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Current Scenario in Anti-Microbial Therapy and Emerging Treatment in Diabetic Foot Ulcer

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ABSTRACT

Diet-related complications such as diabetic foot ulcers are the leading cause of death for diabetics. In clinical studies, a wide variety of medications from various pharmacological families are being used to treat diabetic foot ulcers, but only a few have received regulatory approval. Diabetic foot ulcers are caused by a variety of factors, including neuropathy, peripheral artery disease, infection, gender, smoking, and age. Bacterial resistance to present medications is a problem in the treatment of diabetic foot ulcers. For diabetic foot ulcers, this study focuses on the existing treatment, the current treatment method, and potential pharmaceutical targets. Rather of relying on a single medicine to cure a diabetic foot ulcer, a combination of therapy is the best option because several factors contribute to its development. These studies show that treating diabetic foot ulcers in the absence of routine access to laboratory or radiographic testing is possible despite the various challenges that practitioners confront around the world. DFUs are becoming a more important public health problem as they become more prevalent. Because of the difficulty in distinguishing between infection and colonisation in DFU, MDR bacteria have arisen as an issue. In addition, DFU develops biofilms on the skin's outer surface. Biofilm complicates the pathophysiology of DFU and can impede healing. Antibiotic-resistant conditions, such as those caused by biofilm-forming bacteria and MDR bacteria, can lead to chronic wounds, infection, and even lower-limb amputation. In this case, antibiotic alternatives would be very appreciated in the treatment of DFU. Antibiofilm approaches, which can prevent the production of microbial biofilms as well as wound chronicity, are among the creative alternative treatments for the management of DFU wounds that are discussed in this study. DFU can be treated more quickly and effectively if these cutting-edge therapeutic options are used instead of or in conjunction with more established methods.

Keywords- Foot ulcer, Wound healing, Management, Inflammation, Diabetic.

I. INTRODUCTION

Diabetic foot ulcers are more common in patients with poorly controlled diabetes than in those with well-controlled diabetes. Hypoglycemia, peripheral neuropathy, peripheral vascular disease, and poor foot health are the most common causes of diabetic foot ulcers. Other common causes include foot osteomyelitis and amputations of the lower limbs. Repetitive trauma and strain on the feet are the most common causes of foot ulcers. Staphylococcus aureus is the most common pathogen. A multidisciplinary team approach is optimal for patients with a long-term condition. As a whole, their combined knowledge is extremely beneficial to the patient's general health and well-being. Outpatient and inpatient settings both experience this[1]. Diabetic mellitus (DM) is characterised by hyperglycemia, which can have microvascular, macrovascular, and neuropathic effects. More than 11 million people in Canada have diabetes, and a new case is diagnosed every three minutes[2]. Those of Asian, African, Hispanic, and Indigenous origin are more likely to develop type 2 diabetes. Indigenous people are three to five times more likely to develop diabetes than the general population, and this is exacerbated by a lack of cultural competency among health care providers, a lack of clarity regarding who has jurisdiction over the patient, and limited access to care due to geography and language[3]. 1,2 If you or a loved one suffers from diabetes, it's important to keep an eye on your feet. Poor foot health can start off a chain reaction that can lead to amputations and even death in this high-risk group of people. People with diabetes have a 15% to 25% probability of acquiring a foot ulcer in their lifetime. According to the International Diabetes Federation, people with diabetes have a 15- to 40-fold increased risk of needing lower-leg amputations[4-5]. Nearly all amputations begin with a neuropathic foot ulcer. 3 In the five years following a lower-limb amputation, those with diabetes had a fatality risk of

50%. Breast cancer, prostate cancer, and lymphoma all have higher mortality rates than this particular type of cancer. Diabetic foot ulcers are the most common reason for diabetics to be admitted to the hospital. Diabetes-related non-traumatic amputations are on the rise in the United States. It is estimated that 5% to 1% of diabetic patients have to have their limb amputated due to foot ulceration[6].

Complications can be reduced and patient compliance increased by informing the patient about the problem and the need of medical care. Diabetes is a chronic disease that develops when the pancreas fails to produce enough insulin, or when the body fails to properly utilise the insulin it does produce. Insulin, a hormone, regulates blood sugar levels in the body. Hyperglycemia, or high blood sugar, damages a wide range of physiological systems, including nerves and blood vessels, as a result of uncontrolled diabetes. In 2019, 8.8% of those aged 18 and older were diagnosed with diabetes[5]. 1.5 million people died from diabetes in 2019, with 48 percent occurring in people younger than 70, according to the Centers for Disease Control and Prevention (CDC). Premature mortality caused by diabetes rose by 5% between 2000 and 2016. In high-income countries, the premature mortality rate due to diabetes decreased between 2010 and 2020, but then surged again between 2012 and 2021[7-9]. Premature fatalities caused by diabetes have risen in both high- and low-income countries. However, the probability of dying from any of the four most common noncommunicable diseases dropped by 18% worldwide between 2010 and 2021[10].

Type 2 diabetes mellitus is a major public health issue of the twenty-first century (DM). An estimated 415 million people worldwide have diabetes mellitus (DM), which includes 193 million undiagnosed patients and 318 million adults with impaired glucose tolerance, a condition that predicts an increased likelihood of developing the disease in the future. More than 642 million people throughout the world could be diagnosed with diabetes by 2040 if nothing is done. There has been an increase in deaths from chronic diseases like diabetes over the world. According to the World Health Organization, diabetes killed 1.6 million people in 2015, an increase from less than 1 million deaths in 2000. Some of the most common outcomes of diabetic microvascular and macrovascular complications are death, poor quality of life, and disability. WHO defines diabetic foot as an infection, ulcer, or destruction of the deep tissues in feet associated with nephropathy and/or peripheral arterial disease[11-13].

II. WOUND PREVENTION AND MANGEMENT CYCLE

Based on the most current research, this paper offers direction to all members of a patient's healthcare team, as well as the clinician who is treating them. Two important papers provide evidence-based information and guidance treating wounds of all kinds. ' Skin Physiology and Wound Healing, 14 and "Best Practice Recommendations for the Prevention and Management of Wounds, 15" Best practise recommendation papers (BPRs) propose following these three principles in order to successfully prevent and regulate skin deterioration[14].

1. No matter how small the details may be, the Wound Prevention and Management Cycle can be used to prevent and manage the breakdown of skin.
2. Continuous, accurate, and multidirectional sharing of data among team members and between healthcare providers across the United States and abroad[15].
3. A patient-centered approach to making decisions.

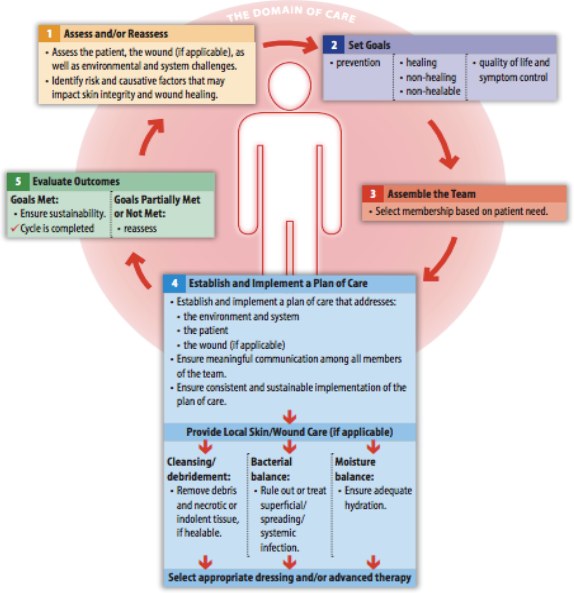

Figure 1: Management and Prevention Cycle of Diabetic Wound

III. PATHOPHYSIOLOGY FOOT ULCER

A diabetic ulcer typically progresses through three stages. The formation of a callus signifies the beginning of the healing process. Neuropathy is the cause of the callus. Deformity in the foot is caused by both motor neuropathy (physical deformity) and sensory neuropathy (sensory neuropathy). Autonomic neuropathy causes the skin to dry up, which is another contributing factor. When repeated trauma causes subcutaneous bleeding, the callus gradually erodes into an ulcer[16].

The small blood vessels in the legs and feet of people with diabetes develop significant atherosclerosis, which leads to vascular compromise and, as a result, to diabetic foot infections. Healing is slowed, which can lead to necrosis and gangrene if blood cannot reach the wound. (FIG-2) Diabetic foot physiopathology is quite complicated. If diabetes is not properly controlled for a long period of time, it can lead to a wide range of health issues. Symptoms of diabetic foot issues include

neuropathy and vascular disease. Even minor injuries can have life-altering consequences. When treating diabetes, primary care physicians must keep three things in mind: There will be an ulcer as a result of vasculopathy/neuropathy/trauma. Amputation is more likely in patients with weak peripheral circulation who become infected[17-19].

Peripheral nerves are affected by diabetic neuropathy, which is a systemic disease (sensory, motor and autonomic). An abnormal walking pattern results in an elevated peak pressure on the plantar region of the foot, which is a symptom of motor neuropathy.

Muscle weakness and joint tightness are to blame. Plantar and dorsal ulcers can form as a result of foot abnormalities. Autonomic neuropathy causes dry, brittle skin as a result of a lack of perspiration[20-22].

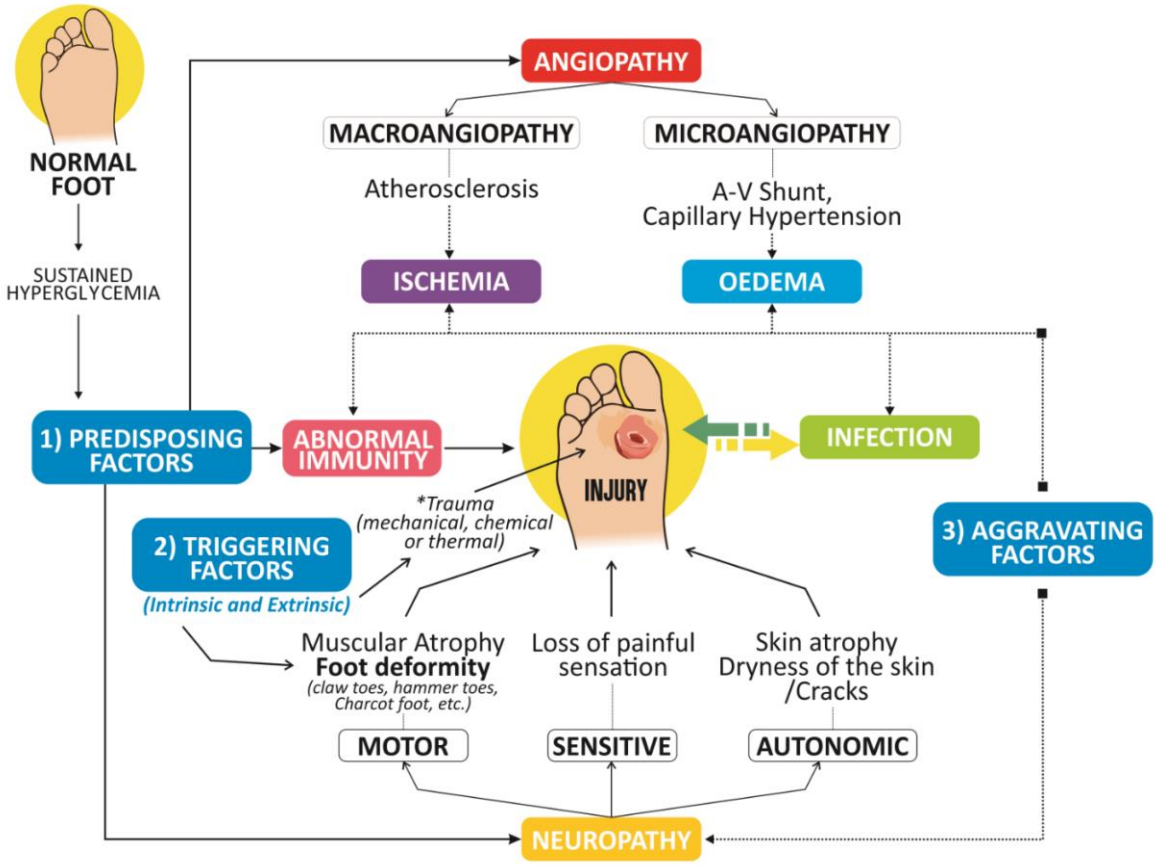

Figure 2: Pathophysiology of Foot Ulcer

IV. CURRENT METHODOLOGY FOR CURE THE FOOT ULCER

Wound Dressing

The skin, the body's largest organ, is composed of three layers: the epidermis, dermis, and hypodermis. It serves as the first line of defence against trespassers. There are two forms of skin injuries: normal wounds, and chronic wounds. When a wound heals, it goes through four distinct stages. To begin, growth factors and cytokines are released immediately after an injury in order to aid in the recovery process[23-24]. Immune cells such as neutrophils can penetrate the injury site within hours of hemostasis, killing bacteria and removing damaged matrix proteins to prevent infection from spreading further. This is the second of two proliferative phases that follow inflammatory activity. PDGF, VEGF, and FGFs, among other growth factors, are released by newly created cells, resulting in the formation of a pink, granulation-like tissue with a soft and supple texture. There is a gradual transition from type I collagen to type III collagen in the dermis as a result of the reorganisation of the extracellular matrix. Due to continuous inflammation and a lack of proliferation, chronic wounds can take longer to heal than typical wounds[25]. Prior to applying a sterile bandage, the wound should be cleaned with an antiseptic solution. Open wounds such as lacerations, abrasions, burns, and chronic ulcers, as well as their use as a prophylactic anti-infective agent, have long been a heated topic in the medical profession. Povidone-iodine, chlorhexidine, alcohol, acetate, hydrogen peroxide (H2O2), boric acid, silver nitrate, silver sulfadiazine, and salt are the most often used antiseptic solution constituents in clinical practise today.

Dressings should be wet enough to prevent them from adhering, so that they may be removed more easily. For dry DFUs, hydrogels have been proposed as a viable alternative approach[26-27].

Antimicrobial Peptides

The stages of wound healing, hemostasis, inflammation, proliferation, and remodelin, all overlap and interact. A fibrin clot is formed by restricting the injured blood arteries with activated platelets, which then stop the bleeding. As the first line of defence against infection, neutrophils are drawn to the clot to clear debris, allowing wound healing to begin[28]. It takes neutrophils 24 to 48 hours to peak in numbers and macrophages come to continue the removal of debris from the wound site[28-29]. The growth factors and proteins released by macrophages attract immune system cells such as Langerhans cells, dermal dendritic cells, and T cells to the wound. When these immune system cells aren't engaged in fighting infection, they're clearing out cellular waste products. Re-epithelialization occurs after wound granulation tissue and inflammation have been cleaned out and the wound margins have contracted, and proliferation begins after these two processes have been completed and proceeds through three distinct stages: wound margin contractions and wound granulation tissue filling[19]. Tensile strength improves once remodelling is completed with the reorganisation of collagen fibres, remodelling, and maturation of tissue. Due to disruptions in local and systemic factors that are necessary for healing, the process may be disturbed or delayed. Chronic wounds that do not heal are more common in diabetics. Antimicrobial peptides (AMPs), which are found in both the innate and adaptive immune systems, are used in most species' immune systems. An amphipathic polypeptide, or AMP, is cationic and has an amphipathic structure[30]. There are a variety of pathogens that are prevented from spreading by most AMP, including bacteria, fungi and viruses. In human clinical trials, the majority of AMPs are now being evaluated for a wide range of illnesses, including diabetic foot ulcers[31]. Neuprex tablets (RBPI 21), for example, have been designated as orphan medicines by the FDA. Toxicological data on Neuprex are sketchy at best, but there is some investigation into a topical delivery method. Most AMPs were classified as potent antibacterial agents, but also as effective modulators of inflammation or toxin-neutralizers, according to the most readily available patent information on their therapeutic applications between 2013 and 2021.

V. ANTI DIABETIC DRUG AND DIABETIC FOOT ULCER

Insulin*:* In the absence of food, your liver releases glucose to keep your body fueled at all times. It is more efficient for the body to utilise this glucose when insulin has a long, ultra-long, or intermediate half-life. Insulins like glargine (Lantus) and Toujeo are just a few examples of this class (Humulin N, Novolin N, Novolin ReliOn Insulin N). These insulins might last anywhere from eight to forty hours, depending on the type[32].

DPP-4: Drugs called DPP-4 inhibitors are used to treat type 2 diabetes, which is a significant risk factor for coronary disease and heart failure as well as a number of other cardiovascular conditions. To better understand the therapeutic applications of the several DPP-4 inhibitors available, you'll take this course. All diabetes care management staff must be aware of the most critical information[33].

Stem Cell in Foot Ulcer:

Diabetic foot ulcers (DFUs) are a major issue when it comes to diabetes and wound healing. Patients with diabetes who acquire one ulcer will almost certainly go on to develop several, with the majority of these ulcers becoming chronic, non-healing diseases. In one-third of instances, lower limb amputation will occur. It has been a decade since wound care advancements have improved the outcomes of patients with DFUs ulcers. It's tough to effectively treat diabetic foot ulcers because there isn't a specific therapy for them. The capacity of stem cells to target and circumvent the wound's aberrant healing mechanisms and disrupted cell signalling, which are at the basis of the problem, holds enormous promise for the treatment of diabetic foot ulcers. To cure DFUs, this research focuses on existing stem cell technology[34-35].

VI. THERAPEUTIC SOLUTION FOR WOUND HEALING

Consider the possibility of wound healing by the use of photodynamic treatment (PDT). Photosensitive substances can be activated by light exposure to kill pathogen cells in this treatment method. However, when exposed to light, this material becomes a potent antibacterial agent. If you have a chronic wound, such as a diabetic foot ulcer (DFU), this therapy may be able to save your limb by preventing amputation. There was only one patient who had to undergo an amputation as a result of photodynamic therapy in comparison to 16 patients in the control group. Rather than using heat, non-thermal plasma uses a different type of energy. Plasma contains a wide variety of ionised elements, including charged particles (electrons and ions), neutral and excited atoms, ultraviolet photons, and radicals[36]. A recent rat study found that the use of this device accelerated the healing of pressure ulcers. Even though human trials are still pending, results from an in vivo mouse model of type 2 diabetes showed that the drug helped kill P. aeruginosa and clean wounds while having no negative effects on the metabolic system. To help speed up the healing process after an accident, scientists have looked into electrical stimulation. Wireless electroceutical dressings were employed in a porcine chronic wound biofilm infection model with P. aeruginosa (PAO1) and A. baumannii (19606).

Researchers discovered that the dressing disrupted wound biofilm aggregates, speeding up wound closure, and found that the dressing elevated P. aeruginosa quorum sensing mvfR (pqsR), rhlR, and lasR genes and silenced E-cadherin (a protein required for skin barrier function). Finally, this research demonstrated that persistent inflammation caused by biofilms lowered the synthesis of cytokines. DFU patients have been successfully treated for several years with hyperbaric oxygen therapy. After passing through a chamber that compresses it, pure oxygen is inhaled[40]. The treatment's main objective is to increase the amount of oxygen delivered to the wound. Whether or whether this treatment works is up for debate, although it appears to be due more to the foot discharge than to the oxygen. According to a Cochrane analysis, individuals with DFUs who received the therapy experienced improved short-term healing, but not long-term recovery[37-39].

VII. CONCLUSION

Preventing pressure injuries should be everyone's first priority. Despite the emphasis on prevention, pressure injuries have not dropped significantly. The healthcare system as a whole requires an integrated, prevention-focused strategy. The best results come from combining departments like purchasing and cleaning with patients and their families. Pressure injuries can be prevented and managed if all care locations and departments collaborate. Our systems may not be set up to support a fast response to a Category/Stage 1 pressure injury, notwithstanding the importance of such systems. Reexamine all patient surfaces and transfer techniques utilised at all points of treatment, including acute care, operating and interventional room tables; emergency room stretchers; ambulatory departments; rehabilitation settings; community and long-term care alternatives. The treatment of suspected causes is vital in preventing pressure injuries. Amputations and deaths from diabetic foot ulcers are avoidable if patients and healthcare providers take preventative measures. A multidisciplinary team is required to manage an ulcer. The patient's overall health must be the primary focus of care. Diabetics must be trained on proper foot care and how to seek medical help if they notice any anomalies. A healthcare system that prioritises long-term needs of diabetics and foot ulcer patients is required. Consider interprofessional guidelines for educational purposes (screening, risk reduction, treatment), patient and family self-management education, clearly defined treatment pathways, and prompt access to care in every community service for detecting people in danger through annual foot examinations and screenings at risk intervals. Constructing integrated teams with specialised training and evaluating all service elements will help ensure that local foot care meets established national and international standards. Diabetic foot ulcers are a common yet serious diabetic condition. A study to find the most cost-effective and safest treatment for DFU is presently underway.Due to the wide range of factors that contribute to DFU, a combination of drugs is the best treatment. Exendin-4, insulin, and DPP-4 inhibitors reduced hyperglycemia and MMP-9 in diabetic wounds in rats and humans treated with batimastat affinity resins. MMP-9 hampered diabetic wound healing, but MMP-8 aided it.

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