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RESEARCH ARTICLE

A PEEP IN TO NOVEL THERAPIES IN DIABETIC FOOT ULCER

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Abstract

Diabetic Foot Ulcer represent a complex entity resulting from several contributing pathways including neuropathy, vascular disease, and metabolic derangement, which may occur alone or in concert with each other. DFU affects patients physically, mentally and economically. Offloading, debridement, infectious controlling and revascularization remains as the mainstay in treatment of diabetic foot. Antibiotic resistance are also observed frequently in these patients. These current standard of treatment is still not showing much recovery in patients. In this era novel approaches to the treatment of DFU gain more interest. This review aims to summarize the novel approaches that are in practice for the diabetic foot ulcer treatment along with clinical evidences from the randomized control trials. Still many procedures lack much evidence and their efficacy and safety need to be determined.

Introduction:-

DFU is primarily characterized by ulceration in a patient with diabetes which is associated with neuropathy and peripheral arterial disease (PAD). Diabetic foot is one of the most serious and significant diabetes complications. This problem is seen mostly in the elderly patients. With approximately 42 million cases, India is among the top ten most affected countries. According to WHO, 360 million people worldwide will be affected by type 2 diabetes by 2030.[1]Diabetic foot ulcers (DFUs) are one of the most popular and awful complications of diabetes, as they precede about 80 percent of all lower limb amputations related to diabetes and are associated with substantial burdens on the patient and health care system. About 1 in 4 patients with diabetes may ultimately develop a foot ulcer.[2]

Etiopathogenesis Of Diabetic Foot Ulcers:-

DFU represent a complex entity arising from several contributing mechanisms including neuropathy, vascular disease, and metabolic derangement, which may occur alone or in combination with each other. The etiology of diabetic foot disease is multifactorial, which involves complications of diabetic neuropathy, vasculopathy, immunopathy, and impaired glycemic control. Diabetic neuropathy results in sensory, motor and autonomic dysfunction of the nerve and is the most common cause of diabetic ulcers at the lower extremities.Through proper screening, in patients with peripheral neuropathy or peripheral arterial disease (PAD), about 75 percent of diabetic patients undergoing foot and ankle surgery will be found to have neuropathy.[3]They are typically caused by repetitive trauma over a foot area in patients with peripheral neuropathy or peripharal arterial disease (PAD). Foot deformities, impaired glycemic control, other microvascular complications and a previous history of DFUs or amputation are other major risk factors.[4]The causal pathway to ulceration also involved ischemia, callus and edema. Infection has seldom been implicated in the etiology of these lesions, although once an ulcer has formed, infection and PAD have been found to be the major causes of amputation.[5] Gender (male), length of DM longer than 10 years, advanced age, high body mass index, previous ulceration, and other comorbidities such as retinopathy, glycopathy, limited joint

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mobility, foot deformity, high plantar pressure and inappropriate foot self-care habits are other contributing causes of ulceration.[6]

The exact pathogenesis mechanism of neuropathy is not clear, but may be due to the accumulation of sorbitol and fructose due to hyperglycemia, leading to the myoinositol deficiency required for normal neuronal conduction; which is associated with the patients' loss of sensation experience that makes them vulnerable to physical, chemical, and thermal trauma.[7]

Without protective sensation, a neuropathic patient lacks the physical symptoms that would normally cue healthy people to examine or rest their feet, thus increasing the extent of skin damage before presenting for treatment. Autonomic neuropathy also leads to ulcer development as it affects both physiological secretions and the venous artery systems contributing to warm, flaccid, and brittle skins. This increases the risk of fissuring and breaking down of the skin, creating potential infection sites. Motor neuropathy can lead to changes in foot structure.Such modifications are partly due to muscle imbalance and weakness induced by intrinsic atrophy, which often appears as claw toes, hammertoes, prominent metatarsals and other deformities. Such deformities alter the pressure patterns on the foot making certain places more vulnerable to inflammation or ulceration.[8]Endothelial damage and vessel sclerosis of both large and small vessels leads to reduced peripheral perfusion. This puts patients at an increased risk of ulceration and contributes to decreased ability to heal wounds and treat infections.In addition, diabetes patients have an impaired ability to mount an inflammatory response (immunopathy) to the infection. Impaired neutrophil function, chemotaxis, phagocytosis and decreased response of t-cells were found in patients with diabetes compared to those without diabetes.[9]

Peripheral arterial disease (PAD): In diabetic patients elevated blood glucose causes change in endothelial cell function and results in peripheral arterial abnormalities. It is the endothelial cells that are responsible for nitric oxide synthesis. Therefore, in the case of hyperglycemia, nitric oxide is disturbed which maintains anticoagulation of the homeostasis, leukocyte adhesion, smooth proliferation of muscle cells and antioxidant capacity.[10]

Management:

Because DFUs are due to different pathological mechanisms, their management requires a multimodal and interdisciplinary approach that should include (1) prevention, (2) addressing the specific mechanisms that contribute to their development, and (3) promoting wound healing.[11] The primary goal in the treatment of DFUs is to achieve wound closure.[12] The initial treatment of DFUs includes sharp debridement, offloading and local wound care. Prompt, effective treatment of DFUs can often avoid the issue from becoming more severe and the possible need for amputation. Therefore, the goal of therapy should be early intervention to enable the lesion to heal quickly and prevent its recurrence once healed.[13]

Current Standards Of Treatment:

The initial treatment of DFUs includes sharp debridement, offloading, and local wound care.One of the most important interventions to facilitate healing is probably the use of devices or surgical procedures to reduce abnormal pressure and shear stress at the site of the ulcer. Inadequate pressure relief at the ulcer site will delay ulcer cure even in sufficiently perfused limbs and increase the risk of recurrence after the ulcer has healed.[14]

Using total contact cast is the traditional gold standard approach for offloading pressure and preserving the ulcer.[15]Other appropriate offloading methods include therapeutic / modified shoes, custom braces, and orthodontics. Debridement involves the excision of necrotic, damaged, or infected tissue to optimize the healing of the remaining viable tissue.[14]It improves healing by encouraging the production of granulation tissue and can be achieved by various means.

The suggested approach recommended by the American Infectious Disease Society and the Wound Healing Society is surgical debridement.[15]It uses a scalpel blade to remove all nonviable tissue until a healthy bleeding ulcer bed is produced.

Mechanical debridement is a traditional form that requires the application of moist and wet flushes or dressings. This method is effective because ulcers heal faster and are less likely to get infected when they are allowed to heal from a moist environment. Enzymatic debridement uses microorganism or plant-derived chemical agents such as collagenase and streptokinase. This attacks necrotic tissue selectively without affecting healthy tissue, and is

recommended for ischemic wounds.[16]Autolytic debridement is a painless and highly selective method used by the body to selectively debride slough and necrotic tissue using its own enzymatic processes and defense mechanisms. It is indicated whenever dead tissue is not extensive or contaminated, and the process is slow and should be checked for infection.[14] Biological debridement uses sterile maggots only to digest bacteria, surface debris, and necrotic tissue. This approach has been shown to be effective in removing drug-resistant pathogens from wound surfaces including Staphylococcus aureus, for example.[16]

Nonetheless, deciding the most appropriate technique involves consideration of host-specific factors (e.g., comorbidities, enforcement, and social support) and wound-related factors (e.g., infection / contamination status, perfusion, and viability), as well as available resources at the treatment center..[17]

Infectious management:
The majority of DFUs are practically colonized with micro-organisms. The effect of the involvement of microorganisms in the ulcer on wound healing is not completely known.[18] Once infection is detected, suitable tissue specimens should be collected for analysis, and empirically antibiotic therapy should be initiated and subsequently updated by sensitivity testing. Current data, mainly of moderate quality, suggests that the antibiotic regimens available are analogous, and the choice of antibiotic agent, route of administration and length of treatment is primarily a matter for expert opinion. To date the FDA has licensed only three antibiotics for the treatment of diabetic foot infections; ertapenem, linezolid, and piperacillin/tazobactam.[19]

Dalbavancin and oritavancin are newer intravenous lipoglycopeptide antibiotics that are effective against gram-positive cocci, including MRSA, and have recently been approved for use in patients with acute bacterial skin and skinstructure infections. Tedizolid, a newer antibiotic agent of the oxazolidinone class for oral and intravenous administration, has similar indications.[20]Ceftaroline is a fifth-generation cephalosporine having activity against gram-positive bacteria, like MRSA, and some gram-negative pathogens and has also been approved for the treatment of acute bacterial skin and skin structure infections.[21]

Revascularisation:
According to the Society for Vascular Surgery Wound Ischemia and Foot Infection (WIfI), clinical staging, revascularization is usually indicated in most DFU patients and those with grade 3 ischemia. However, the decision to continue with revascularization depends on several factors, including wound stage, existence of infection, and patient factors such as older age and comorbidities.[14]While studies have shown that vigorous, timely revascularization can reduce amputation rates among DFU patients, those with higher grade ischemia tend to have higher amputation rates even when aggressive revascularian is performed.[22]

Novel Apprpoches In Treatment Of Dfu:
Negative Pressure Wound Therapy:
NPWT is a biophysical agent consisting of a mechanical unit attached to a dressing by a plastic tube which, when connected to a suction system, allows for sub-atmospheric pressure to be generated at the wound site.[23] It is thought to promote wound healing by removing exudate, contracting wound edges and promoting angiogenesis. Recommended for recalcitrant DFU which needs debridement.[24]

An essential component of any NPWT device is a porous material such as foam or gauze that fills the wound and facilitates the transmission of pressure. A dressing consisting of an occlusive drape is then applied to the wound opening, traversed by a drainage tube, creating a seal in which there is negative pressure. The drainage tube is attached to a negative pressure unit, usually between −50 and −150 mm Hg. Action of negative pressure wound therapy results in two types of tissue deformations: macrodeformation (i.e., wound contraction) and microdeformation occurring at microscopic level. They are believed to be primarily impacting early stages of healing, which is inflammatory and proliferative phases.[25]

Several studies have shown that NPWT changes the local blood flow and decreases local oedema by generating subatmospheric pressure. The change in local blood flow after NPWT depends on the degree of negative pressure provided and the type of foam used.[26]Hyperperfusion close to the wound edge is thought to be beneficial by improving oxygenation and nutrient supply, while hypoperfusion at the wound edge is thought to help by stimulating angiogenesis. Local reduction of oedema results from the removal of excess extracellular fluid and leads to reduced hydrostatic compression at capillaries and reduction of the required diffusion distance.[27] Interestingly, a

rapidly substantial decrease in periwound tissue oedema was found in patients with various wound forms, a few days after therapy.[28] By removing excess wound fluid, NPWT reduces inflammatory cytokines and proteases that can exacerbate healing processes.[29] Furthermore, when NPWT eliminates wound exudates, it also helps to preserve healthy moist wound environments and contributes to fewer dressings. Additionally, some data on the reduction of bacterial load as a result of NPWT use are also available.[30] For example, it has recently been shown that in patients with different characteristics of wounds, bacterial load including the magnitude and amount of different bacteria, was decreased after NPWT treatment.[31]

Hyperbaric Oxygen Therapy:
Hyperbaric oxygen therapy (HBO) consists of short-term, high-dose oxygen inhalation and diffusion therapy, delivered systemically through airways and blood, attained by having concentrated oxygen at a pressure greater than one absolute atmosphere (ATA) in the patient. For diabetic foot ulcers (DFU), 30 to 40 treatment sessions of 90 minutes are usually endorsed at pressures between 2.0 and 2.5 ATA in a hyperbaric chamber.[32]Previous high-quality RCTs showed a significant improvement in ulcer healing and decreased amputation rates among DFU patients treated with adjunctive HBOT compared to Standard care of treatment modalities alone.[33]

Many preclinical and animal studies have shown that HBO stimulates angiogenesis, reduces oedema, increases the formation of granulation tissue by enhancing fibroblasts, improves leukocyte function, and mobilizes bone marrow stem cells.[34]In people with hard-to-heal DFUs, HBO increases the levels of transcutaneous oxygen (TcPO2) in the feet and TcPO2 levels are associated with treatment results.[35]

Several clinical studies, as well as analyzes of real world data have been published since. In short, they didn't weaken the ground for HBO; instead, promising areas were identified for potential study. For the moment, IWGDF Wound Healing Intervention Guidelines' current recommendation to allow the use of HBO as an adjunctive treatment in non-healing ischemic DFUs given the best quality of care is a reasonable interpretation of the available evidence. [32]

Although the recently published International Working Group on the Guidelines for Diabetic Foot Wound Healing Interventions suggested considering the use of HBO in non-healing DFUs, the strength of this recommendation has been graded as weak.[36] Apart from that, use of HBO in DFUs is not endorsed by the National Institute for Health and Care Excellence (NICE) in the UK or by the American Diabetes Association. A group of global hyperbaric experts reviewed the use of HBO in chronic DFUs and highlighted poorly conceived work in this field.[37]

Extracorporeal Shockwave Therapy:
The advent of extracorporeal shockwave therapy (ESWT) is as an effective and safe adjuvant therapy for DFU. Histological analysis indicates that ESWT can promote wound healing through the production of growth factor, tissue neovascularisation and increased blood profusion.[38]

The proposed shockwave therapy mechanism of action is the transfer of mechanical energy from the sound waves to chemical energy to stimulate wound healing. The movement of a sonic wave between 2 tissues with different impedance generates forces with stress that produce bubbles with an interior vacuum. The breakdown of bubbles induces shearing forces into local tissues, creating radicals free of oxygen and hyperpolarizing cell membranes. This triggers the release of kinases and growth factors, for example the growth factor of the vascular endothelial. These kinases and growth factors induce a local healing and inflammatory response that is uncommon in diabetes mellitus.[39]

In a pooled analysis of two RCTs comparing ESWT and sham for DFU, Snyder et al . found that a significantly higher proportion of patients receiving ESWT and standard care of treatment reached complete closure after 20 (35.5 vs 24.2 percent, $p = 0.027$) and 24 weeks (37.8 vs 26.2 percent, $p = 0.023$) of treatment compared to those receiving sham and Standard care of treatment.[40] Adverse ESWT reactions are reported to be minimal and include transitory skin reddening, slight pain, and small hematomas.[38]

Wireless Micro Current Stimulation:
This technology uses oxygen to transfer negatively charged electrons to the wound area to reinitiate or accelerate the healing process.[41]It has been shown that electrostimulation influences a variety of mechanisms that are helpful for wound healing, including:

- Improvement of blood flow
- Improvement in tensile strength
- Stimulation of protein and DNA synthesis
- Reductions in oedema
- Decreased bacterial growth
- Promotion of epithelial, fibroblast, neutrophil and macrophage cells
- Reduction in pain[42]

This promotes angiogenesis, collagen production, and keratinocyte migration by releasing many factors, including vascular growth factors, hypoxia-inducing factor 1α (HIF-1α), and VEGF in ischemic DFUs.[43] Peters et al., performed an RCT to evaluate the impact of a 50V current applied overnight (eight hours) to an individual's wounds using a microcomputer. Standard treatment was also given for both the intervention and the control groups. Results indicate that in the treatment group 65 percent healed versus 35 percent in the control group (p=0.058). The reduction in wound size was not statistically different among groups, and the more concordant patients had better results in both groups.[44]

Unfortunately , the majority of RCTs (limited in number) show no benefit in improving wound healing outcomes.[45] However, Kloth, looking specifically at lower extremity wounds, concluded that the 22 studies examined provide a rationale for electrostimulation being used in conjunction with standard care to improve the healing of venous, arterial and neuropathic aetiologies of lower extremity wounds..[46]

Specifically, WMCS healed the ulcers completely after four and 45 sessions in two DFU patients with chronic and contaminated wounds that had failed standard treatment. Neither patient indicated any pain. In addition, the risk of contamination was reduced, as there is no direct contact with the device.[41]

Large randomized clinical trials are needed to validate the efficacy and safety of patients with diabetic foot ulcers.

Pressure and Temperature Feedback Devices:
Some of the newest developments in DFU adjuvant therapy includes the use of pressure and temperature sensing instruments to avoid DFU in patients with diabetic peripheral neuropathy.[47]An important breakthrough in plantar pressure measurements in recent years is that biomechanical and clinical evidence now supports the use of plantar pressure measurements in the design and assessment of therapeutic footwear for high-risk diabetic patients.[48]SurroSense Rx (Orpyx Medical Technologies Inc., Calgary, CA) is a pressure-sensing shoe insole that offers real-time warnings via smartwatch when eight individual sensors sense elevated plantar pressures, so that users can adjust their activities and reduce unsafe pressures. The system has FDA approval, and is available for $3399 per set in the United States.[47]

Such improved footwear will reduce the risk of recurrence of ulcer by 46–65%, provided the footwear is worn. More efficient footwear can now be obtained for high-risk diabetic patients when driven by plantar pressure measurements. The use of such a data-driven approach to footwear forms part of the new guidelines of 2015 on footwear and offloading of the International Diabetic Foot Working Group.[49]

Similarly, continuous monitoring of temperature alerts patients of changes in feet temperature and can promote early detection of DFU. andheld, infrarot, dermal thermometers showed that temperature variations of approximately 4 ° F (2.22 ° C) between comparable spots on both feet acted as an early indication of DFU. In a pilot observational study aimed at assessing the accuracy of temperature sensor socks in diabetic patients with peripheral neuropathy Reyzelman et al found strong agreement with a reference standard high precision water bath. Patients also reported them easy to use and relaxed, and investigators could compare observed temperatures.[50]

Although temperature sensing systems have demonstrated accuracy and feasibility, there are currently no published RCTs evaluating their effectiveness in ulcer prevention and thus endorsing their use in overall DFU management.

Growth Factors:
The rationale behind the use of growth factors stems from the fact that growth factors can facilitate the replacement of cells and/or cell products lost during ulceration, which, in effect, accelerates the DFU's healing process.

Topical growth factors are also increasingly being used in the DFU treatment. Regranex (OMJ Pharmaceuticals, Inc., San German, PR) is the only topical recombinant human platelet-derived growth factor (PDGR) FDAapproved therapy for the treatment of DFU.[51] A synthetic form of PDGF has been developed and is sold as a topical cream called Becaplermin ®. Ma et al. reported 66% full DFU healing at 4 months and 77 percent after 9 months using a topical recombinant PDGF cream.[52]There is also growing evidence for the use of topical platelet-rich plasma (PRP) gel. Platelets contain numerous hemodynamically active molecules that help in wound healing, such as growth factors, neurotransmitters and calcium.[53] Platelets are known to contain many growth factors, including PDGF, transforming growth factor-beta and human epidermal growth factor, all of which are involved in the wound healing process and have been suggested for possible use in DFU patients after the complete healing of ulcers 7 months after the use of platelet-rich plasma.[54]

Four forms of Vascular Endothelial Growth Factors(VEGFs) were identified: VEGF-A, -B, -C and -D. Of these four isoforms, VEGF-A is involved in angiogenesis induction and thus promotes the recruitment and development of de novo blood vessels within the injury. VEGF-A can be secreted by a number of cells including, though not limited to, endothelial and smooth muscle cells, thromobocytes, neutrophils and macrophages.[55] Clinical trials performed on topical use of Telbermin (a recombinant form of VEGF) demonstrated a degree of effectiveness in the treatment of DFUs.The rate of complete ulcer cure was 41.4 % when 72 μg of Telbermin was applied per cm2 of wound area, versus 26.9 percent in placebo group. In addition , the time for Telbermin to complete DFU healing was 32.5 days, compared with 43 days for placebo.[56]

Though promising, this therapy is still very novel and lacks long-term , high-quality evidence to determine its true effectiveness.

Human Epidermal Growth Factor (hEGF) allows new epithelial cells to shape, assemble, and mature. Despite some adverse effects some of the patients, such as oedema and pruritus, intralesional administration of EGF (75 μg three days a week) resulted in total DFU closure within 4 weeks in 66.7 percent of the 174 patients recruited for the trial. Intralesional injections of EGF were used to treat DFU and low amputation levels were reported.[57]

Fibroblast growth factor (FGF): Fibroblasts produce connective tissue matrix like collagen, which is the building block of a large portion of the dermis. Therefore, many investigators speculated that adding a specific type of FGF (bFGF) to a wound could replace degenerated fibroblasts and the matrix of the connective tissue. While Uchi et al. recorded that in more than 82 percent of patients, a 0.01 percent bFGF ointment had decreased the size of a 900 mm2 DFU by three quarters over an 8-week period.[58]

Transforming growth factor-β (TGF- β): Experimental studies have shown that the TGF-β1 in tissues affected by ulceration is down-regulated. This finding indicates that local administration of TGF-β to ulcerated tissues may also be useful for treating DFUs. TGF-β helps to deposit extracellular matrix in fibroblasts, and promotes collagen production.[59]

Bioengineered Skin Substitutes:

Bioengineered skin substitutes, are increasingly being used as adjuncts to treat acute and chronic wounds including DFU. These improve wound healing by removing the extracellular matrix (ECM) and providing proper wound healing with a physical barrier to infection and trauma, antimicrobial activity and a moist environment for healing. Skin substitutes include dermal substitutes made up of cellular or acellular ECM and composite substitutes made up of both dermal and epidermal components. Dermagraft (Organogenesis Inc., Canton, MA , USA) is a dermal allograph made from newborn human foreskin and is the latest Food and Drug Administration (FDA) approved dermal replacement indicated for full thickness DFU therapy.[60]

Skin substitutes made from a human amniotic membrane are also new DFU therapies. Amniotic membrane comprises complex cytokines, signaling molecules, and growth factors essential to tissue regeneration and wound healing.[61]Epifix (MiMedxGroup Inc., Marietta, GA, USA) is a multi-layered, cellular bioactive tissue matrix allograft consisting of dehydrated human amnion and chorion membrane.[60]

The long-term outcomes of these products and their cost-effectiveness remain unclear.For this reason, after cost-benefit calculations are carefully considered, skin substitutes can be suggested for treatment of DFU.

Stem Cell Therapy:
In DFU management, stem cell therapy (SCT) is emerging. Stem cells cure wounds through the secretion of cytokines and growth factors that stimulate cell growth and angiogenesis. They also have the potential to differentiate into different types of cells which aid in healing wounds.[62]

Adipose-derived stem cells (ADSC): while humans have been tested for the use of ADSC, most research on the effect of ADSC in DFU wound healing is still being done on animal models of DM. Application of human ADSC (hADSC) significantly reduced the size of diabetic ulcer wounds 2 weeks after the onset of DFU and strengthened tissue granulation, the development and proliferation of cells, and the formation of de novo blood vessels.[63] ADSC was assembled in a flat-sheet form in another experimental study and transplanted to a DFU wound in Zucker diabetic fatty rats. Within 2 weeks of the transplant, wound healing was observed, during which the ADSC sheets were able to produce growth factors that could improve angiogenesis.

Endothelial progenitor cells (EPC): DFU is associated with a reduced number of cells and growth factors, resulting in impaired angiogenesis and subsequent reduction of the blood flow around the ulcer. In view of this, EPC has been used topically to enhance angiogenesis and hence to boost wound healing; to increase the degree of vascularisation by raising the tissue level of VEGF, tissue cytokines and basic FGF.[65]

Granulocyte-macrophage colony stimulating factor (GMCSF):GMCSF has been shown to significantly improve wound healing through a high tissue granulation rate, re-epithelialization and reduction of wound pain.[66]
Mesenchymal stem cells: mesenchymal stem cells include a variety of different types of progenitor cells that differentiate into e.g. bone, adipose tissue, and epithelial cells and can thus be a powerful source of cells that can reconstruct the extracellular matrix and blood vessels that are damaged in DFU.[67]

Conclusion:-
A reliable and recurrent preventive treatment strategy can sustain a stable, intact diabetic foot. The choice of advanced choices of treatment should be based on both patient and wound characteristics, treatment availability and cost-effectiveness. The divergent nature of DFU is a key issue in finding a proper evaluation for the effectiveness of the different types of treatment. Some DFUs have more vascular pathology than neural pathology while others have both. Although there are many novel treatment options for diabetic foot patients, there is still a need to evaluate safety and applicability.As a higher level of evidence develops on these therapies, existing DFU treatment concepts combined with innovative adjunctive therapies can become the latest modalities of DFU management.

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