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EFFECT OF DIABETES MELLITUS ON DIABETIC FOOT ULCER: A REVIEW

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ABSTRACT

Diabetes mellitus is a metabolic disorder, caused by Hyperglycemia and many other factors which is affecting all age individuals. It also affects the organs which can later dysfunction. By proper management, some treatment strategies and a healthy lifestyle is required. DM is mainly of 3 types- Type 1, Type 2 and Gestational diabetes. It has multiple symptoms and complications which can be prevented by taking some necessary precautions. It has some risk factors like family history, age, obesity, genetic, smoking, etc. Symptoms like blurred vision, more urination problem, feeling of thirst, etc. DM causes various complications so likewise Diabetic foot ulcer (DFU) which is a serious complication. It affects the foot by forming infection/ ulcer caused due to hyperglycemia or bacterial infections and by other factors as well. If not treated early it can lead to amputation. Various preventive measures and practices that can be taken to avoid foot wounds including off-loading of the foot, checking glucose levels, using non-surgical agents and dressings, wearing clean socks, avoiding walking barefoot, washing feet daily, inspecting feet daily, undergoing O2 therapies, and consulting doctors. Pathophysiology of DFU is due to various factors but the important factor is neuropathy. It has 5 stages to develop ulcer which starts from small wound to gangrene of foot and some molecular mechanisms which affects the tissue damage to find out DFU. It has molecular tissue changes that affects the layer of foot skin to get eroded and it can be prevented by various antibiotics, antiplatlet agents to treat such as Clindamycin , vancomycin, carbapenmas. Piperacillin, etc.

KEYWORDS: Diabetes mellitus, Complications, Foot ulcers.

INTRODUCTION

Diabetes is major problem which is affecting globally. It is a chronic, non-communicable disease that is increasing at higher rate.[1] It is a metabolic disease and due to metabolic problems in carbohydrates, proteins, lipids it affects the insulin. Diabetes is affected by low level insulin or insulin resistance to the target tissue like adipose tissue, skeletal muscles even genes are responsible for this metabolic abnormalities.[2] Diabetes is caused by high blood sugar level (hyperglycemia) in the body due to deficiencies in insulin secretion or its action. As hyperglycemia can lead to long-term damage and dysfunction of multiple organs, including the eyes, kidneys, nerves, heart, and blood vessels etc.[3] It is a complex condition that has various categories and 3 types - Type 1, Type 2 and gestational diabetes. The two main sub-types of DM are Type 1 diabetes mellitus (T1DM) it is diagnosed in children or adolescents and is caused by defective insulin secretion so living with type 1 diabetes could be challenging, but with proper knowledge and guidance it can be managed and on the other hand Type 2 diabetes mellitus (T2DM) it is non-insulin dependent which is also known as adult onset diabetes as it is commonly observed in middle-aged and older adults who have hyperglycemia due to poor lifestyle and dietary choices,[4] and lastly Gestational diabetes it is a condition where diabetes is diagnosed during pregnancy (gestation) so these women possibly their children can have type 2 diabetes in future . It is due to hormonal changes in body and also it affects the cells in body use sugar (glucose), resulting in high blood sugar levels that can have an impact on both - pregnancy and the baby's health. By following a healthy diet, or by regular exercise, and taking medication if necessary, you can help to control blood sugar levels and maintain a healthy pregnancy. This will also help to prevent any complications during delivery process.[5] According to many studies people are less aware about diabetes and about its complication specially in rural areas. It is important to aware people about diabetes to prevent some the risk factors such as history of diabetes, Obesity, presence of hypertension, gestational diabetes, fat distribution, and many more.[6] Symptomsof diabetes- sometimes the symptoms are not noticable or there there are only mild symptoms before the diabetes is diagnosed. common symptoms are feeling tired, blurred vision, weight loss, more urination, feeling of thirst and hungry,

slow healing of cuts or wound having tingling sensation or pain, etc.[7] Microvascular complications of DM are- Eye problems (retinopathy), foot ulcers, cardio vascular disease (CVS), kidney problems (nephropathy), nerve damage (neuropathy), Peripheral artery disases, gum disease and other mouth problems, DM also link with some types of cancer as well.[8] So likewise this, Diabetic Foot Ulcer (DFU) is also a most serious complication of diabetes causing medical, social and economic problem. Diabetic Foot Ulcer is a most challenging complication and it is one of the most expensive complications to treat. Macrovascular and microvascular damage is affected by Neuropathy which is a major cause of ulcers, infections and gangrene. This ulcers are usually in that area where there is more pressure sensations of the feet. Staphylococcus bacteria, Pseudomonas aeruginosa, Escherichia coli, Proteus species, Enterococcus, and gram positive bacteria is responsible for the infection which makes the wound infective. The other causes are poor glycemic control, foot problems, ill fitted shoes, poor circulation of blood to the dry skin area and long term hyperglycemia leads to peripheral nerve damage.[9] The stages of ulceration includes loss of sensation of feet, ischemia and the last stage is amputation. DFU is classified into 3 types: purely neuropathy as 35%, ischemic as 15% and neuroishemic as 50% as these complications are based on neuropathy or PAD for prevention of DFU. Ischemic ulcers are irregular lesions with pale base and round ulcers are due to friction at dorsal area of toe joints.[10] The various preventive measures and practices that can be taken to avoid foot wounds including off-loading of the foot, proper knowlegde of foot,[11] checking glucose levels which can control neuropathy and thereby foot ulcer.[12] Foot disability can also cause foot infection because pressure is applied by foot.[13] Also by preventing the problem by the using proper footwear for diabetic ulcer.[14] The diabetic patient requires long term treatment for the amputation process so they are hospitalized in the hospital for amputation of lower limb. The amputation rate is very high in patients as they don't treat their complication in the early times.[15] Risk factors that are associated includes metabolic characteristics and an extrinsic factors which the patient is interacting with the environment and it also includes the patients age, education of that disease, weight of the patient, type of DM, patients habits regarding foot care and Peripheral neuropathy, and foot pressure.[16] As foot ulcer is occuring among people with diabetes which requires epidemiological knowledge by health care providers and effective strategies, to overcome this infection.[17]

So from the above study, it was observed that foot damage is a serious complication of DM and can be treated by various approaches.

PATHOPHYSIOLOGY

The pathophysiology of the diabetic foot ulcer is due to neuropathy, angiopathy, trauma, peripheral artery disease (PAD). Diabetic neuropathy leads to more foot pressure while walking which affects the foot and gets deformed. It can also affect the digestive system, urinary tract, blood vessels and CVS. It can have mild symptoms. But for others, diabetic neuropathy can be quite painful. Diabetic neuropathy is a serious complication which may affect many patients with diabetes. It can be prevented or slow its progress with regular blood sugar control and a healthy lifestyle.[18] Charcot arthropathy is the another reason for patients with neuropathy as it is caused by fractures or dislocations of bone by which the bottom layer of foot is visible.[19,20] Autonomic neuropathy is also responsible as it causes vasodilation in the foot. It also controls the sweat glands which reduces perspiration and lead to dry skin that cause friction to feet by which the foot upper gets erode and wound occur.[21,22] According to the results, the development of a diabetic ulcer occurs in five stages. These stages are as follows: Stage 0, which involves no lesions or damage; Stage 1, where a superficial ulcer is present, meaning the skin is broken but the wound is small and only affects the upper layer of skin; Stage 2, are deep ulcers; Stage 3, known as otitis, which involves inflammation and partial visibility of the bone; Stage 4, where partial gangrene or necrosis of the foot occurs; and Stage 5, which involves gangrene of the entire foot, with the ulcer appearing black in colour. The initial stage of ulcer development begins with the thickening of the skin, known as callus formation. Calluses are caused by friction or pressure on the feet and are a result of neuropathy. Motor neuropathy leads to physical impairment of the foot, while sensory neuropathy causes sensory loss, increasing the risk of trauma. Autonomic neuropathy can also lead to dry skin. Ultimately, the trauma to the callus can erode and result in an ulcer. Other reason can be atherosclerosis. It can be one of the main complications of DFU. The small blood vessels in the legs and feet, leading to vascular problem, which is another cause for diabetic foot infections because blood is not able to reach to the wound, healing gets delayed, and eventually it leads to necrosis and gangrene.[23]

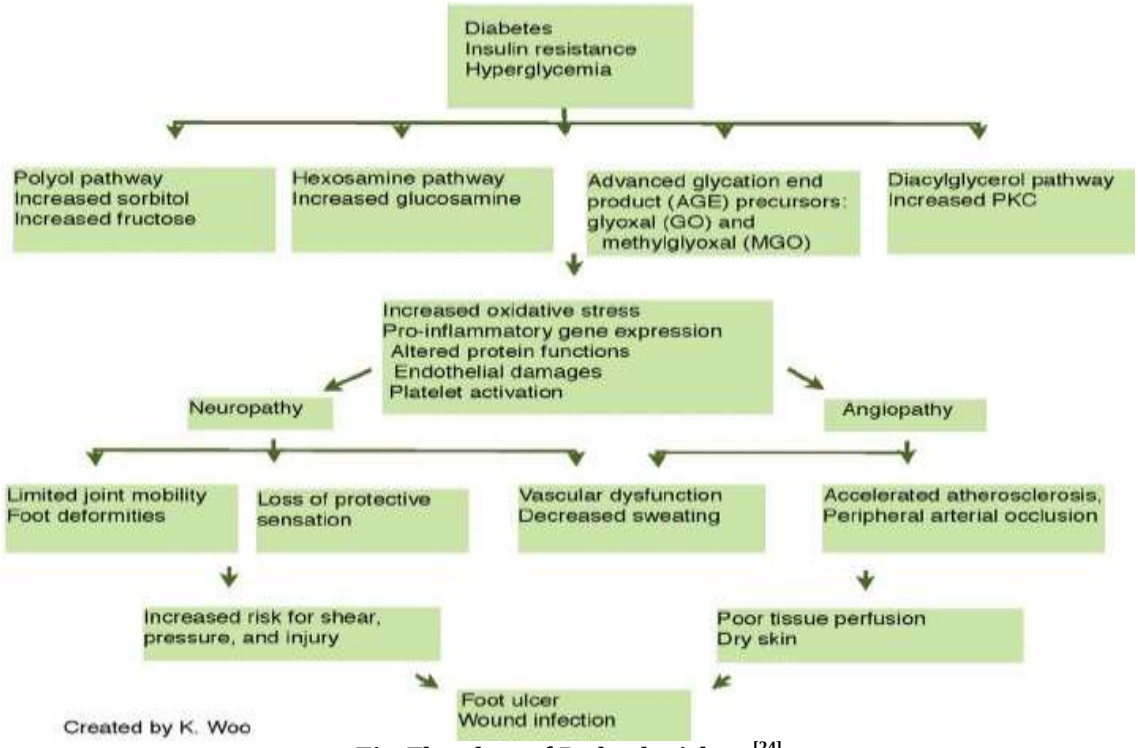

Fig. Flowchart of Pathophysiology.[24]

DFU also includes many scientific reasons, which includes neuropathy, as neuropathy impacts to sensory loss, motor neuron dysfunction, autonomic dysfunction, etc. DFU also impacts to vascular dysfunction which involves ischemia, impaired wound healing and lastly due to secondary infection which causes trauma/injury and reduced angiogenesis of the foot. The sensory disability occurs due to more glucose level in body to cause hyperglycemia which alters the upregulation of aldose reductase and sorbitol dehydrogenase, which increases the production of fructose and sorbitol in the body so due to this, the glucose products starts to accumulate and cause osmotic stress which stops the nerve cell conduction.[25] In addition to sensory neuropathy, diabetes can also cause neuronal autonomic problems which results in decrease in sweat production, leaving the foot to dry then skin cracking, and major injury/hole.[26] Another reason called- Advanced glycation end products (AGEs) which must be consider, as they are the harmful compounds as they are formed when protein or fat combine with sugar in the bloodstream and cause diabetes.[27] In the starting stage of wound healing, neutrophils releases some molecules to kill the pathogens so this process is called as NETosis.[28] In a diabetic environment, NETosis (cell death) becomes uncontrollable and stops the inflammatory- cascade (it is a immune mechanism which is responsible to overcome from tissue injury and start wound healing process) and overproduction of cytokines causes delay in wound healing.[29,30] AGEs can bind to the receptor of advanced glycation end-products (RAGE) which causes cell stress and leads to cellular dysfunction and activates nuclear factor kappa-B (NF-κB) from where cytokine release gets enhanced and inhibit the insulin signal transduction mechanism with a self-sustaining cascade that prolongs inflammation and lead to apoptosis.[31,32] Another reason is Extracellular Matrix (ECM) as during the time of injury it gets damaged, so alterations of the ECM plays a significant role in maintaining the wound healing process and scar formation, and the production and degradation of ECM proteins such as collagen and elastic fibrin helps in the regeneration of dermis layer.[33] Here, the Collagen-degrading enzymes also known as matrix metalloproteinases (MMPs) become hyperactive, which results in highly-proteolytic environment with reduces the collagen content and ECM gets alter and inadequate to support wound healing process.[34,35] Increase level in MMP activity, and the accumulation of AGEs in body results in a reduction of fibroblast growth factor (FGF) makes it critical for normal wound healing.[36,37] Another reason is improper Angiogenisis which also plays an important role in wound healing and if angionesis process gets damaged there is a disruption in wound healing process and it is also responsible for the formation of tissue and it delivers nutrition and oxygen to the wound.[38] As in case of DFU, there is a decrease of angiogenic growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor(FGF), tumor necrosis factor-alpha(TNF-a).[39]

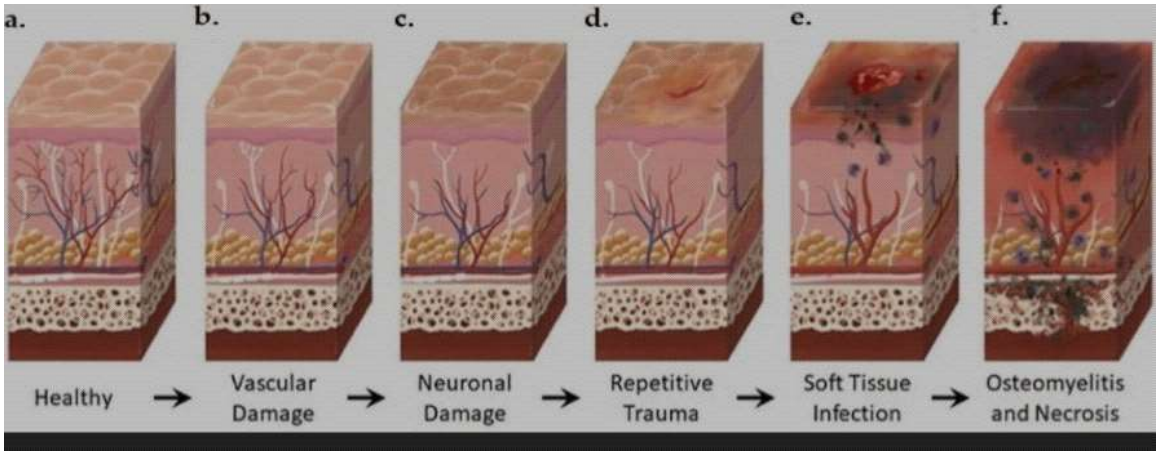

Fig. 2: Molecular mechanisms of Diabetic Foot Infection.

As currently diagnostic test rely on tissue level so the molecular changes in the tissue damage is required for diagnosis and treatment of DFI. The Anatomical Changes associated with Diabetic Foot Pathophysiology are multiple which contributes to an increased risk of ulceration, infection, and amputation. Sustained hyperglycemia affects the endothelial lining of the blood vessels which is affecting the healthy tissue (a), lead to improper circulation of blood and without sufficient vascular support, nerves die and the skin becomes dry and cracked as sweat secretions are decrease (b). During the stage of injury, numbness in the foot is due to neuronal ischemia (c). Cracks in the dried skin can attracts the microorganisms easily, to the wound infection. Entering of micro- organsisms to the trauma site leads to inflammation, vasodilation, and soft tissue necrosis (d). Decreased blood vessels into a tissue affects the immune response to infection and increases the healing time and the infection stays in the soft tissue, because of delayed care or ineffective treatment (e) and lastly microbes enter in the bone tissue, leading to osteomyelitis and Necrosis (f).[41]

Treatment

Antibiotics such as

1. Vancomycin (Vancocin, ViroPharma) given parenterally as an therapy due to its narrow spectrum. Physicians should use vancomycin empirically in conjunction with other agents such as ceftazidime (Fortaz), cefepime (Maxipime, Pfizer), piperacillin-tazobactam (Pfizer), aztreonam or carbapenems if they suspect a polymicrobial infection in a moderate or severe diabetic foot infection.[41] According to resistance, vancomycin has minimum inhibitory concentrations (MICs) for methicillin-resistant Staphylococcus aureus (MRSA) which is rapidly growing. In patients with normal renal function, it is recommended that a vancomycin dose of 15 to 20 mg/kg every eight to 12 hours when the S. aureus MIC is equal to or less than 1 mg/L. Vancomycin is known to be associated with a risk of nephrotoxicity, especially when one combines it with other nephrotoxic antibiotics such as an aminoglycoside.[42]

2. Ceftazidime is a third-generation cephalosporin use parenterally. This is a bactericidal antibiotic, which physicians use empirically with vancomycin for moderate to severe diabetic foot infections.[41] It has the ability to penetrate bones in ischemic limbs.[43] High serum concentrations of ceftazidime could result in serious adverse nervous effects. This antibiotic is used by patients who have penicillin allergies.[44] Use precaution with this drug in patients with a history of seizure disorders as drug levels could increase significantly.[45]

3. Piperacillin/tazobactam (Zosyn, Pfizer) is a bactericidal parenteral antibiotic used by the clinicians diabetic foot for broad spectrum coverage. Zosyn is available in combination of aminopenicillin and beta-lactamase inhibitor.[46] The Food and Drug Administration (FDA) has approved Zosyn for the treatment of skin and diabetic foot infections but not for any accompanying osteomyelitis. Zosyn is useful as an empiric therapy as it provides broad spectrum coverage for moderate to severe diabetic foot infections.[41] It is useful against bacterium with spectrum beta-lactamases.[47] Use combination of vancomycin and piperacillin/tazobactam therapy in severe DFI to cover MRSA, Enterobacteriaceae, Pseudomonas and anaerobes.[48] An advantage of using Zosyn is that it has minimal nephrotoxicity effect.[49] The main side effect is diarrhea. Zosyn provides a safe and effective empiric treatment for moderate to severe diabetic foot infections.[50]

4. Clindamycin- It covers Gram positive and anaerobic infections which involves the diabetic foot. It do not have good activity towards Gram negative bacteria. The FDA guidelines states that the drug is effective against skin and soft tissue infections caused by bacteria such as Staphylococci. It is also effective against Gram-positive bacteria, except Enterococcus and MRSA. Clindamycin is active against Clostridium species and Bacteroides species. Clindamycin has excellent oral bioavailability. It is also a very useful drug in patients who are sensitive to penicillin and vancomycin. Combining clindamycin and ciprofloxacin can be effective for severe and life-threatening diabetic foot infections. It is an FDA

pregnancy category B drug which is not harmful to fetus. Common side effects of the drug include diarrhea and gastrointestinal problem. Clindamycin is a good choice in DFIs because it does not require renal dosing.[51]

5. Ampicillin-sulbactam it is a broad-spectrum antibiotic used in treat moderate to severe diabetic ulcers. It is effective against and Strep species, E. coli, Proteus species, Bacteroides species and other species.[52]

6. Doxycycline It is a tetracycline antibiotic. Covers both Gram positive and Gram negative.[53] Mostly used as an oral prescription. This antibiotic is bacteriostatic. Advantage of this medication is that it do not cause any adverse effect with antibiotics, it also lowers the GIT side effects.[54]

8. Linezolid- It is active against pathogens. They are mild and van be reversible. Available in 2 forms oral and parenteral formulations. Produces more adverse effects than ampicillin-sulbactam as compared to ertapenem with or without vancomycin.[55] It is a new drug for antimicrobial action and to treat complications of skin and its tissue along with DFU treatment. Used against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci. It has 2 forms oral and intravenous form which do not require dose adjustment in hepatic failure.[56]

CONCLUSION

Diabetic Foot Ulcer is a serious complication of diabetes which is caused by Hyperglycemia and many other factors. It affects the skin of foot as pressure is applied by the foot. Some the bacteria like cocci bacteria is also responsible to make wound infective. It has various risk factors that should be check accordingly. Due to Poor patient education, lack of preventive care it can cause a major concern and lead to amputation. By taking early medications it can be managed or controlled. Medications are antibiotics such as Clindamycin, Amoxicillin, Metronidazole, Piperacillin, Vancomycin, etc which can reduced the minor effects of diabetic wound. There are various new approches to treat DFU but they have their own limitations.

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