Review Article

Overview of Cellular Therapy: Reshaping the Wound in Diabetic Foot Ulcer

ABSTRACT

Background: Diabetic Foot Ulcer (DFU) occurs due to a number of factors that compromises of peripheral neuropathy, mechanical changes in conformation of the bony architecture of the foot. Different types of cellular therapy and the particularly Stem cells that have been used by various medical groups around the world in treating a number of conditions. Stem cells can be generally derived from bone marrow, Placenta, Fat or Umbilical cord and has shown that stem cells have anti-inflammatory properties and immunomodulatory properties that can be beneficial in angiogenesis, cartilage synthesis and reshape the wounds. **Key Facts:** Cells based treatment help to increase the re-epithelization in the foot ulcers. Stem cells have paracrine effects that improve angiogenesis, decrease inflammation, have anti-apoptotic and chemotactic signaling effects encourage beneficial extracellular matrix remodeling. **Conclusion:** Cellular therapy could support wound healing by stimulating the formation of new blood vessels, presence of cocktail of growth factors or up-regulating local growth factors that increase blood supply, re-growth the necrotic cells, and relieve lower limb ischemia.

Keywords: Cellular therapy, Growth Factors, Diabetic, Foot Ulcer and Wound

1. INTRODUCTION

An international public health threat Diabetes mellitus has long been one of the world's most serious medical emergencies. It is accompanied by high levels of blood glucose, leading after a long time to serious deterioration in the functioning of various vital organs including heart and its blood vessels, retinopathy and more common with diabetic neuropathy. [1] While there are countless kinds of complications arising from diabetes mellitus, vascular problems in particular tend to be extremely serious and become nominal indicators for morbidity and mortality. [2]

Dyslipidaemia and chronic inflammation are the key factors in promoting atherosclerosis, which leads to frequent accumulation of lipid-rich plaques inside arteries. These all combine into one big enhanced risk factor for diabetes patient. In the case of diabetes, for example, atherosclerosis is by far the most important cause of reduced life expectancy. Also, it is now recognized that diabetic retinopathy and nephropathy are the major reasons for blindness or end-stage renal diseases. [3]Strategies for effectively preventing vascular complications in diabetics should be comprehensive. Intensive blood glucose reduction is crucial both to reduce the risk of nephropathy, a progressive decline in kidney function and retinopathy but perhaps even more importantly as active protection. Also, antihypertensive drug and statin use are suggested to continue controlling vascular complications of diabetes. [4]

Individuals diagnosed with type 2 diabetes mellitus (T2DM) may experience heart failure as their initial indication of cardiovascular disease. Both those with Type 1 diabetes mellitus (T1DM) and T2DM exhibit elevated mortality rates.[5]

The International Diabetes Federation (IDF) approximates that nearly 50% of individuals affected by diabetes remain unaware of their condition.[6]All of those afflicted with diabetes mellitus bear a heavy psychological and economic burden.[7] This is particularly the case with respect to diabetic foot, which can be a devastating complication of diabetes.

Approximately 20% of individuals with diabetes necessitate hospitalization for Diabetic Foot (DF) at some point in their lives.[8] The main pathological features of DF are neuropathy and ischemia leading to ulceration, potentially resulting in amputation or death.[9,10]

2. DIABETIC FOOT ULCER AND ITS PATHOPHYSIOLOGY

A serious complication of diabetes mellitus, diabetic foot ulcer represents a major burden for mortality and morbidity worldwide. Its intricacies and expense are significantly high. Foot ulcers increase the average lifetime risk by between 19 % and 34 %. Also, its pathophysiology can be neuropathy or trauma. It frequently coexists with peripheral arterial disease as well. In particular, diabetic neuropathy makes the feet bowed inward and leads to the formation calluses. It also causes loss of sensitivity so that patients are less likely to notice traumatic or pressure injuries than non-diabetes sufferers would be. The standard procedure for treating diabetic foot ulcers involves assessing the extent of damage, removing devitalized tissues through surgical debridement, promoting wound healing by means of dressings and other methods to relieve pressure; examining vascularity in order better determine medical interventions further downstream; exerting attention toward glycemic control or adequately controlling infection. Surgical interventions are sometimes necessary, but they do not make good prognostic indicators for the outcome of diabetic foot ulcers. [11]

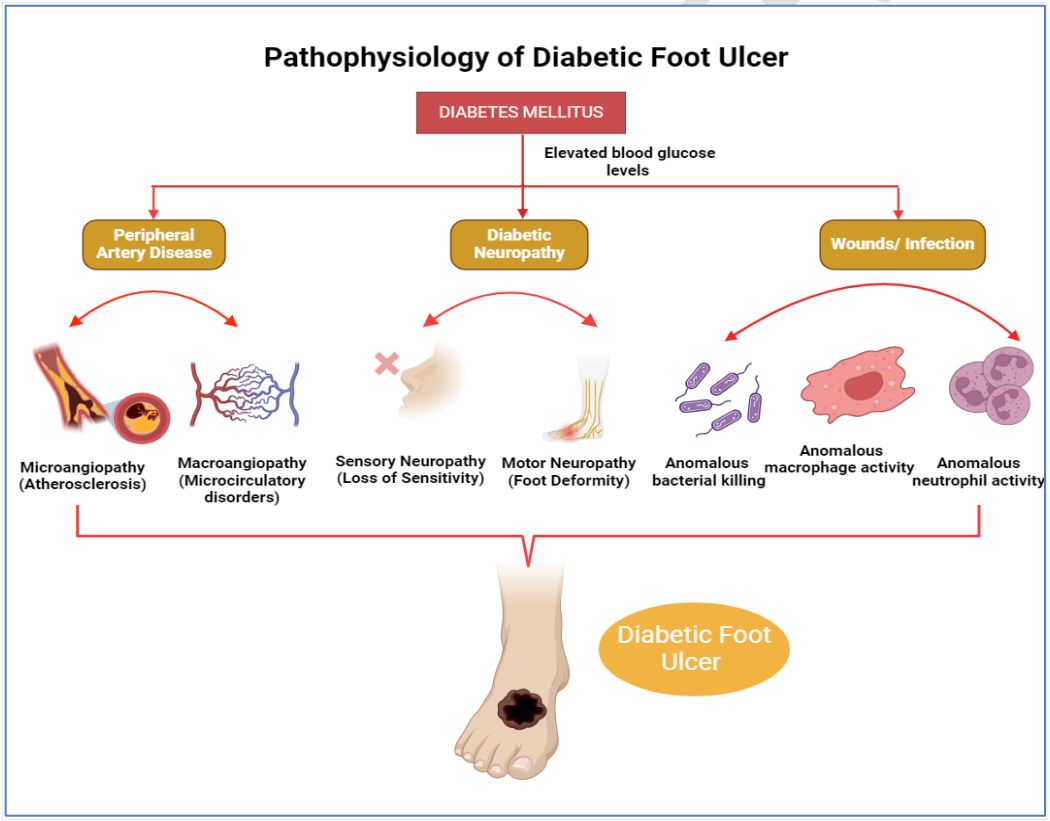


Fig. 1 Pathophysiology of Diabetic Foot Ulcer: A comprehensive grasp of factors contributing to the formation of DFU. Diabetic foot ulcers originate from diabetic neuropathy reducing sensation, and peripheral artery disease (PAD) limiting blood flow. These factors increase susceptibility to wounds, potentially progressing to ulcers if left unattended.

The development of diabetic foot ulcers is contingent upon a variety of factors. Contributing factors include lose control over blood sugar, hardened skin on the feet and foot malformations. Other issues are insufficient attention to one's own feet; bad-fitting shoes that don't allow for room in case of swelling or cuts caused by mosquitoes crawling up your ankle like tiny tadpoles); underlining right amounts worse than in particular, neuropathy--which affects at least 60 % of diabetics--plays an important part in raising the risk for foot ulcers. This danger is multiplied for anyone with a flat foot, where there isn't even pressure distribution across the entire foot: inflammation naturally arises in high-risk areas.[12]

The development of the diabetic ulcer takes a course that can be divided into phases. In the initial phase, the initiation of callus formation is prompted by neuropathy. Motor neuropathy contributes to physical foot deformities, while sensory neuropathy diminishes sensation, thereby resulting in ongoing traumatic incidents. Drying out the skin accelerates the process of autonomic neuropathy. However, the callus is injured repeatedly until there are internal hemorrhages beneath the skin. The serious case of erosion becomes an established ulcer which cannot be regarded as having been solved.[13]The onset and progression of diabetic foot ulcers is not age-restricted but especially occurs in patients aged 45 and up with diabetes mellitus. Elders with diabetes mellitus who have severe atherosclerosis may find blocked Minute blood conduits in the lower limbs, including the feet. This reduced vascular flow becomes another cause of diabetic foot infections. Because the circulation of blood is insufficient, wounds are slow to heal and finally lead to necrosis or gangrene. [12]

3. CATEGORIES OF DIABETIC FOOT ULCERS

Two types of diabetic foot ulcers; 1) Warm feet with good perfusion, palpable pulsation breaking surface; reduce sweating and cracked skin. These are the characteristics of neuropathic ulcers. 2) Neuro-ischemic ulcers, by contrast, are marked with cold feet and lack of palpable pulsation as well as thin skin which is often hairless. The subcutaneous tissue mass has also atrophied but many cases will not have either intermitted claudicating or rest pain due to neuropathy interference in the conduction pathways for nerve impulses.[14,15]Inflammation and granulation should occur to start the repair processes; new connective tissue matrix needs to form once scarring begins; angiogenesis and vasculogenesis need to take place so that capillaries can return with their blood cells before fibroblast activity diminishes.[16]

4. DEVELOPMENT OF WOUND HEALING IN HEALTHY INDIVIDUALS AND COMPROMISED CONDITION

When a person is healthy and gets wounded, the healing process happens in three stages. The first phase is the inflammatory stage, which lasts several days and when injury will damage cells in a local area. This is preceded by the formation of a clot to stop bleeding. This period, which lasts about two weeks, is the proliferative stage during which new tissue begins to form. There is the period of remodeling which lasts a few weeks up to several months depending on how bad the wound was. At these stages, different cells that remove pathogens are involved (WBC) as well as those responsible for forming new tissue and fresh areas of skin (fibroblasts). Among these processes are the formation of blood capillaries, regrowth and regeneration of skin tissue. Also involved is development of a basic 'platform' structure known as the extracellular matrix (ECM) consisting at this stage in immature type III collagen cells and fibronectin protein; it requires a painstakingly choreographed sequence controlled over by several when the rates of collagen degradation and disappearance come into balance, the remodeling phase begins. During this stage, collagen remodeling continues unabated. As time progresses, the transformation from Type III to mature Type I collagen becomes evident. Simultaneously, cross-linking events occur within the extracellular matrix (ECM). This intricate process highlights the dynamic nature of collagen composition in tissues. [17]

A diabetic foot ulcer (DFU) is considered a chronic wound that defies orderly progression through healing phases and cannot be resolved within a timely manner. The main causes for DFU's include Nerve Damage in Diabetes (NDD), Peripheral artery disease and improper foot care, underline neuropathy, and many more. These things warn us before an event of DFU happens if we don't take action immediately. Also, things like not having blood sugar level under control and chronic kidney disease increase the chances of getting DFU. Diabetic people should be carefully placed in groups based on how much they can get sores, checking for things that might cause DFU. This helps us get ahead and lower the chances of getting this problem.

Finding new ways to heal long-lasting wounds means using special materials and growth factors. These things work together like they would in the body, set off important healing paths required for successful wound recovery. Many studies show that DDS methods can improve wound healing and skin renewal. This is done by controlling the release of growth factors from medicine formulations. However, dealing with safety and cost issues of growth factor-packed DDS products in clinical areas is very important. It's very important to make strong nonclinical models that can show if growth factors are safe and how our bodies handle them. This is a big requirement in making treatments for growing children better, safer and more effective in the future. Also, knowing that one growth factor might not be enough for the best healing of a wound, complex system is

needed to deliver these factors. This means using new materials or combining different delivery methods in order to control when and where they get released over time. This method tries to copy the teamwork of things that help cells grow and elements found in natural situations. So, pharmaceutical scientists and other experts need to work together on creating drugs using this new idea. This will help make it easier for injured people to heal faster with better formulas of growth factors in medicine that are safe and effective.[18]

5. PREVENTIVE MEASURES FOR DIABETIC FOOT ULCERS [19, 20]

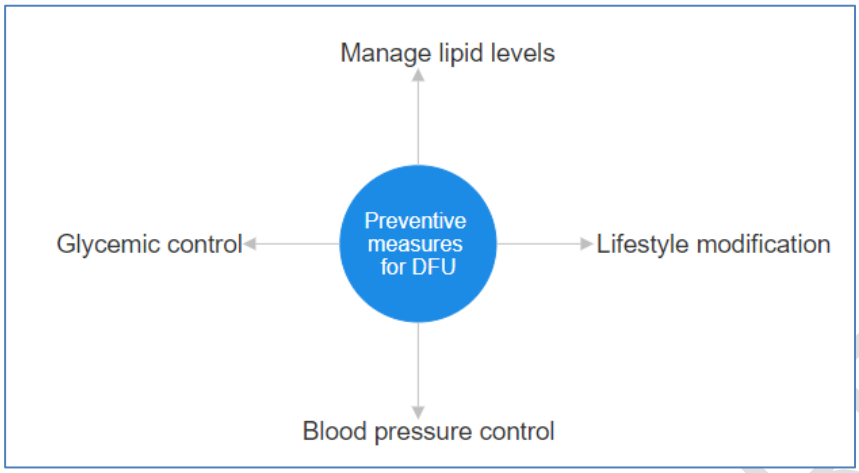


Fig. 2: Preventive measures for DFU: The Effective prevention strategies for diabetic foot ulcers (DFU) encompass a multifaceted approach. This includes meticulous blood pressure control, lifestyle modifications promoting healthy habits, management of lipid levels, and stringent glycemic control. By addressing these key factors comprehensively, individuals with diabetes can significantly reduce their risk of developing DFUs.

6. THERAPEUTIC MEASURES

Diabetic Foot Ulcer Care: Combining Advanced Therapies and Integrative Therapies to Promote Optimal Recovery;

1. Targeted Infection Management
2. Vascular Assessment
3. Surgical Debridement for Localized Wound Care
4. Strict Glycemic Control
5. Cellular Therapy

6.1 Targeted Infection Management

Properly examining Diabetic Foot Ulcers (DFUs) is essential in effectively treating them. The first step is to carefully evaluate the size, depth, and infection level of the wound, choosing appropriate care and categorizing the wound aids in prognosis. Key interventions such as surgical removal of damaged tissue, draining infection pockets, and implementing debridement are crucial. While there are different methods of debridement available, surgical intervention is the preferred option for achieving thorough cleansing and healing. [21,22,23]

6.2 Vascular Assessment

About 40% of people with Diabetic Foot Ulcers (DFUs) are believed to have Peripheral Arterial Disease (PAD). People having DFUs and PAD at the same time, take longer to heal. They are also more likely to need big toe amputations or die sooner than others who just have one of these problems.[24]It's advice to check for PAD in DFU people using touch foot pulse or ankle brachial index (ABI).[25]A score of less than 0.7 in the ABI shows some blood vessel problems, while severe PAD is found when it's below 0.4 on these tests done to measure flow in large arteries leading into limbs and other areas away from your heart or lungs where many small branches divide off for their specific tasks such as keeping our body cool

by sweating out heat People with ABI more than 1.4 might have tough ankle blood vessels because of hardening in their veins, often found after diabetes and checked during kidney problems.[26]People with blood vessels that don't squash down should do different tests, like measuring pressure at the toes or recording changes in pulse. Then they check oxygen and use a special sound machine called duplex ultrasound if any of these are abnormal it shows you have PAD. [27]

6.3 Surgical debridement

Removing dead or damaged tissue during wound cleaning helps the healing process. This includes nearby hard skin too. This encourages the growth of skin-forming tissues, healing and less pressure on calloused areas in feet. [28] Also, removing tissue is very important for treating infections. It helps get rid of parts that bacteria can grow on. Not working tissues not only help bacteria to grow but also make it hard for medicine and the body's defense against infections. The partnership established between the Infectious Disease Society of America (IDSA) and the Wound Healing Society (WHS) exemplifies a synergistic alliance aimed at addressing healthcare challenges - say that removing dead skin with a sharp tool is better than using creams or natural substances to do it. They recommend cutting it off instead. [29]

6.4 Glycemic control

In people with diabetes, high blood sugar can harm the immune system and slow down healing. Some studies using observational research have different results about the connection between blood sugar control and chances of amputation or wound healing. [30]High blood sugar can hurt the body's defense system and make it easier for someone to get sick. For hospital patients with diabetes foot ulcers, healthcare experts suggest trying to keep blood sugar levels between 140 and 180 mg/dL.[31]In individuals diagnosed with type 2 diabetes and pre-existing cardiovascular conditions, some oral medicines like Canagliflozin have been linked to a higher chance of LEA mostly in the toes or foot area. These drugs work on sugar moving back into cells using special carrier proteins (SGLT-2 inhibitors). [32]There is disagreement about the risk of LEA with SGLT-2 blockers. This means we need to be careful when using them for patients that have problems in their feet or legs getting better. [33]

6.5 Cellular Therapy

6.5.1 Stem Cells

Stem cells are functionally distinguished by their distinctive capability for both regeneration and generation differentiated cells. These amazing cells can produce identical daughter cells, renew with the potential to distinguish into various cell types Scientists often call them stem cells because of their unique feature. They possess the capability to differentiate into various types of bodily cells. [34]The marrow of the bones produces two major groups of stem cells. 1 First ones are those in charge of producing all hematopoietic cells, including red and white blood cells in platelets, lymphocytes; macrophages etc.[35]Second, there are stems cell from ectoderm and endoderm which can easily convert into tissues all over in the body. Most stem cells differentiate into a prominent forms of cell, which aids in their identification Mesenchymal stem cells, for example, are distinguished by their ability to develop into bone, cartilage, and adipose tissue, but they can also differentiate functional cardiomyocytes, blood arteries, and even neural tissue. This ability to differentiate applies to Mesenchymal cells, derived from bone marrow, adipose tissue, and the umbilical cord, or even the placenta, exhibit diverse origins. [36]

The purpose of stem cells is critical in giving rise to a multitude of cell types essential for an organism. Consequently, stem cells possess the capability to mature into fully matured cells with distinct configurations and distinct functionalities, such as those found in the heart, skin, or nerves. They possess the unique ability to divide or self-replicate over extended periods, potentially continuing throughout the organism's lifespan. These capacities of Stem cells have the potential to generate a diverse array of cell types is known as differentiation. Another term used to describe this transformative ability, even changing from one cell type to another, is referred to as "plasticity."[34, 37]

Specialization takes place through a series of levels, and as for each step the possibility to develop further diminishes. This implies that a unipotent stem cell has less ability to undergo differentiation into various cell types, as compared to the pluripotent stem cell. [38]

Totipotent stem cells have high differentiation potency, which can divide and also transform into each cell type present in a whole organism. Totipotent cell, is the zygote that results from the fertilization of an egg by sperm. 4 days later The

innermost cell grouping within the blastocyst changes into pluripotent stem cells, such as embryonic stem cells ESCs. Pluripotent cells can only form the different germ layers but not structures in extra embryonic region. Instigated pluripotent stem cells, iPSCs, artificially produced from somatic cells for regenerative medicine. Other multipotent stem cells, such as hematopoietic stem cell lines have a more limited differentiation profile but can become specialized to target particular lineages some of which are capable to be reprogrammed into the genes for other cell variants. [37]

Oligo potent stem cells exhibit the ability to specialize into multiple cell types. A myeloid stem cell can illustrate this with their ability to produce white blood cells but not red ones in contrast, unipotent stem cells have the most limited differentiating abilities and are unique as they can undergo multiple divisions this attribute Implies potential solution for application in Rejuvenate therapeutic applications since they are responsible for producing just individual cellular form, e.g. dermatocytes only. [39]

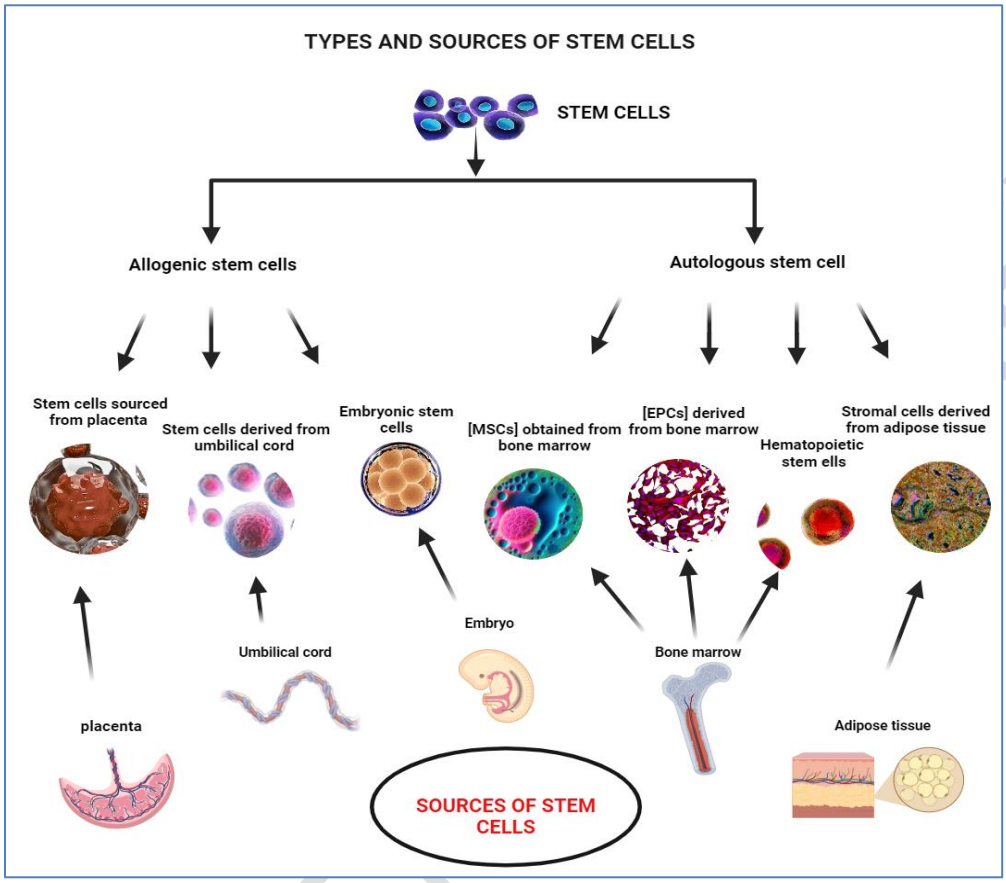


Fig. 3: The figure explains various types of stem cells and their respective sources, providing a visual overview of the diverse origins and classifications within the field of stem cell research. [40-45]

6.5.1.1 Sources of Stem Cells:

Allogenic placental, Umbilical cord and Mesenchymal Stem cells

Human placenta-sourced mesenchymal stem cells (hPDMSCs) are derived non-surgically, and they have less immunological activity and can be prepared in large quantities (hPDMSCs) exhibit the ability to release various cytokines and growth factor that have a key impact on wound repair (hPDMSCs) contributes to the reduction of pro inflammatory levels within the wound thus actively increasing the healing process.[40, 41] Umbilical cord blood is a beneficial reservoir of stem cells, mesenchymal stem are extracted through enzymatic digestion displaying a favorable presence of typical MSC surface markers. [46] (MSCs) can be derived from several segments of the umbilical cord including umbilical blood and the endothelium of sub umbilical vein (MSCs) can also be segregated from both perivascular and non-perivascular layers (sub amniotic membranes) These cells possess the capability to transform into different cell variants like adipocytes, chondrocytes , osteocytes of bone tissue and cardiomyocytes, skeletal myocytes, hepatocytes, insulin producing cells and cells resembling neurons .Human amniotic cells' production of thrombocyte-derived growth factor may promote Migration of cells from the vascular system to the amnion.[42]

Embryonic stem cells (ESCs) reside within the inner cell mass of the human blastocyst can be identified during the fourth to seventh day of fertilization each represents the initial phase of embryonic development. These cells undergo disappearance by seventh day transitioning into the formation of three embryonic tissues. Endothelial cells and endothelial progenitor cells have been found to secrete growth factor, facilitating a stimulation of neovascularization angiogenesis from embryonic stem cells (ESCs). Specifically, increased levels of epidermal growth factor, vascular endothelial growth factor and fibronectin.[43,44]

Mesenchymal Stem cells (MSCs), MSCs from bone marrow are obtained in a more invasive and relatively costlier process compared to the less intrusive means used to obtain MSCs from amniotic, placental or umbilical cord sources. The process of extracting of BMMSCs is aspiration, density gradient centrifugation and some additional steps to maintain and grow these cells. MSCs can differentiate into cells of endodermal, mesodermal and ectodermic lineages. Adipose tissue and bone marrow (BM) are among the most easily accessible reservoirs of MSCs due to their easy harvesting, plentiful progenitors at hand, with little ethical concern.[41,45]Bone marrow derived MSCs exhibit compromised proliferative and differentiation capabilities, along with altered cytokine release as well anti-apoptotic abilities. Yet, two simplified strategies for isolating BM-MSCs arose including the Ficoll and Harvest systems which produced adequate cell populations to give similar degrees of therapeutic outcomes. MSCs sourced from adipose tissue and bone marrow (BMMSCs) share similar immunoregulatory and hematopoiesis Scientific support properties, but adipose tissue derived MSCs favor less the commitment to differentiate Chondrogenic and osteogenic lines compared with BMMN.[45,46,47]

The bone marrow source of endothelial progenitor cells (EPCs) is a specialized stem cell that has the capability to transform into mature, adult vascular tissue organelles known as endothelial cells. The endothelial cells form an integral part of blood vessels and are critical components required for the construction as well as stabilization of vascular system. [48]

Hematopoietic stem cells are multipotent stem cells they have their origins in bone marrow, peripheral blood, and cord blood the process of blood cell formation Hematopoiesis, relies on the capability of hematopoietic stem cells, these versatile cells are pivotal in committing to various lineages, giving rise to the production of diverse blood cell types including RBC, WBC and platelets.[49]

Stromal cells derived from adipose tissue are referred to as ADSCs. They have most of the characteristics with MSCs from bone marrow but their proliferation remains uncertain. ADSCs are pluripotent and having the ability to transform along many lineage trajectories, including adipocyte chondrocytes as well as osteoblast They also produce diverse cytokines and growth factors that have the potential to facilitate tissue healing.[50,51]

6.5.2 Mononuclear Cells

Mononuclear cells, characterized by a singular, circular nucleus, represent a subtype of white blood cells encompassing lymphocytes, monocytes, and stem cells. Isolation of Peripheral Blood Mononuclear Cells (PBMCs) from human peripheral blood is a common practice in diverse scientific disciplines, including immunology, cancer research, and pharmacology. Wound healing involves mononuclear cells, including PBMCs. The secretome of PBMCs may promote wound healing, which indicates that the secretome might serve as a potential therapeutic agent. Further, the selection of mononuclear cell types like lymphocytes and macrophages from leucocyte precursors is a key component in wound repair. They increase Immune protection against microorganisms, encompassing mycobacteria, fungi, bacteria, protozoa, and viruses. Cellular debris clearance, inflammatory process immunity, and immune surveillance of tumors involve mononuclear phagocytes. They also initiate red blood cells breakdown and foreign matter phagocytosis, which provides another line of defense against harmful particles. It should also be noted that mononuclear phagocytes play a role in tissue repair and remodeling, inflammation resolution, as well as homeostasis maintenance. In addition, the process of production antibodies by B lymphocytes increases mononuclear phagocyte system's cells ability to engulf different particles which implies that these two types are interrelated. Thus, mononuclear cells exhibit a dual role in both innate and adaptive immunity being an integral part of the immune system. Various mononuclear cells those are specific in function to the immune system (Fig. 4). [52]

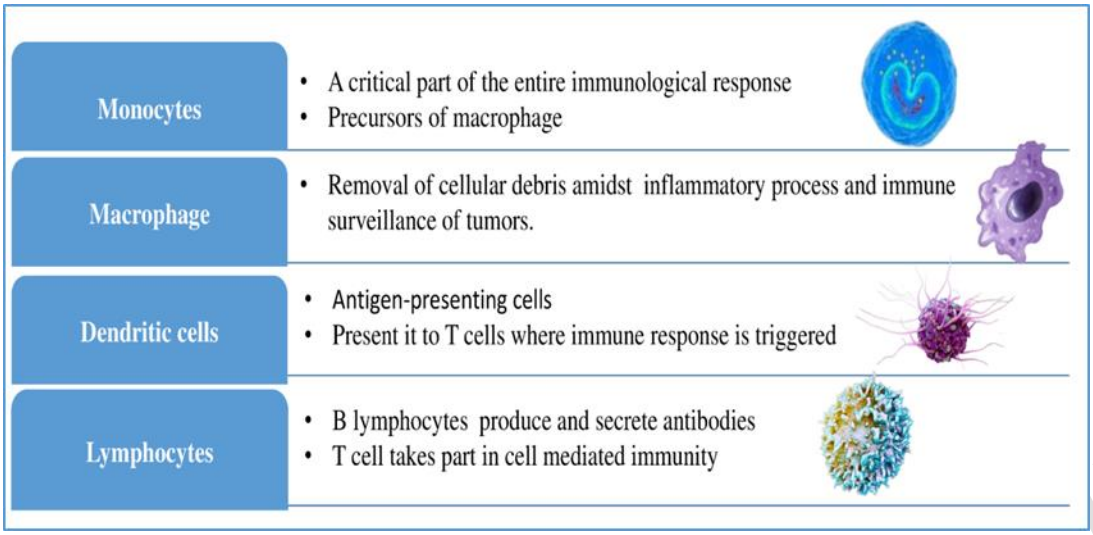


Fig.4: Functions of Mononuclear cells

Process of Angiogenesis

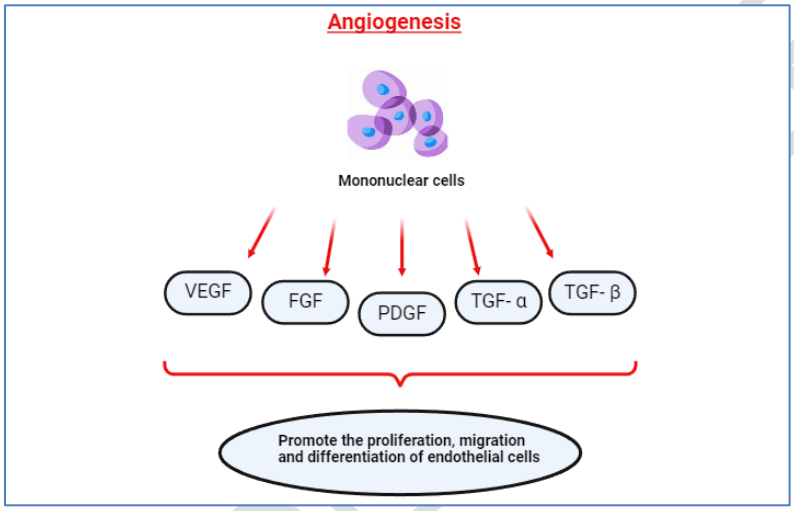
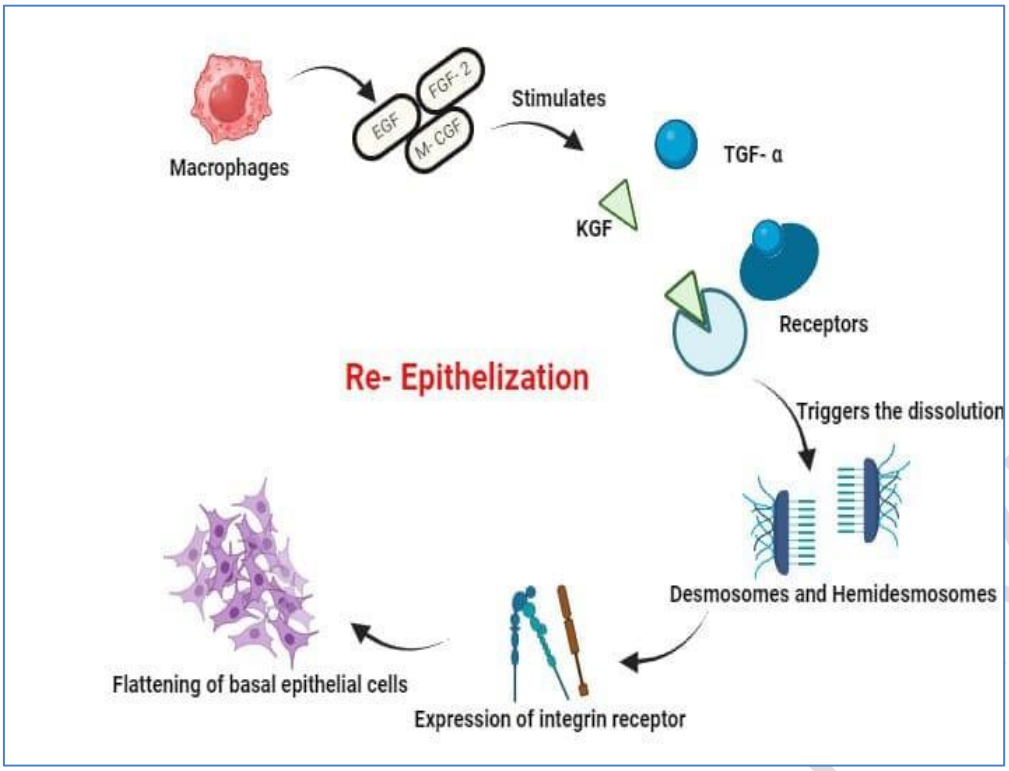


Fig. 5: Process of Angiogenesis

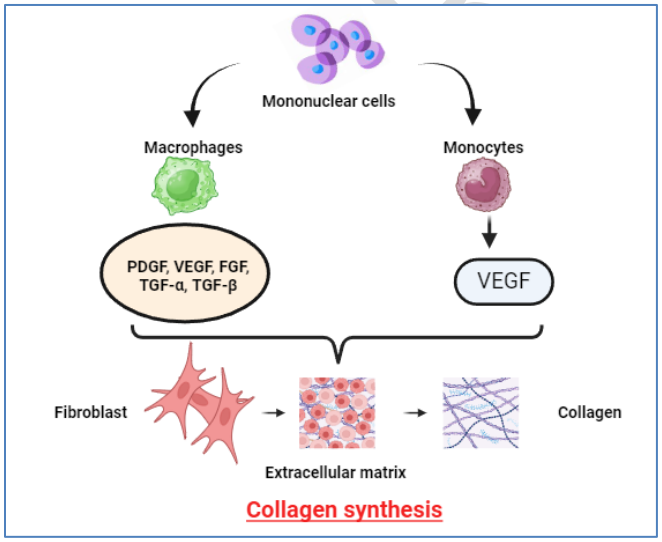
The dynamic process of angiogenesis is significantly influenced by mononuclear cells, including peripheral blood mononuclear cells (PBMNCs) and bone marrow-derived mononuclear cells (BM-MNCs) among these factors, vascular endothelial growth factor (VEGF) stands out as an efficacious stimulator, driving the replication and specialization of endothelial cells. Fibroblast growth factor-2 (FGF-2) contributes to angiogenesis by promoting the growth of blood vessels. Placental growth factor (PLGF), with its unique role in pregnancy and placental development, also plays a crucial part in angiogenesis. Platelet-derived growth factor (PDGF) supports angiogenesis by fostering the propagation and migration of endothelial cells. Transforming growth factors (TGF-α and -β) further enhance blood vessel growth, solidifying the multifaceted role of mononuclear cells in orchestrating angiogenic processes. These cells actively contribute to the intricate process of angiogenesis by fostering the proliferation, migration, and differentiation of endothelial cells. [53]

Process of Re-epithelization (Fig. 6)



During wound healing, mononuclear cells play a critical role in promoting re-epithelialization (Fig. 6). Specifically, macrophages secrete important growth factors such as keratinocyte growth factor (KGF) and transforming growth factor-alpha (TGF-α). These growth factors not only stimulate the migration and growth of epithelial cells, but also interact with receptors on the surface of these cells to trigger the breakdown of desmosomes and hemi desmosomes. As a result, integrin receptors are expressed, causing basal epithelial cells to flatten. This flattening is crucial for the necessary migration and proliferation required for successful re-epithelialization.[54]Keratinocytes play a vital role in the body's immune response by releasing a variety of substances, including cytokines, chemokines, antimicrobial peptides, and extracellular vesicles. These powerful secretions serve a dual purpose: calling upon and activating immune cells, while also directly eliminating harmful pathogens. Overall, the multifaceted impact of keratinocytes highlights their crucial function in promoting immune responses and bolstering the body's defense against harmful invaders. [55]

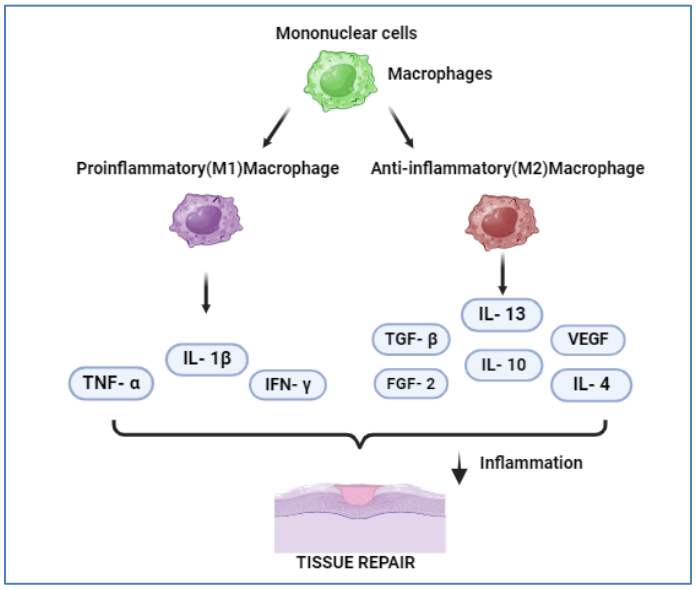
Collagen synthesis (Fig. 7)



During wound healing, mononuclear cells, specifically macrophages play a crucial role in promoting collagen production (Fig. 7). Through the release of growth factors like PDGF, FGF, VEGF, TGF-α, TGF-β, and KGF, macrophages coordinate the activation of fibroblasts. This activation incites fibroblasts to carry out important tasks, including movement, division, and

the creation of extracellular matrix components, particularly collagen. The strength and integrity of the healing wound greatly depend on the formation of strong connections between collagen fibers. [56]

Active role of MNCs in controlling inflammations (Fig. 8)



Mononuclear cells, specifically macrophages, play an active role in controlling inflammation during the wound healing process. They do this by transforming from a pro-inflammatory (M1-like) to an anti-inflammatory (M2-like) phenotype (Fig. 8). Initially, macrophages have pro-inflammatory functions such as engulfing harmful particles and releasing cytokines that promote inflammation. However, as the healing process progresses, these macrophages undergo a change in phenotype, becoming more anti-inflammatory. During this phase, they produce important molecules such as TGF-β, PDGF, FGF-2, IGF1, TNF-α, and VEGF, which work together to reduce inflammation and promote tissue repair. Furthermore, anti-inflammatory macrophages play a crucial role in restructuring the extracellular matrix and phagocytizing residual debris, thereby enhancing the resolution of inflammation and propelling the progression of the wound healing process. [56]

7. FUTURE CLINICAL APPLICATION

As per the report, through cellular therapy for diabetic foot ulcer, major improvements can be seen in the condition. The improvements that the wound's healing process speeds up, the size of the wound reduces, swelling of the foot. As shown the database 80 percent of patients with diabetic foot disease who have treated with cells based therapy and demonstrated well improved outcomes. Hence, this could be optional treatment if primary treatments get fails or not respond well.

8. CONCLUSION

It has been concluded that the cells based therapy especially targeting regeneration part and can help diabetic foot ulcer patients. These cells take advantage of their potential to up-regulating the local growth factors and cytokines that promote angiogenesis and collagen remodeling. It can increase the blood supply to nerve vessels which has blockade by limb ischemia. It also increases macro vascular circulation, decrease cytokines level, decrease inflammation, and apoptosis which eventually relieve the foot ulcers.

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