distribution in Study group

		Sex					
		Female		Male		Total	
		Count	%	Count	%	Count	%
Age Group	30 - 40 Years	1	9.1%	8	23.5%	9	20.0%
	41 - 50 Years	4	36.4%	8	23.5%	12	26.7%
	51 - 60 Years	3	27.3%	8	23.5%	11	24.4%
	61 - 70 Years	1	9.1%	7	20.6%	8	17.8%
	> 70 Years	2	18.2%	3	8.8%	5	11.1%

$\chi 2 = 2.7$, df $= 4$, $p = 0.609$

In Study group, majority of patients were in the age group of 41 to 50 years (12 patients) (26.7%) followed by 11 patients, who were in age group of 51-60 years and least common were in age group more than 70 years.

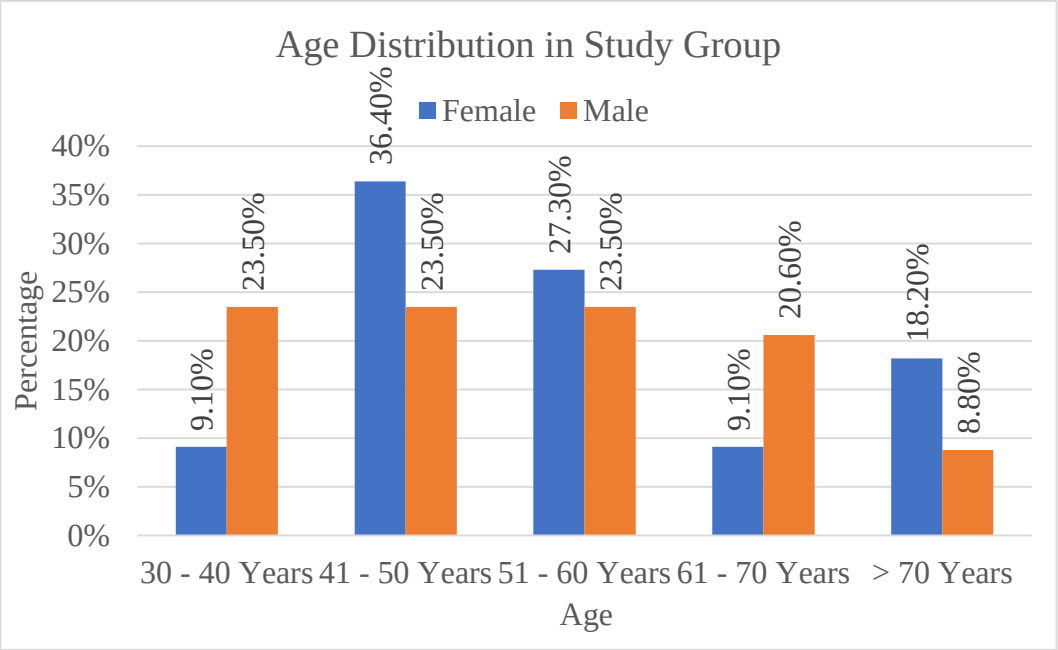


Chart 2: Bar Diagram Showing Age distribution in Study group

Table 13: Age distribution in Control group

		Sex					
		Female		Male		Total	
		Count	%	Count	%	Count	%
Age Group	30 - 40 Years	0	0.0%	4	10.8%	4	8.9%
	41 - 50 Years	3	37.5%	12	32.4%	15	33.3%
	51 - 60 Years	4	50.0%	9	24.3%	13	28.9%
	61 - 70 Years	1	12.5%	9	24.3%	10	22.2%
	> 70 Years	0	0.0%	3	8.1%	3	6.7%

χ 2 =3.479, df =4, p =0.481

In Control group, majority of patients were in the age group 41 to 50 years (18 patients) (33.3%) and least common were in age group more than 70 years.

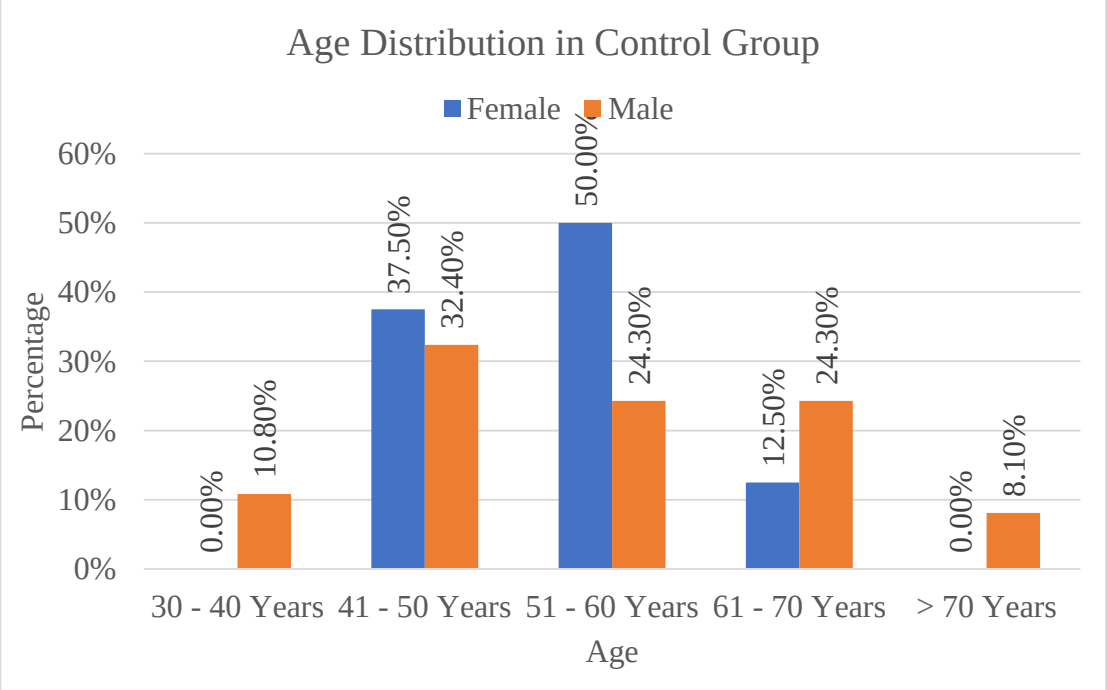


Chart 3: Bar Diagram Showing Age distribution in Control group

Table 14: Sex distribution

		Count	%
Sex	Male	71	78.9%
	Female	19	21.1%

In the study of 90 patients the male patients constituted 78.9% (71 patients) and female patients constituted 21.1% (19 patients).

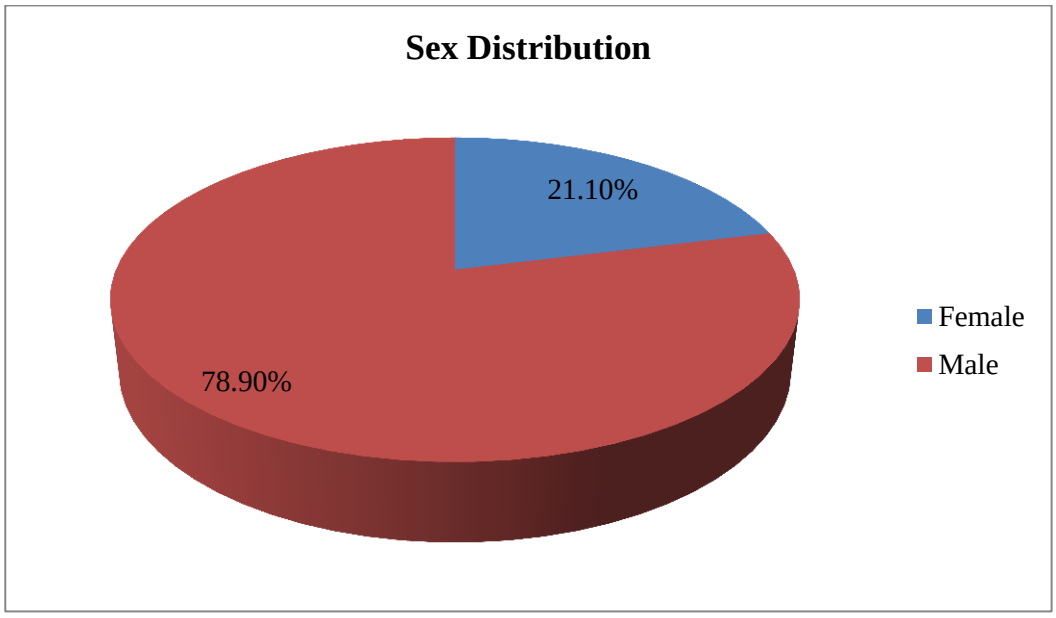


Chart 4: Pie Diagram Showing Sex distribution

Table 15: Sex distribution in each group

		Group			
		Control Group		Study Group	
		Count	%	Count	%
Sex	Male	37	82.2%	34	75.6%
	Female	8	17.8%	11	24.4%

$\chi 2 = 0.6000$, df $= 1$, p $= 0.438$

In Study group, 34 patients were males (75.6%) and 11 patients are females (24.4%) and in control group, 37 were males (82.2%) and 8 were females (17.8%) and the difference is not statistically significant in sex distribution.

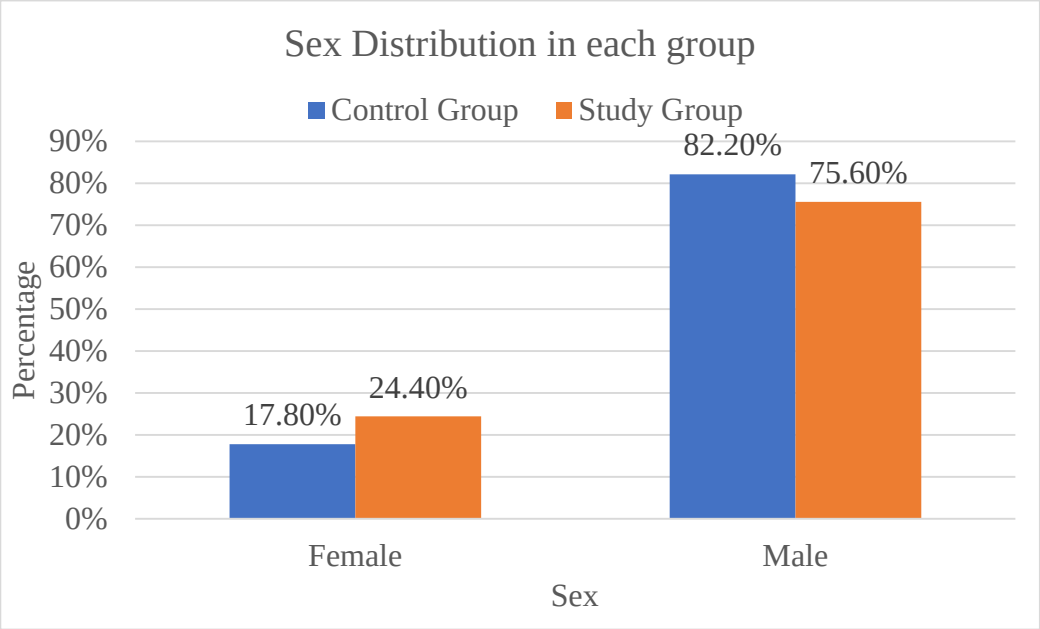


Chart 5 : Bar Diagram Showing Sex distribution in each group

Table 16: Mean Percentage of reduction of ulcer size in each group based on gender

	Group				P value
	Control Group		Study Group		
	Mean	SD	Mean	SD	
Male	19.94	6.72	38.81	6.03	<0.001*
Female	18.19	7.66	36.29	5.10	<0.001*

In our study it was observed that the mean percentage of reduction was higher in study group male patients (38.81%) and female patients (19.94%) compared to control group male patients (19.94%) and female patients (18.19%) respectively.

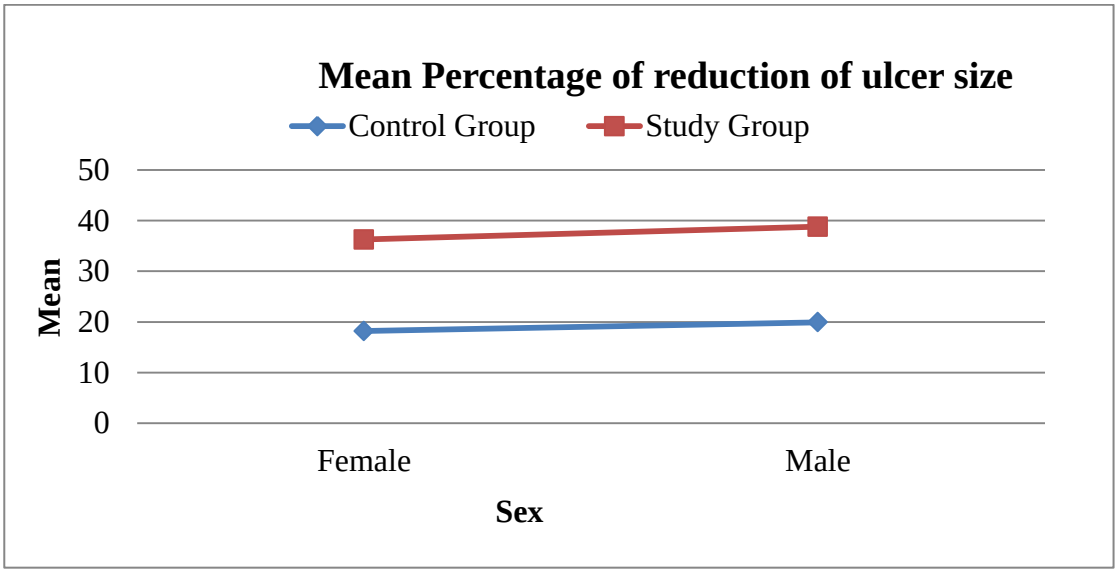


Chart 6: Line Diagram Showing Mean Percentage of reduction of ulcer size in each group based on sex

Table 17: Overall Mean reduction in ulcer size among each gender

	Sex				P value
	Female		Male		
	Mean	SD	Mean	SD	
% Reduction	28.67	11.03	28.98	11.42	0.916

In our study it was observed that over all mean percentage of reduction of ulcer size was higher in males (28.89%) as compared to female patients (28.67%) in females.

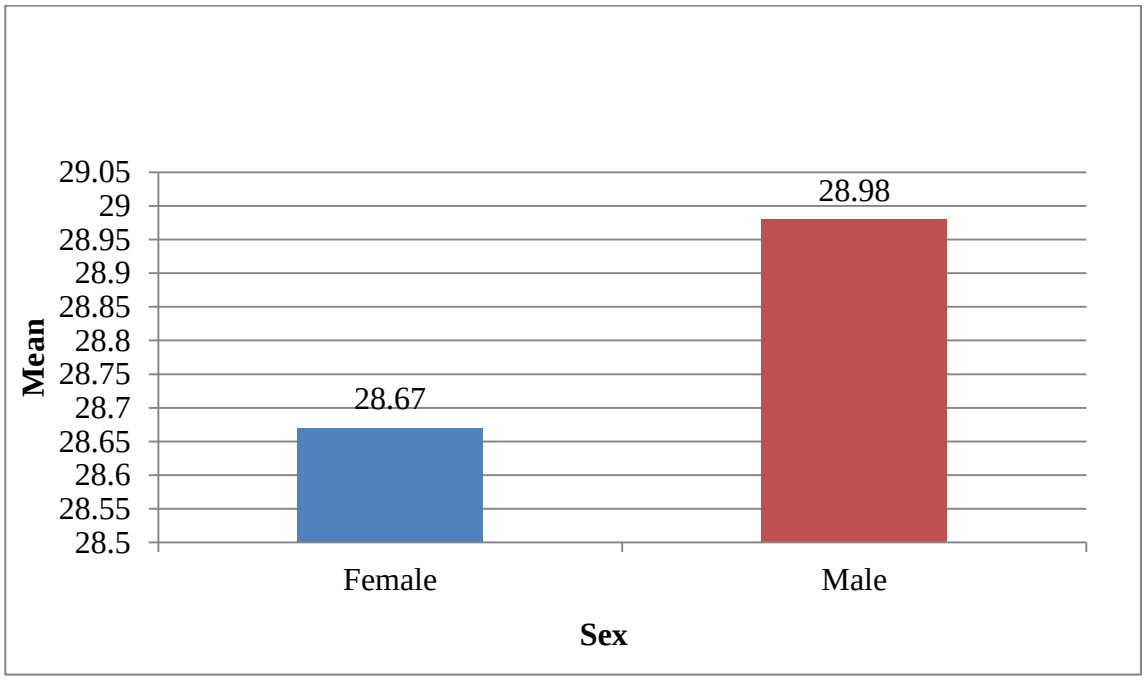


Chart 7: Bar Diagram Showing Overall Mean reduction in ulcer size among each gender

Table 18: Onset of Ulcer distribution in both groups

		Count	%
Onset	Traumatic	57	63.33%
	Spontaneous	33	26.67%
	Total	90	100%

In the study, 57 patients (63.3%) had traumatic onset and 33 patients (26.67%) had spontaneous onset of diabetic foot ulcer.

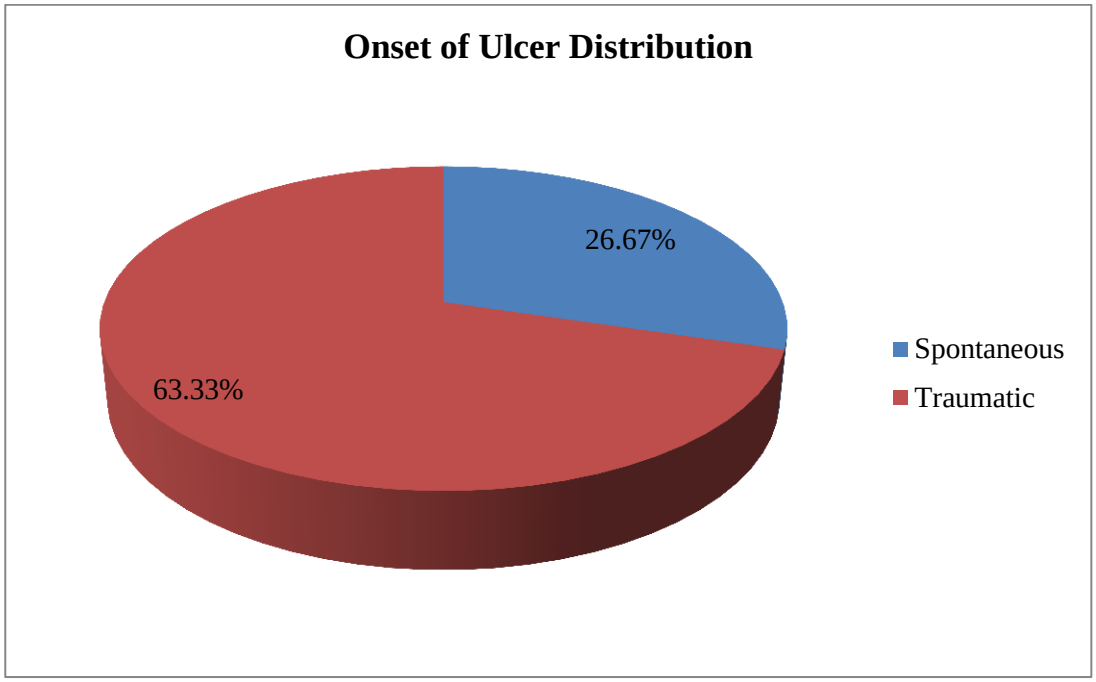


Chart 8: Pie Diagram Showing Onset of Ulcer distribution in both groups

Table 19: Onset of Ulcer in each group

		Group					
		Control Group		Study Group		Total	
		Count	%	Count	%	Count	%
Onset	Spontaneous	17	37.8%	16	35.6%	33	36.7%
	Traumatic	28	62.2%	29	64.4%	57	63.3%

$\chi 2 = 0.048$, df =1, p =0.827

It was observed in the study, the common cause of diabetic foot ulcer in study group, was due to trauma (64.4%) than compared to spontaneous cause (36.7%).

In control group, traumatic onset of ulcer was in (62.2%) than compared to spontaneous onset (37.8%).

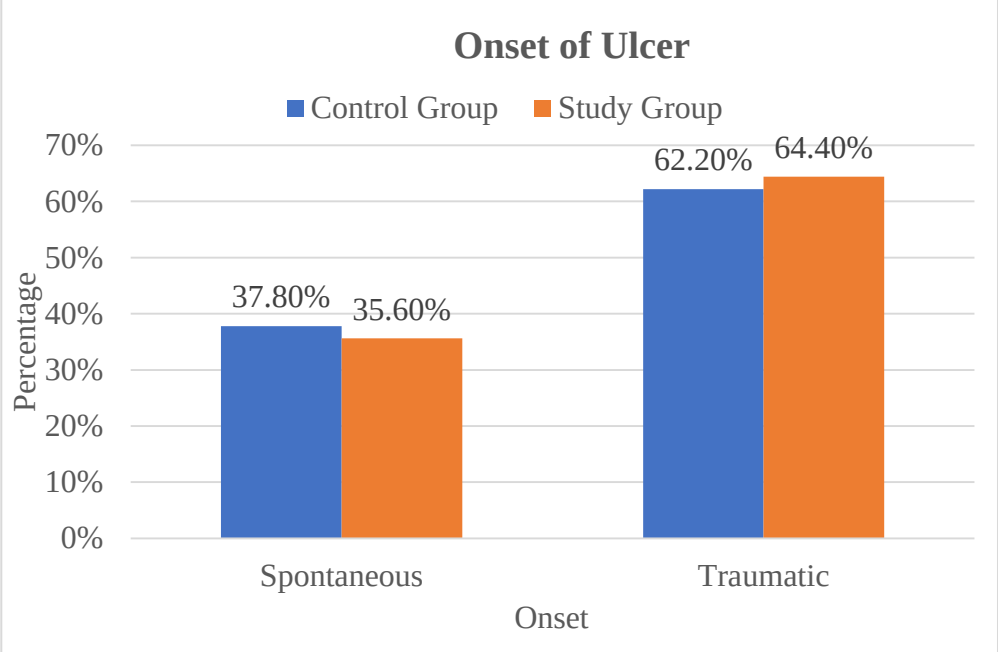


Chart 9: Bar Diagram Showing Onset of Ulcer in each group

Table 20: Mean reduction of ulcer size in both groups based on onset

	Group				P value
	Control Group		Study Group		
	Mean	SD	Mean	SD	
Spontaneous	18.75	6.49	37.62	5.02	<0.001*
Traumatic	20.16	7.10	38.51	6.34	<0.001*

In the study, it was observed that the mean reduction of ulcer size was higher in study group than compared to control group. The mean reduction in ulcer size due to spontaneous cause was higher in study group (37.62%) than compared to control group (18.75%).

In mean reduction in ulcer size due to trauma was higher in study group (38.51%) than compared to control group (20.16%).

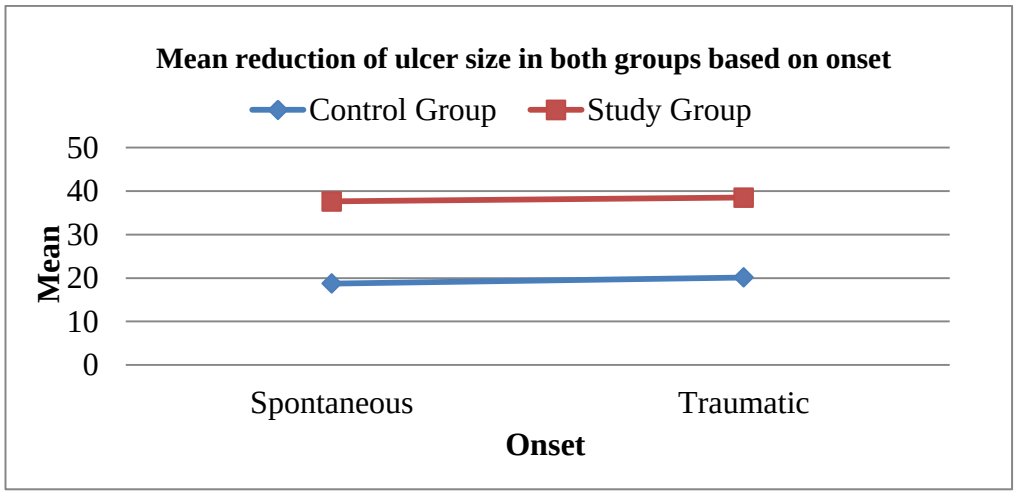


Chart 10: Line Diagram Showing Mean reduction of ulcer size in both groups based on onset

Table 21: Site of Ulcer distribution in both groups

		Count	%
Site	Dorsal	38	42.2%
	Plantar	52	57.8%

In the study, 52 patients (57.8%) had ulcer on plantar aspect and 38 patients (42.2%) had over the dorsal aspect.

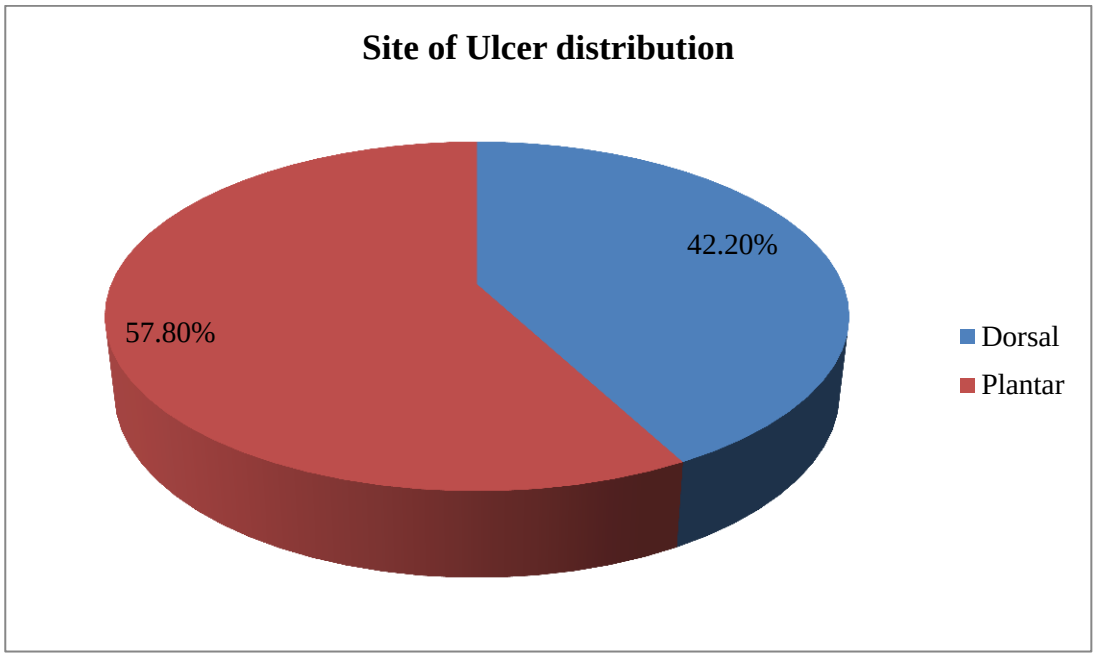


Chart 11: Pie Diagram Showing Site of Ulcer distribution in both groups

Table 22: Site of Ulcer distribution in each group

		Group					
		Control Group		Study Group		Total	
		Count	%	Count	%	Count	%
Site	Dorsal	22	48.9%	16	35.6%	38	42.2%
	Plantar	23	51.1%	29	64.4%	52	57.8%

$\chi 2 = 1.640$, df =1, p =0.200

In the study group, it was observed that diabetic foot ulcer occurred more commonly in plantar aspect (64.4%) compared to dorsal aspect of the foot (35.6%). In control group, it was observed that ulcer over plantar aspect was more (51.1%) as compared to dorsal aspect of the foot (48.89%).

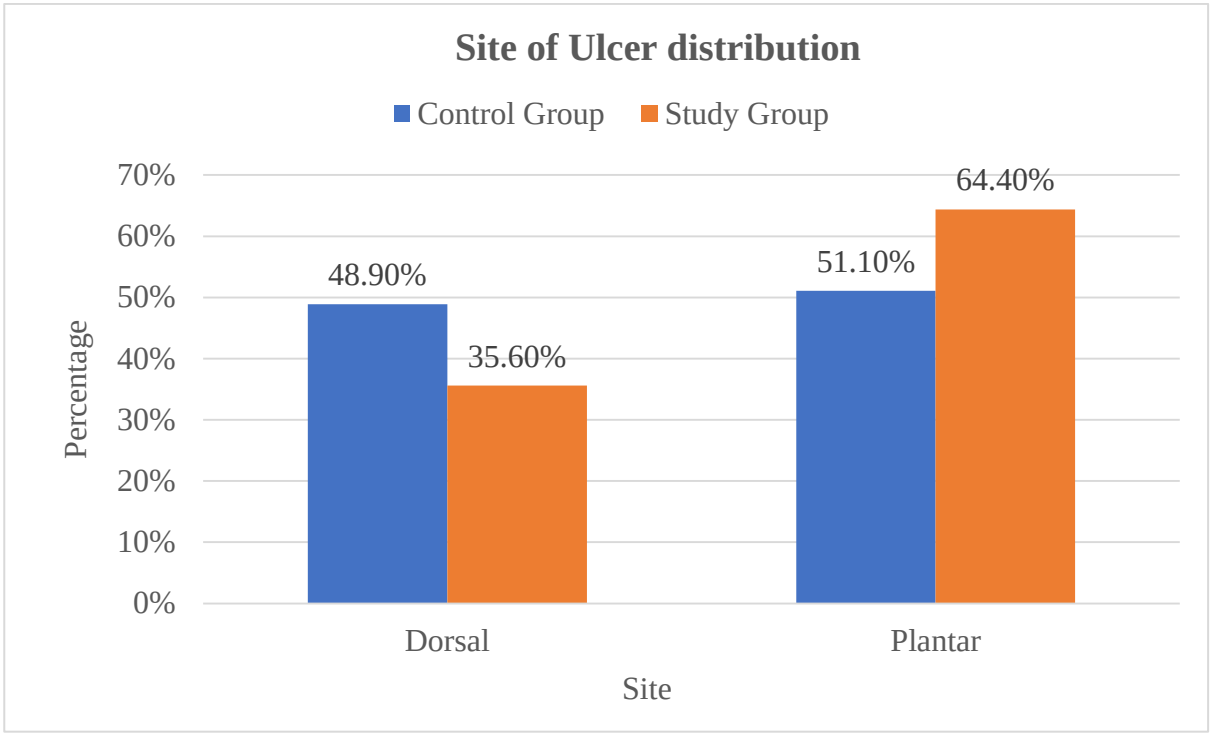


Chart 12: Bar Diagram Showing Site of Ulcer distribution in each group

Table 23: Mean reduction in Ulcer size in each group based on site

	Group				P value
	Control Group		Study Group		
	Mean	SD	Mean	SD	
Dorsal	17.14	5.87	36.81	5.33	<0.001*
Plantar	22.01	6.96	38.96	6.09	<0.001*

In the study, it was observed that the mean reduction of ulcer size was higher in study group (37.75%) compared to control group (19.22%) depending on the site of ulcer.

It was observed that patients with diabetic foot ulcer in plantar aspect of the foot had higher mean reduction of ulcer size in study group (38.96%) than compared to control group (22.01%).

It was observed that patients with diabetic foot ulcers in dorsal aspect had higher mean reduction of ulcer size in study group (36.81%) than compared to control group (17.14%).

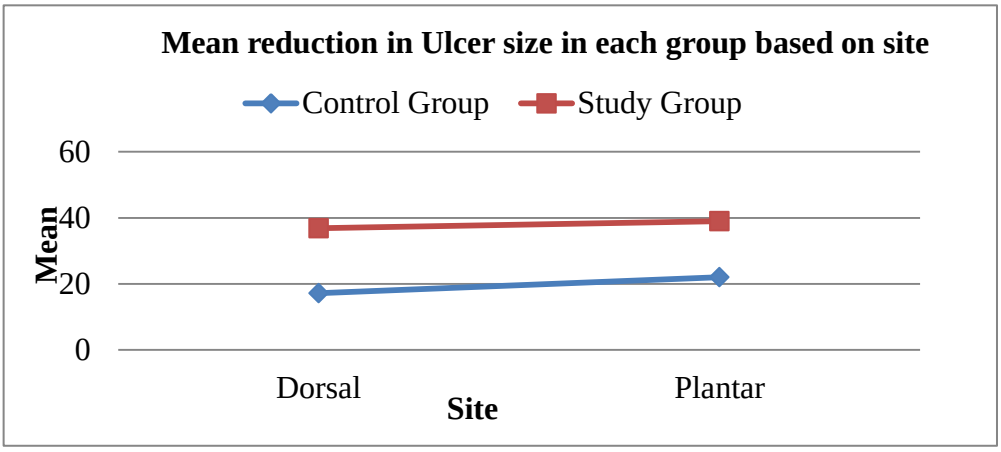


Chart 13: Line Diagram Showing Mean reduction in Ulcer size in each group based on site

Table 24: Ulcer distribution in both groups based on Wagner grading

		Count	%
Wagner grade	1	38	42.2%
	2	52	57.8%

In the study 52 patients (57.8%) had Wagner grade 2 and 38 patients (42.2%) had Wagner grade 1.

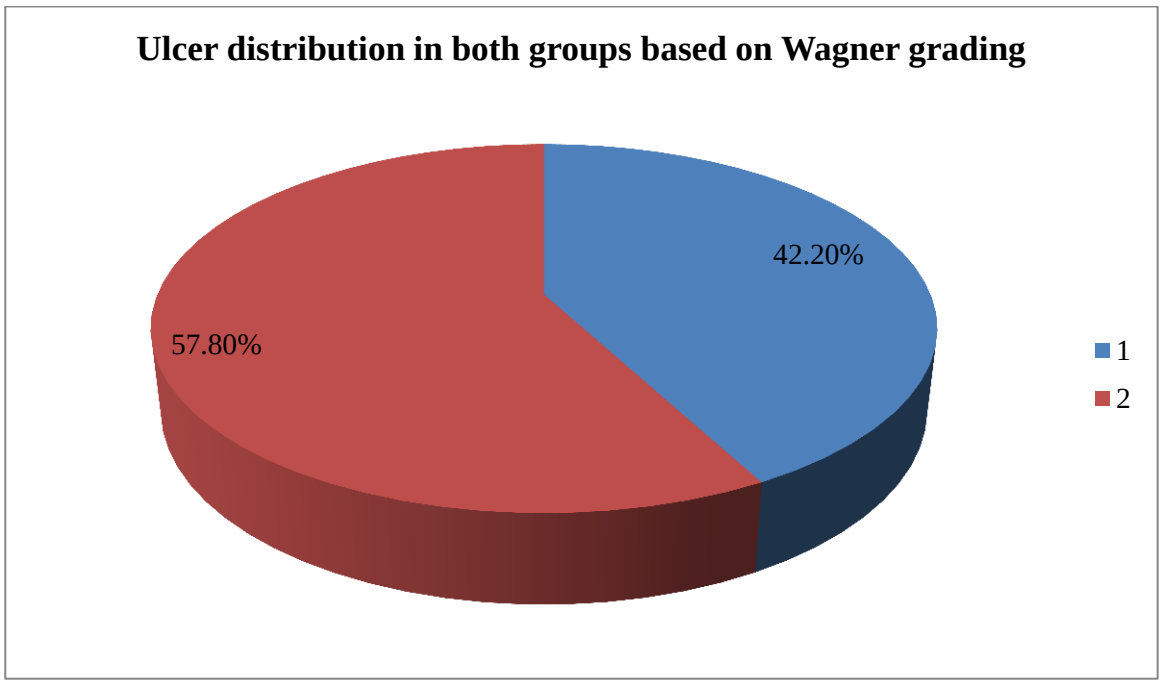


Chart12: Pie Diagram Showing Ulcer distribution in both groups based on Wagner grading

Table 25: Ulcer distribution in each group based on Wagner grading

		Group					
		Control Group		Study Group		Total	
		Count	%	Count	%	Count	%
Wagner Grade	1	18	40.0%	20	44.4%	38	42.2%
	2	27	60.0%	25	55.6%	52	57.8%

$\chi 2 = 0.182$, df $= 1$, $p = 0.670$

In the study, it was observed that study group comprised of 55.6% patients having Wagner 1 grade, 44.4% patients having Wagner 2 grade of diabetic foot ulcer. It was observed that control group comprised of 40% patients having Wagner 1 grade, 60% patients having Wagner 2 grade of diabetic foot ulcer.

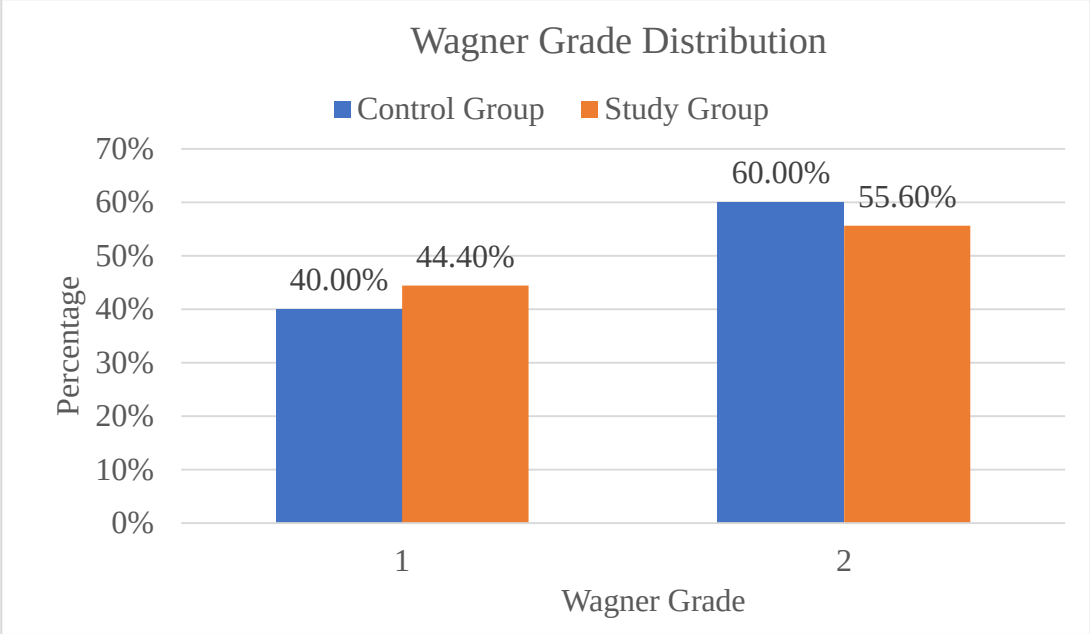


Chart 15: Bar Diagram Showing Ulcer distribution in each group based on Wagner grading

Table 26: Mean reduction of Ulcer among Wagner grade in each group

		% reduction				P value
		Control Group		Study Group		
		Mean	SD	Mean	SD	
Wagner grade	1	19.32	6.84	38.09	4.81	<0.001*
	2	19.84	6.95	38.28	6.69	<0.001*

In our study, mean percentage reduction of ulcer size in Wagner grade 1 patients was higher in study group (38.09) as compared to control group (19.32).

It was observed that mean reduction of ulcer size in Wagner grade 2 patients was higher in study group (38.28) as compared to control group (19.84).

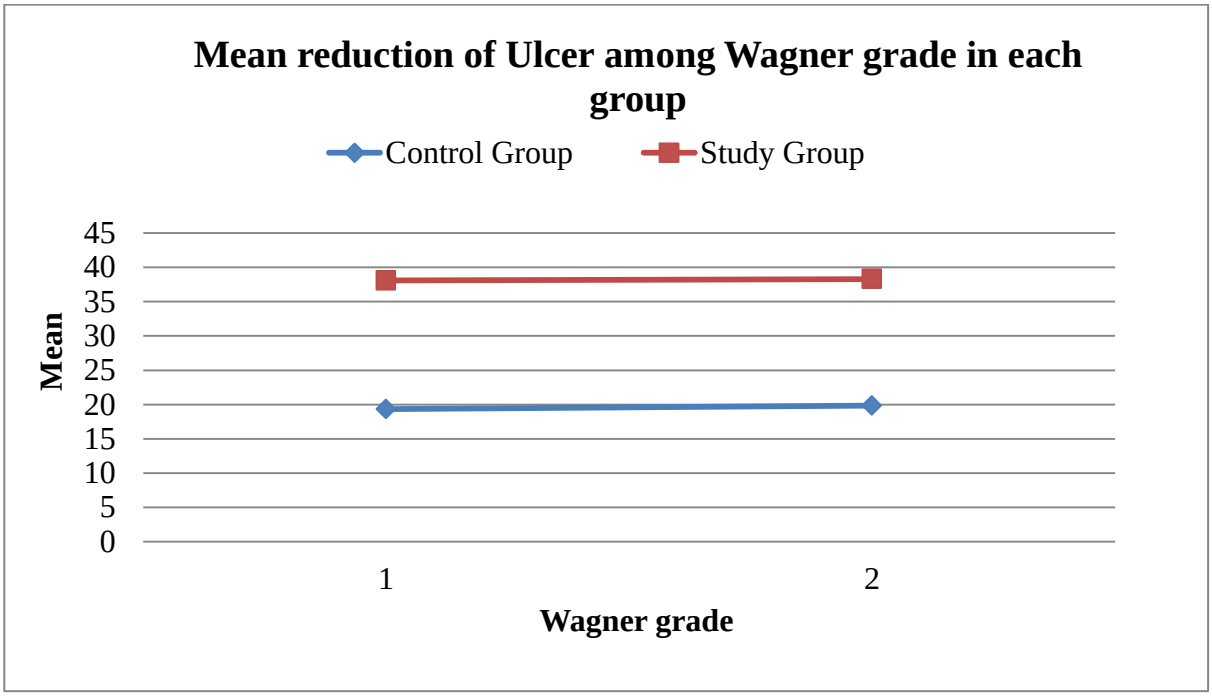


Chart 13: Line Diagram Showing Mean reduction of Ulcer among Wagner grade in each group

Table 27: Distribution of patients in both groups based on Diabetic treatment

		Group					
		Control Group		Study Group		Total	
		Count	%	Count	%	Count	%
Treatment	OHA	28	62.2%	29	64.4%	57	63.3%
	Insulin	17	37.8%	16	35.6%	33	36.7%

$\chi 2 = 0.048$, df $= 1$, $p = 0.827$

In the study it was observed that patients who are only on OHA constituted 63.3% and patients who are on insulin constituted 36.7%.

In the study group, who were on OHA was 64.4% whereas patients who were on insulin was 35.6%.

In the control group it was observed that patients who were on OHA were 62.2% whereas who were on insulin was 37.8%.

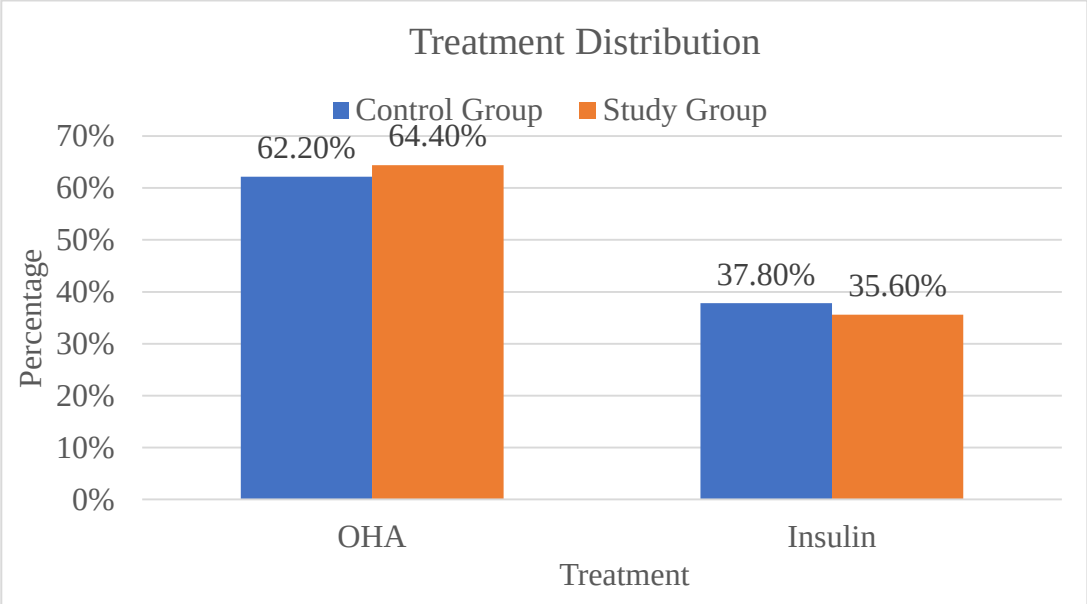


Chart 17: Bar Diagram Showing Distribution of patients in both groups based on Diabetic treatment

Table 28: Overall mean reduction in ulcer size between two diabetic treatment groups

		% reduction		
		Mean	SD	P value
Treatment	OHA	28.70	11.13	0.818
	Insulin	29.27	11.69	

In the study mean % reduction of ulcer size among those on OHA was 28.70% and among those on insulin was 29.27%. The size of ulcer reduction was slightly higher in patients who were on insulin when compared to patients who were on OHA.

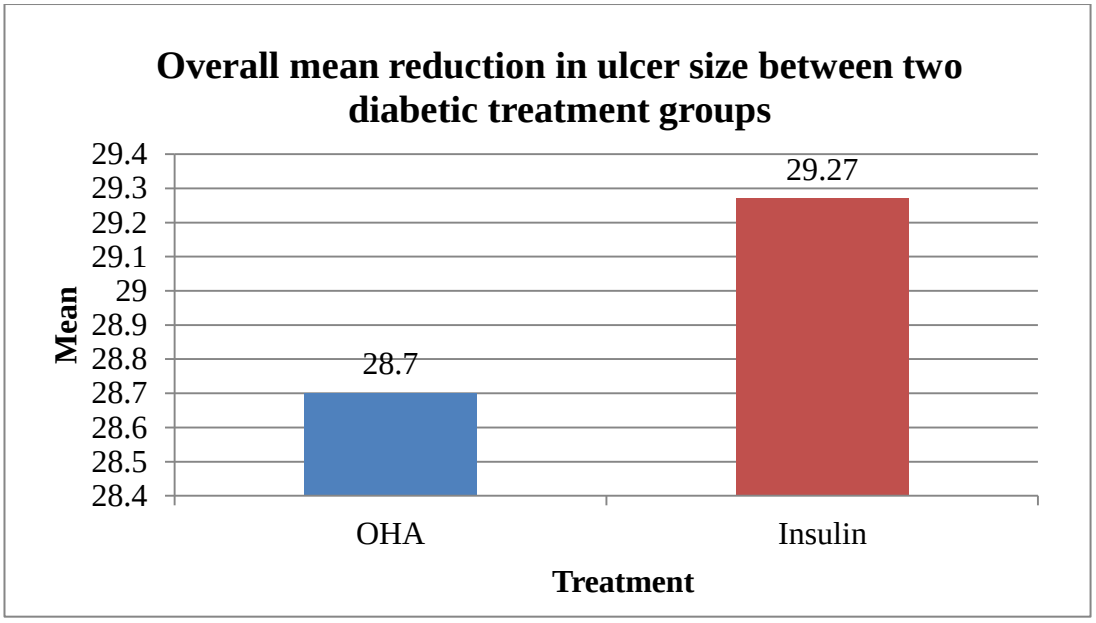


Chart 18: Bar Diagram Showing Overall mean reduction in ulcer size between two diabetic treatment groups

Table 29: Mean reduction of ulcer size in each group based on diabetic management

	Group				P value
	Control Group		Study Group		
	Mean	SD	Mean	SD	
OHA	19.59	6.68	37.50	6.47	<0.001*
Insulin	19.69	7.30	39.46	4.46	<0.001*

In our study, it was observed mean reduction of ulcer size was higher in study group with patients on insulin (39.46%) as compared to control group (19.69%).

It was observed mean reduction of ulcer size was higher in study group with patients on OHA (37.50%) as compared to control group (19.59).

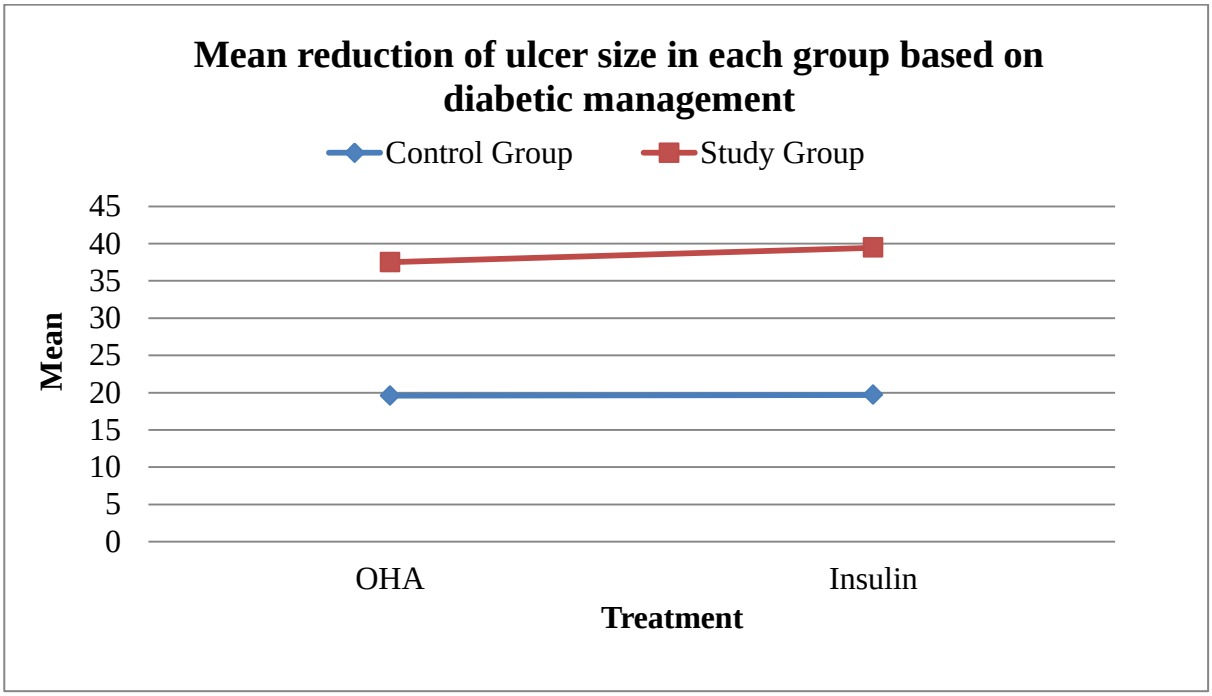


Chart 19: Line Diagram Showing Mean reduction of ulcer size in each group based on diabetic management

Table 30: Contraction of wound between 2 groups

		% reduction			P value
		Mean	SD	Median	
Group	Control Group	19.63	6.83	17.36	<0.001*
	Study Group	38.19	5.86	38.40	
	Total	28.91	11.28	30.32	

In our study, it was observed that the overall mean percentage of area of reduction in diabetic foot ulcer was higher in study group (38.19%) than the control group (19.63%)

The standard deviation for study group was 5.86 and 6.83 for control group.

The median for study group was 38.40 and 17.36 in control group.

In our study we obtained the P value of < 0.001 which is statistically significant.

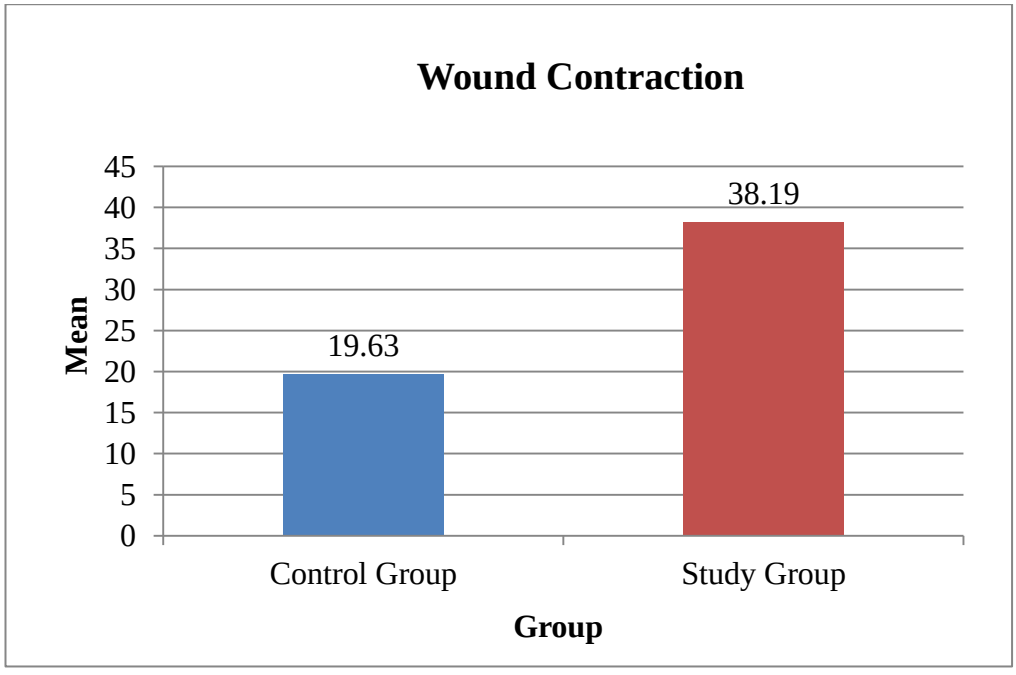


Chart 20: Bar Diagram Showing Contraction of wound between 2 groups

DISCUSSION

DISSCUSSION

Diabetic foot ulcers represent a major cause of morbidity between diabetic patients that can seriously impair quality of life and often results in limb loss. Platelet rich plasma is a useful adjunct in order to achieve ulcer healing in these patients. These are biologically active polypeptides that act to alter the growth differentiation and metabolism of target cells stimulating cellular proliferation, chemotaxis and angiogenesis.

Patients admitted in department of general surgery, in female and male surgical wards of R.L Jalappa hospital and research centre Tamaka, Kolar from December to June 2019 to study the effect of use of PRP dressing in healing of diabetic foot ulcer.

Age distribution

It was observed that of 90 patients with diabetic foot ulcers, 13 patients were upto 40 years, 51 patients were between age group 41-50 years, 25 patients were age group of 65. This observation correlates with WHO reports which also shows that prevalence of diabetes increases with age and highest incidence occurs at age group of 45-65 years.[187]

Kapur et al, also reported a similar findings where maximum number of cases were diagnosed between 40-60 years of age with no significant difference between genders.[188]

Gender distribution

It was observed that 80% of studied population were males and 20% were females. The male to female ratio was 4:1. This observation was similar to Jali et al and Flatau E et al , who reported, the diabetes was more prevalent in men than in women.[189,190]

This was in contrast to Arthur M. Michalek et al who reported that prevalence of diabetes among women was higher than in men. The occurrence of diabetic foot ulcer among male and middle aged patients which was confirmed by Merza et al and Unachukwu et al.[191,192,193]

Onset of diabetic foot ulcer

It was observed that traumatic origin of the diabetic foot ulcer was the common cause (64%) followed by spontaneous onset, may be blister or minor unattended trauma. The importance of awareness and self examination of one's foot regularly is important in early treatment and prevention of further complications. Studies show that spontaneous ulceration is the main cause, but in the study, we found that diabetic foot ulcer due to trauma was more common, the opposite findings could be due to small sample size of our study.

Diabetic management

It was observed that patients who were on OHA alone had (28.7%) mean reduction in ulcer size than compared to patients who were on insulin (29.27%). This observation was contradictory to N.K Rai et al study which showed significant

increase in apoptosis in diabetic wounds, which in turn contributes to delayed wound healing, more in patients on OHA's than those on insulin.[157]

Wagner grade

It was observed that 58% patients had Wagner grade 2 ulcer, 42% patients had Wagner grade 1 ulcer. The mean reduction of ulcer size was (19.32% in control group and 38.09 in study group) in Wagner grade 1 patients compared to mean reduction in Wagner grade 2 patients (19.84% in control group and 38.28%).

Yao hung et al reported similar observation that Wagner grade 1 has better rate of healing than other Wagner grades.[194]

Site of diabetic foot ulcers

It was observed that diabetic foot ulcer was more common on the plantar aspect (58%) than on the dorsal aspect. Mean reduction of ulcer size (in control group is 17.14% and study group is 36.81%) compared to plantar aspect (control group 22% and study is 38.96%). This observation was similar to Edmonds et al study which showed foot ulcers occurred more commonly on plantar and fore foot region. The underlying factor for ulceration is due to neuropathic foot which is painless and develops at the sites of high mechanical pressure on the plantar surface, often under the metatarsal heads.[195]

Wound dressing

It was observed that mean area of contraction of wound size was more in study group (38.19%) compared to control group (19.63%). The observation was similar to

saad seta et al performed a randomized trail to compare the effects of platelet rich and platelet poor plasma(PRP and PPP), respectively, in ulcer healing demonstrating that this was significantly faster in the PRP group. Anitua et al measured the mean percentage of ulcer surface area healed in the study population, which was 72.94% in patients treated with GFs versus 21.48% in those requiring standard care, a difference that was significant statistically.[21,73,196]

Steed studied the effects of topical recombinant human platelet derived Growth factor versus placebo. The study included 118 patients and suggested that the group treated with Growth Factors achieved significantly higher healing rate (48% vs 21%) while the median reduction in wound area was greater in the former group (98.8% vs 82.1%).[\197,198]

Kontopodis et al also observed PRP serve as a useful adjunct during treatment of diabetic foot ulcers even in diabetic patients with unreconstructable arterial disease.[199]

The ulcer size is measured at the presentation and total initial area is calculated and recorded. The size of the ulcer is again measured after respective treatment for each group was carried out for 30 days. The final area of the ulcer is calculated and recorded for control group the dressing is changed on daily basis, whereas for the study group, the dressing is changed once in 5 days.

We observed that irrespective of age, gender, onset of ulcer, site of diabetic foot ulcer, Wagner grading of ulcer and on diabetic management. The patients who were treated with PRP shows better healing and faster reduction in ulcer size and

duration of treatment was also decreased. Hence autologous PRP is better option in treating diabetic foot ulcers.

We observed that there was significant improvement in wound healing between PRP dressing and normal dressing. The standard deviation for study group was 5.86 and 6.83 for control group. The median for study group was 38.4 and 17.36 in control group and on applying the unpaired t test, we obtained a p value of <0.001. since any value of $p < 0.05$ is significant, our study was also statistically significant.

SUMMARY

SUMMARY

The study sample included 90 patients with diabetic foot ulcers admitted in surgical wards. Each patient was clinically assessed, ulcer details recorded and proceeded for treatment with initial and final size of the wound measured and recorded.

1. In our study, it was observed that the diabetic foot ulcer was commonest among 5^{th} and 6^{th} decade of age.
2. 34 male, 11 female constituted the study group and 37 male, 8 female constituted the control group.
3. Predisposition of diabetic foot ulcer was common among males than in females.
4. More number of diabetic patients presented with diabetic foot ulcer arising from trauma than those occurring spontaneously. The spontaneous onset ulcers healed better with PRP than those arising due to traumatic onset.
5. The common occurrence of diabetic foot ulcer was found to be in the plantar aspect than on dorsal aspect.
6. The ulcers on dorsal aspect heal faster than on plantar aspect.
7. Patients presenting early with less severe Wagner grade improved in healing than those who came with later stage of Wagner grade. PRP dressing improved the rate of healing in lower Wagner grade ulcer than in higher grade ulcer.
8. Patients who were on insulin alone showed better healing than those on OHA.
9. Over all PRP dressing group showed higher rate of ulcer size over reduction than those on saline dressing. This shows PRP as a good alternative to regular dressing.

10. In our study the median area of reduction of ulcer size over period of 1month was more in study group as compared to control group**.**

CONCLUSION

CONCLUSION

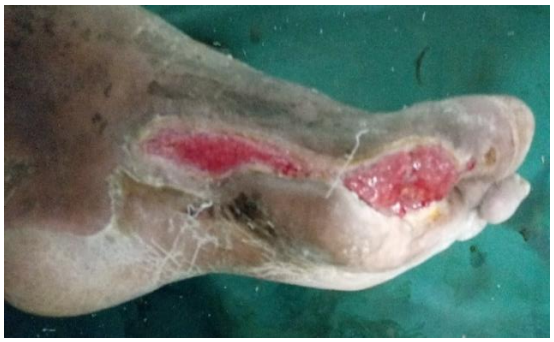
1. The vulnerable age group for Diabetes is in 5^{th} and 6^{th} decade of life.
2. Male population is affected from diabetes and its complications are more compared to female population.
3. Foot ulcers following trauma is more common than spontaneous onset.
4. Ulcers on the sole of the foot is common than on the dorsal aspect.
5. Healing of ulcers with Wagner grade 1> grade 2> grade 3.
6. The patients who are treated with insulin has good glycemic control and shows good results in healing when compared to those on OHA.
7. The diabetic ulcer in the study group treated with PRP dressing contracted in wound size more than in the control group (38.19% vs 19.63% with p value < 0.001 which is statistically significant).
8. This indicates that PRP dressing is an effective method to facilitate wound contraction in diabetic patients with foot ulcer.
9. PRP dressing is found to be more effective, cost efficient and safe promoter of ulcer wound healing and can be used as an adjunct to saline dressings for enhanced healing of diabetic wounds.

CLINICAL PICTURES

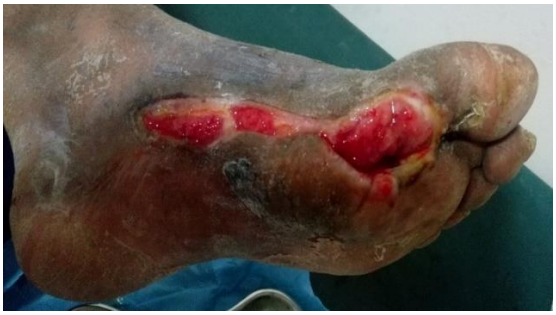
EFFECT OF PRP IN DIABETIC WOUND HEALING

CASE 1

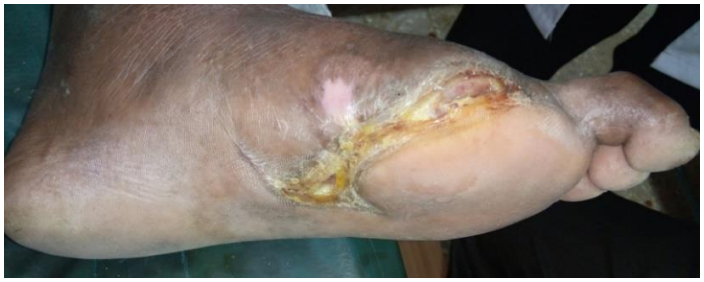
BEFORE



DURING STUDY

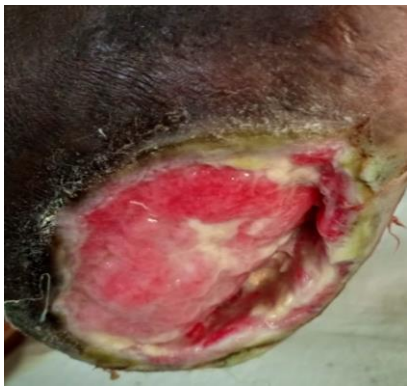


DURING FOLLOW UP

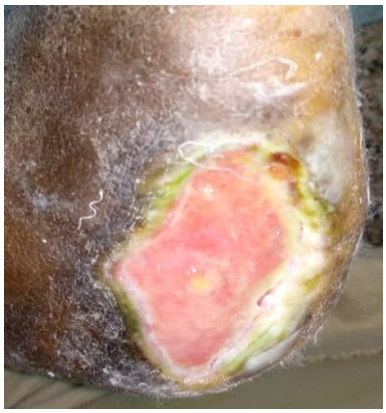


CASE 2

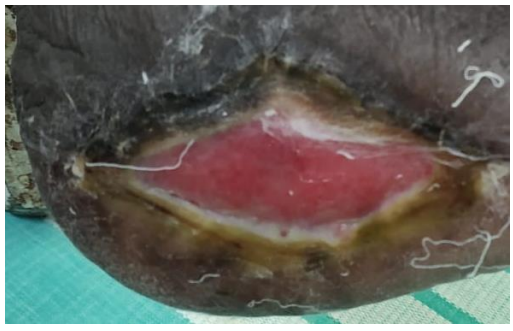
BEFORE



DURING STUDY



DURING FOLLOW UP



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ANNEXURES

ANNEXURES

PROFORMA

Particulars of the patients:

- Name :
- Age:
- Gender:
- Occupation:
- Date of admission:
- Date of discharge:
- UHID NO :
- Religion :
- Socio economic status :

HISTORY

- Chief complaints:
- HOPI :
- Past History:
- Family History:
- Personal History:
- Cause of ulcer:

- Duration of ulcer:
- Duration of Diabetes Mellitus:
- Treatment of Diabetes Mellitus:

SYSTEMIC ILLNESS

- CVS :
- RS :
- CNS:
- PER ABDOMEN:

VITALS

- Pulse rate :
- Blood pressure :
- Respiratory Rate:
- Temperature :

LOCAL EXAMINATION

FOOT EXAMINATION

- Skin dry :
- Edema (site):

- Erythema :

- Heel fissures :

- Scratch marks :

- Signs of infection :

ULCER

Right lower limb Left lower limb

- Site :

- Margin:

- Size :

- Shape :

- Depth :

- Edge :

- Floor :

- Granulation:

- Peri ulcer edema :

- Slough

VASCULAR EXAMINATION

PULSES Right Left

- Femoral
- Popliteal
- Posterior tibial
- D. Pedis

INVESTIGATIONS

1.HEMATOLOGICAL

Hb% - PCV - TC- DC- RBC-

Platelets-

ESR- BT - CT- Blood grouping-

Blood Urea - Serum Creatinine –

GRBS -

FBS - PPBS- HbA1c-

2. URINE EXAMINATION:

Albumin - Sugar - Ketones –

3. Doppler studies (if required):

4. X- Ray of foot:

5. Pus for culture sensitivity**:**

PATIENT INFORMATION SHEET

Study title: "A COMPARATIVE STUDY OF PLATELET RICH PLASMA DRESSING VS NORMAL SALINE DRESSING IN THE MANAGEMENT OF DIABETIC FOOT ULCER "

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details-

All Patients who are admitting in surgical ward for diabetic foot ulcer will be included in this study. Patients with significant co morbid conditions and chronic venous insufficiency of lower limbs will be excluded from the study.

Patients in this study will have to undergo routine investigations, urine routine analysis, hematological investigations, Diabetic work up,X ray lower limb, GRBS charting, Doppler if required.

Patient and patient attenders have been completely explained about the procedure being done i.e Dressing with platelet rich plasma vs normal saline dressing in 2 groups. Patients can be randomly allotted into either group, and also has been explained that there is no compromise in standard care given as both method of treatment is widely used in treatment of diabetic ulcer.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or

both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been submitting for review by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

Dr. Vijay kumar. S (Post graduate)

Department of General Surgery

SDUMC, Kolar

INFORMED CONSENT FORM

I Mr/Mrs. have been explained in my own understandable language, that I will be included in a study which is A COMPARTIVE STUDY OF PLATELET RICH PLASMA DRESSING VS NORMAL SALINE DRESSING IN THE MANAGEMENT OF DIABETIC FOOT ULCER being conducted in RL JALAPPA HOSPITAL.

I have been explained that my clinical findings, investigations, will be assessed and documented for study purpose.

I have been explained that, I might fall into either of the groups i.e group with PRP Dressing and group with Normal Saline Dressing, yet there is no compromise in the care given as both methods has shown satisfactory results in treatment of diabetic patients.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have been explained about the follow up details and possible benefits and adversities due to interventions, in my own understandable language.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile no for enquiries.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place:

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಶೀರ್ಷಿಕೆ: ಪ್ಲೇಟಲೆಟ್ ರಿಚ್ ಪ್ಲಾಸ್ಮಾದ ತುಲನಾತ್ಮಕ ಅಧ್ಯಯನ ಸಾಧಾರಣ ಸಲೈನ್ ಡ್ರೆಸ್ಸಿಂಗ್ ವಿರುದ್ಧ ಮಧುಮೇಹ ಕಾಲಿನ ಹುಣ್ಣಿನ ನಿರ್ವಹಣೆಯಲ್ಲಿ

ಮಾರ್ಗದರ್ಶಿ: ಡಾ.ಭಾಸ್ಕರನ್.ಎ

ಡಾ.ವಿಜಯ್ ಕುಮಾರ್.ಎಸ್ ಮೂಲಕ ನಡೆಸಲ್ಪಟ್ಟ ಅಧ್ಯಯನ

ಅಧ್ಯಯನದ ಸ್ಥಳ: ಕೋಲಾರದ ಶ್ರೀ ಆರ್.ಎಲ್.ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ವೈದ್ಯಕೀಯ ಮಹಾವಿದ್ಯಾಲಯ ತಮಕ.

ಆರ್.ಎಲ್.ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆಯ ಸಾಮಾನ್ಯ ಶಸ್ತ್ರ ಚಿಕಿತ್ಸೆ ಇಲಾಖೆಯಲ್ಲಿ ದಾಖಲಾಗುವ ಮಧುಮೇಹ ಕಾಲಿನ ಹುಣ್ಣು ಹೊಂದಿರುವ ರೋಗಿಗಳ ಅವರ ಸಮ್ಮತಿಯೊಂದಿಗೆ

ತೀವ್ರ ಅಸ್ವಸ್ಥ ಸ್ಥಿತಿಗಳು ಮತ್ತು ಕಾಲಿನ ದೀರ್ಘಕಾಲದ ರಕ್ತ ಹೀನತೆ ಹೊಂದಿರುವ ರೋಗಿಗಳನ್ನು ಈ ಅಧ್ಯಯನದಿಂದ ಹೊರಗಿಡಲಾಗುತ್ತದೆ.

ಈ ಅಧ್ಯಯನದ ರೋಗಿಗಳು ರಕ್ತದ ಸಾಧಾರಣ ತನಿಖೆಗಳು, ಮೂತ್ರ ವಿಶ್ಲೇಷಣಾ ತನಿಖೆ, ಡಯಾಬಿಟಿಸ್ ತನಿಖೆಗಳು, ಎಕ್ಸರೆ ಕಾಲು, ಜಿ.ಆರ್.ಬಿ.ಎಸ್ ಚಾರ್ಟಿಂಗ್ ಮತ್ತು ಡಾಪ್ಲರ್ ತನಿಖೆಗಳು ಅಗತ್ಯವಿದ್ದಲ್ಲಿ ಪರೀಕ್ಷಿಸಲಾಗುತ್ತದೆ.

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಸಮ್ಮತಿಸುವ ರೋಗಿಗಳನ್ನು ಪ್ಲೇಟಲೆಟ್ ರಿಚ್ ಪ್ಲಾಸ್ಮಾ ಮತ್ತು ಸಾಮಾನ್ಯ ಸಲೈನ್ ಡ್ರೆಸ್ಸಿಂಗ್‌ಗಳಿಗೆ ಎರಡು ಗುಂಪುಗಳಾಗಿ ವಿಭಾಗಿಸಲಾಗುತ್ತದೆ. ರೋಗಿಗಳು ಯೋಗದೃಷ್ಟಿಯಿಂದ ಎರಡು ಗುಂಪುಗಳು ಮಂಜೂರು ಮಾಡಬಹುದು. ಮತ್ತು ಅವರ ಆರೈಕೆಯಲ್ಲಿ ಯಾವುದೇ ಕೊರತೆ ಇರುವುದಿಲ್ಲ ಎಂದು ವಿವರಿಸಲಾಗಿದೆ. ಚಿಕಿತ್ಸೆಯ ವಿಧಾನ ಡಯಾಬಿಟಿಸ್ ಆಲ್ಸರ್ ಚಿಕಿತ್ಸೆಯ ವ್ಯಾಪ್ತಿಯಲ್ಲಿ ಒಳಪಡುತ್ತದೆ.

ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ, ಅಧ್ಯಯನದ ಬಗ್ಗೆ ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆಯನ್ನು ಕೇಳಬಹುದು. ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪಿಕೊಂಡರೆ, ನಿಮ್ಮಿಂದ ಅಥವಾ ಇಬ್ಬರಿಗೂ ಜವಾಬ್ದಾರರಾಗಿರುವ ಮಾಹಿತಿಯನ್ನು ನಾವು (ಮಹಿತಿ ಪ್ರಕಾರ) ಸಂಗ್ರಹಿಸುತ್ತೇವೆ. ಸಂಬಂಧಿತ ರೋಗಲಕ್ಷಣಗಳನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು. ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿಯನ್ನು ಪ್ರೌಢಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆಗಾಗಿ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿರಿಸಲಾಗುವುದು. ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಗೊಳ್ಳುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವು ಸಾಂಸ್ಥಿಕ ನೀತಿಶಾಸ್ತ್ರ ಸಮಿತಿಯಿಂದ ಪರಿಶೀಲಿಸಲ್ಪಟ್ಟಿದೆ ಮತ್ತು ನೀವು ಸಂಸ್ಥೆಯ ಎಥಿಕ್ಸ್ ಸಮಿತಿಯ ಸದಸ್ಯರನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತವಾಗಿರುತ್ತೀರಿ. ಈ ಅಧ್ಯಯನಕ್ಕೆ ಒಪ್ಪಿಗೆ ನೀಡಲು ಯಾವುದೇ ಕಡ್ಡಾಯವಿಲ್ಲ. ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುವ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಸ್ವಯಂ ಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪಿಕೊಳ್ಳುವುದಾದರೆ ಮಾತ್ರ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆಗೆ ನೀವು ಸಹಿ ನೀಡಬೇಕಾಗಿದೆ.

ಹೆಚ್ಚಿನ ವಿವರಗಳಿಗೆ ಸಂಪರ್ಕಿಸಿ:

ಡಾ.ವಿಜಯ್ ಕುಮಾರ್.ಎಸ್(ಸ್ನಾತಕೋತ್ತರ ವಿದ್ಯಾರ್ಥಿ)

ಶಸ್ತ್ರಚಿಕಿತ್ಸೆ ಇಲಾಖೆ,

ಮೊ: 7760121969

ಶ್ರೀ ದೇವರಾಜ್ ಅರಸು ವೈದ್ಯಕೀಯ ಮಹಾವಿದ್ಯಾಲಯ, ತಮಕ, ಕೋಲಾರ

ಮಾಹಿತಿದಾರರ ಒಪ್ಪಿಗೆ ಪತ್ರ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಫ್ಲೆಬೆಲೆಬ್ ರಿಚ್ ಪ್ಲಾಸ್ಮಾದ ತುಲನಾತ್ಮಕ ಅಧ್ಯಯನ ಸಾಧಾರಣ ಸಲೈನ್ ಡ್ರೆಸ್ಸಿಂಗ್ ವಿರುದ್ಧ ಮಧುಮೇಹ ಕಾಲಿನ ಹುಣ್ಣಿನ ನಿರ್ವಹಣೆಯಲ್ಲಿ

ನಾನು ಶ್ರೀ/ಶ್ರೀಮತಿ_____ ಈ ಒಪ್ಪಿಗೆ ಪತ್ರದಲ್ಲಿ ತಿಳಿಸಿರುವ ಎಲ್ಲಾ ಕ್ರಮಗಳನ್ನು ಅರಿತುಕೊಂಡು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿರುತ್ತೇನೆ.

ನನಗೆ ತಿಳಿದಿರುವ ಸ್ಥಳೀಯ ಭಾಷೆಯಲ್ಲಿ ಎಲ್ಲವನ್ನು ಓದಿ ವಿವರಿಸಿರುತ್ತಾರೆ. ಮತ್ತು ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶವನ್ನು ಅರಿತುಕೊಂಡಿರುತ್ತೇನೆ. ಈ ಅಧ್ಯಯನದ ಸಂದರ್ಭದಲ್ಲಿ ಸಂಗ್ರಹಿಸಲ್ಪಡುವ ಎಲ್ಲಾ ವಿಷಯಗಳು ಗೋಪ್ಯ ರೀತಿಯಾಗಿರುತ್ತೆ. ಮತ್ತು ಅಧ್ಯಯನಕ್ಕಾಗಿ ಮಾತ್ರ ಬಳಸಲ್ಪಡುತ್ತೆಂದು ಗೊತ್ತಿರುತ್ತೆ. ಈ ಸಂದರ್ಭದಲ್ಲಿ ನನ್ನಲ್ಲಿ ಉದ್ಭವಿಸಿದ ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳನ್ನು ಸಮರ್ಪಕವಾಗಿ ಉತ್ತರಿಸಿರುತ್ತಾರೆ ಮತ್ತು ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಗಳನ್ನು ಸಂಶೋಧನೆಗಾಗಿ ಬಳಸುವರೆಂದು ತಿಳಿದಿರುತ್ತೇನೆ.

ಡಾ.ವಿಜಯ್ ಕುಮಾರ್. ಎಸ್.

ಮೊ. ಸಂ: 7760121969

ಭಾಗವಹಿಸುವ ಡಾಕ್ಟರ್ ಸಹಿ:

ರೋಗಿಯ ಸಹಿ/ಎಡ ಹೆಬ್ಬೆರಳಿನ ಗುರುತು:

ಸಾಕ್ಷಿಗಳು:

1.ಸಹಿ/ಹೆಸರು ದಿನಾಂಕ:

2.ಸಹಿ/ಹೆಸರು ದಿನಾಂಕ:

KEY TO MASTER CHART

UHID NO: Unique Hospital Identification Number

OHA : Oral Hypoglycemic Agents

T : Traumatic

S : Spontaneous

P : Plantar

D : Dorsal

SLNO	UHID NO	AGE	SEX	HTN	HbA1c	OHA	insulin	onset	site	wagner gr	initial length	initial breadth	initial depth	initial area	final length	final breadth	final depth	final area	% reduction
1	670479	78	M	NO	N	NO	YES	S	D	1	26	22	14	2288	24	20	4	1920	16.08
2	513408	55	M	NO	N	YES	NO	S	D	1	12	16	2	384	11	15	2	330	14.06
3	507565	48	M	YES	H	NO	YES	S	D	1	30	22	4	2640	29	20	3	1740	34.09
4	553388	60	M	NO	H	NO	YES	S	P	1	11	15	2	330	10	14	2	280	15.15
5	713549	65	M	YES	N	NO	YES	S	D	1	23	15	17	2415	22	14	6	1848	23.47
6	505889	60	F	NO	N	YES	NO	T	P	1	17	22	8	2992	16	21	8	2688	10.16
7	590388	63	M	NO	H	YES	NO	T	D	1	26	23	5	2990	23	21	5	2415	19.23
8	592088	58	M	NO	N	YES	NO	T	P	1	22	19	4	2400	20	18	4	1701	29.12
9	650856	50	M	NO	N	YES	NO	T	D	2	16	14	3	672	15	13	3	585	12.94
10	576871	45	M	NO	N	YES	NO	T	P	2	21	19	3	1197	19	17	3	996	16.79
11	544799	63	M	YES	H	NO	YES	T	P	2	18	16	3	864	17	14	3	714	17.36
12	639114	50	M	NO	N	NO	YES	T	D	1	16	10	10	1600	14	10	10	1400	12.52
13	212323	49	F	YES	N	NO	YES	T	P	1	11	15	2	330	10	14	2	280	15.15
14	635407	66	M	NO	H	YES	NO	S	P	1	12	8	8	768	10	7	8	560	27.08
15	643742	50	M	NO	H	YES	NO	S	P	1	13	10	10	1300	11	10	10	1100	15.21
16	621207	35	M	NO	H	YES	NO	T	P	1	21	14	6	1764	20	14	5	1400	20.6
17	619023	60	F	NO	N	YES	NO	T	P	2	20	14	4	1120	19	14	3	798	26
18	576871	44	M	NO	N	YES	NO	T	D	2	17	15	6	1530	16	14	6	1344	12.16
19	584972	58	F	NO	H	NO	YES	S	P	1	14	21	3	882	13	20	3	780	11.12
20	548601	65	F	NO	H	YES	NO	T	D	2	11	16	7	1232	9	16	7	1008	18.18
21	535879	35	M	YES	N	NO	YES	S	D	2	14	10	3	420	12	10	3	360	14.2
22	556820	45	F	YES	H	NO	YES	T	P	1	22	17	7	2618	21	16	6	2016	22.9
23	579825	55	M	YES	H	YES	NO	T	P	2	23	18	5	2070	22	16	4	1408	30
24	588551	40	M	NO	N	NO	YES	S	D	1	14	10	4	560	13	9	4	468	16.42
25	600448	58	M	YES	H	YES	NO	S	D	2	12	18	3	648	11	17	3	561	13.42
26	600970	70	M	NO	N	YES	NO	S	D	2	26	23	5	2990	23	21	5	2415	19.23
27	566502	59	M	NO	N	YES	NO	T	D	2	27	17	17	7803	26	16	16	6656	14.7
28	619549	45	M	YES	H	NO	YES	T	P	2	24	16	8	3072	23	15	7	2415	21.3
29	538996	58	M	NO	N	YES	NO	T	D	2	27	17	17	7803	26	16	16	6656	14.7
30	544132	49	M	YES	N	YES	NO	T	P	2	20	18	9	3240	18	16	8	2304	28.89
31	505889	42	M	NO	H	NO	YES	S	P	2	21	14	6	1764	20	14	5	1400	20.6
32	540324	70	M	NO	N	YES	NO	T	D	2	15	21	4	1260	13	21	4	1092	13.3
33	599656	70	M	YES	N	YES	NO	T	P	2	34	28	10	9520	33	26	9	7722	18.8
34	625739	60	M	YES	H	YES	NO	T	P	2	23	18	4	1656	22	17	3	1122	32.5
35	621341	42	M	NO	N	NO	YES	T	P	2	29	15	15	6525	19	15	15	4275	34.45
36	525373	80	M	YES	N	YES	NO	T	P	1	21	19	3	1197	19	17	3	996	16.79
37	575443	45	F	YES	N	NO	YES	S	D	2	30	22	4	2640	28	21	3	1827	30.7
38	564815	38	M	NO	N	YES	NO	S	D	2	18	23	8	3312	16	22	8	2816	14.98

39	630772	80	M	YES	N	YES	NO	S	P	2	12	9	9	972	11	8	9	792	18.51
40	626017	63	M	YES	H	YES	NO	T	P	2	24	10	10	2400	21	9	9	1701	29.12
41	619549	45	M	NO	N	NO	YES	S	D	2	27	17	17	7803	26	16	16	6656	14.5
42	624736	55	F	YES	N	YES	NO	T	D	2	14	21	3	882	13	20	3	780	11.3
43	626017	63	M	YES	N	NO	YES	T	D	2	27	17	17	7803	26	16	16	6656	14.7
44	655241	48	M	NO	H	YES	NO	T	P	1	18	18	5	1620	17	17	4	1156	28.64
45	656118	59	M	NO	N	YES	NO	T	D	2	9	10	10	900	7	10	10	700	22.22

SLNO	UHID NO	AGE	SEX	HTN	HbA1c	OHA	insulin	onset	site	wagner grade	initial length	initial breadth	initial depth	initial area	final length	final breadth	final depth	final area	% reduction	
1	657859	55	M	NO	N	YES	NO	S	P	1	14	10	10	1400	9	10	9	810	42.14	
2	696351	65	M	NO	N	YES	NO	S	D	1	24	21	5	2520	23	19	4	1740	30.6	
3	630762	35	M	YES	H	NO	YES	T	P	1	30	18	18	9720	20	16	16	5120	47.32	
4	621875	63	M	NO	H	NO	YES	T	P	1	19	21	4	1596	17	19	3	969	39.96	
5	713548	40	M	YES	N	YES	NO	T	P	2	17	22	4	1496	15	20	3	900	39.86	
6	724352	75	F	NO	N	YES	NO	T	P	2	27	18	4	1944	25	16	3	1200	38.27	
7	590288	33	M	NO	H	YES	NO	S	D	2	26	14	3	1092	24	12	2	576	45	
8	628034	55	M	NO	N	NO	YES	T	P	2	20	19	3	1140	18	18	2	648	43.15	
9	718452	50	F	NO	N	NO	YES	T	P	2	16	19	5	1520	14	18	4	1008	33.68	
10	771698	70	F	NO	N	NO	YES	T	D	2	22	18	4	1584	20	17	4	1360	32.8	
11	636798	38	M	YES	H	NO	YES	S	D	2	30	17	17	8670	20	16	16	5120	40.94	
12	442275	46	M	NO	N	YES	NO	S	D	1	22	18	4	1584	20	17	4	1071	32.8	
13	639081	80	M	YES	N	YES	NO	S	P	2	16	8	8	1024	15	7	7	735	28.22	
14	550209	45	M	NO	H	NO	YES	T	P	2	27	18	4	1944	25	16	3	1200	38.27	
15	564780	68	M	NO	H	YES	NO	S	D	1	19	21	4	1596	17	19	3	969	39.96	
16	411575	60	F	NO	H	YES	NO	T	P	1	10	8	8	640	9	7	7	441	31.02	
17	637637	49	M	NO	N	YES	NO	T	P	1	22	17	17	6358	20	15	15	4500	29.22	
18	628034	51	M	NO	N	NO	YES	T	P	1	28	14	14	5488	20	13	13	3380	38.4	
19	575442	45	F	NO	H	NO	YES	T	P	2	26	14	3	1092	24	12	2	576	45	
20	623961	31	M	NO	H	YES	NO	T	P	1	30	17	17	8670	20	16	16	5120	40.94	
21	645832	654	M	YES	N	YES	NO	T	P	2	24	14	14	4704	20	12	12	2880	38.72	
22	625157	57	M	YES	H	YES	NO	S	D	1	18	19	5	1710	16	16	4	1024	40.12	
23	625734	48	M	YES	H	YES	NO	S	D	1	11	12	3	396	10	11	2	220	44.44	
24	651395	80	F	NO	N	NO	YES	S	P	2	32	20	20	12800	22	19	19	7942	37.89	
25	633684	70	M	YES	H	YES	NO	T	P	2	26	18	18	8424	16	17	16	4352	48.3	
26	630772	70	M	NO	N	NO	YES	S	D	2	15	10	10	1500	14	8	8	896	40.2	
27	648342	55	M	NO	N	YES	NO	T	P	1	40	22	22	19360	30	20	20	12000	38.01	
28	619118	45	F	YES	H	YES	NO	T	D	1	25	17	3	1275	22	16	2	704	44.2	
29	503841	55	F	NO	N	YES	NO	S	P	1	15	18	4	1080	13	17	3	663	38.61	
30	561775	40	M	YES	N	YES	NO	T	D	2	18	18	6	1944	17	16	5	1360	30.04	
31	607521	65	M	NO	H	YES	NO	T	P	1	28	22	4	2464	27	20	3	1620	34.25	
32	500114	50	F	NO	N	YES	NO	T	D	2	25	16	8	3200	23	14	7	2254	29.56	
33	513408	31	M	YES	N	YES	NO	S	D	2	20	42	9	7560	18	39	7	4914	35	
34	507565	37	F	YES	H	YES	NO	T	P	2	25	26	5	3250	23	24	4	2208	32.06	
35	525373	75	M	NO	N	YES	NO	T	P	2	22	18	4	1584	20	16	3	960	40	
36	574830	57	M	YES	N	NO	YES	S	P	1	18	19	5	1710	16	16	4	1024	40.12	
37	593219	45	M	YES	N	YES	NO	S	D	2	20	42	9	7560	18	39	7	4914	35	
38	603145	50	M	NO	N	NO	YES	T	P	2	18	22	4	1584	16	20	3	960	39.3	
39	594491	58	M	YES	N	NO	YES	T	P	2	12	14	2	336	12	13	1	172	46	
40	625017	52	M	YES	H	YES	NO	T	P	2	14	12	2	336	13	11	1	143	56.54	

41	577864	42	M	NO	N	NO	YES	T	D	2	23	18	4	1656	22	17	3	1122	32.24	
42	579907	54	F	YES	N	NO	YES	T	D	1	16	22	4	1408	15	20	3	900	36.07	
43	582483	76	M	YES	N	YES	NO	S	P	2	22	20	5	2200	20	19	4	1560	30.9	
44	568786	50	M	YES	N	YES	NO	T	P	1	21	17	5	1785	19	15	4	1140	36.13	
45	573104	31	M	NO	N	YES	NO	T	P	1	15	12	2	360	16	12	2	360	37.5	