

Why Diabetic Foot Ulcers do not heal?

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Abstract: Diabetic foot ulcers are known for their chronicity and they pose challenges to even the most experienced health care professionals. Three basic reasons of chronicity of Diabetic Foot Ulcers are Diabetic Triopathy (neuropathy, vasculopathy & immunopathy), inadequate levels of growth factors & presence of biofilm. Following an injury to the skin, a set of complex biochemical events take place in a closely orchestrated cascade in order to repair the damage. The natural healing process can be divided into four stages: inflammation, granulation, epithelialisation and maturation. However, when a wound becomes delayed in healing, these four stages are interrupted and a large number of changes occur that result in the wound becoming chronic, lasting sometimes for years without healing. Unstable diabetes and colonization of bacteria are two of the primary causes of this chronicity.

The decisions of when to use antimicrobials, offloading and antibiotics, are not always straightforward and inexperienced assessors can choose inappropriate and unnecessarily expensive dressings. Infections with methicillin resistant *Staphylococcus aureus* have been increasing worldwide and they are difficult to treat. Diabetic Foot Ulcers carrying drug resistant bacterial strains such as methicillin resistant *Staphylococcus aureus* (MRSA) have more chronic wounds and Wound Chronicity: Inpatient Care, and Chronic Kidney Disease Predispose to MRSA Infection in Diabetic Foot Ulcers. In diabetic patients there is failure of fibroblasts to produce adequate ECM proteins and keratinocytes to epithelize the wound. Fibroblast gene expression is different in chronic wounds than in acute wounds. Localized Pressure also plays a major role in the formation of non healing diabetic foot ulcers that's why off-loading of the DFU is mainstay of treating DFU.

Diabetic patients are always under emotional stress which can negatively affect the healing of a wound, possibly by raising blood pressure and levels of cortisol, which lowers immunity. Co morbid ailments that may contribute to the formation of chronic wounds include vasculitis, immune suppression, pyoderma gangrenosum, and diseases that cause ischemia.

INTRODUCTION

60–80% of all human infectious diseases comprise of Chronic human infections, including chronic wounds¹.

Diabetic extremity ulcers develop in approximately 15 percent of people with diabetes and are a leading cause of hospitalization and amputation among such patients². Wound infection, faulty wound healing, and ischemia in combination with a foot ulcer are the most common precursors to diabetes-related amputations; and eighty-five percent of lower-limb amputations in patients with diabetes are preceded by biofilm infected foot ulceration³⁻⁵.

More than 80,000 amputations were performed on the United States' diabetic population each year (National Diabetes Statistics 2005)⁶. According to vascular Society of India (2010) no. of amputations in India are 80,000 to 100,000 every year, which are tip of Iceberg because of poor registry in India. Diabetic foot ulcer infection followed by amputation contribute dramatically not only to the morbidity among persons with diabetes⁷ but are also associated with severe clinical depression and dramatically increased mortality rates⁸. Such infected ulcers resulting in amputation account for a threefold increased risk of death within 18 months. Additionally, the psychological impact of an amputation dramatically increases this risk of mortality within a similar time period. As such, diabetic foot ulcers are the most common, disabling, Chronic and costly complications of diabetes^{9,10}.

CHRONIC NONHEALING METATARSAL DIABETIC FOOT ULCER

Following an injury to the skin, a set of complex biochemical events take place in a closely orchestrated cascade in order to repair the damage. The natural healing process can be divided into four stages: inflammation, granulation, epithelialization and maturation¹¹.

However, when a wound becomes delayed in healing, these four stages are interrupted and a large number of changes occur that result in the



wound becoming chronic, lasting sometimes for years without healing. Unstable diabetes and colonization of bacteria are two of the primary causes of this chronicity¹².

Diabetic foot ulcers pose challenges to even the most experienced health professionals¹³.

The decisions of when to use antimicrobials, offloading and antibiotics are not always straightforward and inexperienced assessors can choose inappropriate and unnecessarily expensive dressings.

CAUSES OF CHRONOCITY OF DIABETIC FOOT ULCERS CAN BE

- A. Triopathy of Diabetes
- B. Inadequate levels of Growth Factors
- C. Biofilm
- D. Miscellaneous causes

A. Triopathy of Diabetes

DURING the observation of patients whose diabetes has been for no. of years, a triad is being recognized with increasing frequency; It is well established that poorly controlled diabetes mellitus leads to vasculopathy, immunopathy and neuropathy¹⁴. This triopathy collectively & individually is responsible for chronicity of Diabetic Foot Ulcers.

1. Immunopathy: Diabetic patients have Impaired Poly Morpho Nuclear Function. Their polymorphs have reduced capacity to migrate at infective

site and have decrease capability to engulf micro-organisms. There is reduced chemo taxis & intracellular killing. These defects in Immune system are more so when patient has ketosis.

Because of poor Immune response & abundant food(i.e. sugar) in blood & wound, bacterias flare up & wound gets infected which is usually Polymicrobial ,difficult to treat hence chronicity of wound.

2. Neuropathy : Diabetes causes neuropathy, which inhibits nociception and the perception of pain. Thus patients may not initially notice small wounds of legs and feet, and may therefore fail to prevent infection or repeated injury.

Galkowska H et al from Poland observed reduction of foot skin innervation and neurogenic factors expression in Diabetic Foot Ulcers and they correlated low inflammatory cell accumulation and subsequent chronicity of diabetic foot ulcer healing process in both neuropathic and non-neuropathic patients¹⁵.

3. Vasculopathy: Almost all Diabetic patient have Micro & or Macroangiopathy causing decrease oxygenation of tissue. Ischemia causes tissue to become inflamed and cells to release factors that attract neutrophils. While they fight pathogens, neutrophils also release inflammatory cytokines and enzymes that damage cells. They also produce ROS (**Reactive oxygen species**) to kill bacteria, for which they use an enzyme called myeloperoxidase. The enzymes and ROS produced by neutrophils and other leukocytes damage cells and prevent cell proliferation and wound closure by damaging DNA, lipids, proteins, the ECM, and cytokines (who speed healing).

Neutrophils remain in chronic wounds for longer than they do in acute wounds, and contribute to the fact that chronic wounds have higher levels of inflammatory cytokines and ROS¹⁶.

B. Inadequate levels of Growth Factors

Chronic wounds also differ in makeup from acute wounds in that their levels of proteolytic enzymes such as elastase and matrix metallo proteinases (MMPs) are higher, while their concentrations of growth factors such as PPDGF and Keratinocyte Growth Factor are lower. As we know Growth factors (GFs) are imperative in timely wound healing hence **inadequate GF levels** may be an important factor in chronic wound formation¹⁷.

C. Biofilm

Legwound with (Rt. Side) & without (Lt. side) Biofilm

Biofilms are bacterial cities clinging to wound. Bacterial biofilms, or sessile communities of bacteria that reside in a complex matrix of exo polymeric material, contribute to the severity, chronicity and refractoriness of diabetic wounds.

Biofilms are highly resistant to both phagocytes and antibiotics

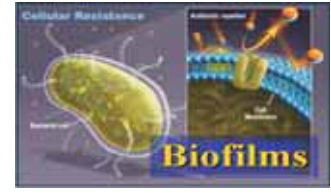
The NIH has estimated that more than 80% of chronic bacterial infections involve biofilms, and it has been demonstrated that bacterias residing in biofilms can be up to 1000 times more resistant to antibiotics than free floating planktonic bacteria.

P. aeruginosa forms biofilms more readily in the diabetic wound environment, which leads to increased resistance to antimicrobial agents, and could help explain why diabetic wounds are typically slower to heal, and more difficult to treat than non-diabetic wounds¹⁸.

D. Miscellaneous Causes

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been increasing worldwide and they are difficult to treat. Diabetic Foot Ulcers carrying drug resistant bacterial strains such as methicillin resistant *Staphylococcus aureus* (MRSA) have more chronic wounds¹⁹ and Wound Chronicity, Inpatient Care, and Chronic Kidney Disease Predispose to MRSA Infection in Diabetic Foot Ulcers²⁰.

In diabetic patients there is Failure of fibroblasts to produce adequate ECM proteins and keratinocytes to epithelize the wound. Fibroblast



Leg wound with (Rt. Side) & without (Lt. side) Biofilm

gene expression is different in chronic wounds than in acute wounds²¹. Localized Pressure also plays a major role in the formation of diabetic ulcers.

Diabetic patients are always under tremendous emotional stress. Emotional Stress can also negatively affect the healing of a wound, possibly by raising blood pressure and levels of cortisol, which lowers immunity²².

Co morbid ailments that may contribute to the formation of chronic wounds include vasculitis, immune suppression, pyoderma gangrenosum, and diseases that cause ischemia.

Clinical Causes of Delayed/Non Healing DFU

Primary Causes

Inadequate Off Loading
Incorrect Vascular assessment
Inadequate Debridement

Secondary Causes

Inadequate Antibiotic Therapy
Incorrect Method of Dressing
Associated Tuberculosis/
Nephropathy Drugs

Agents which Delay Wound Healing In Diabetes

Corticosteroids
Nitrofurantoin
Liquid Detergents
Neomycin Sulphate
Povidone Iodine
Eusol Solution
Chlorhexidine 2%
Hydrogen Peroxide

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