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STEM CELL THERAPY IN THE TREATMENT OF DIABETIC FOOT ULCER

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ABSTRACT

Diabetic foot ulceration poses a heavy burden on the patient and the healthcare system, but prevention thereof receives little attention. In preclinical and clinical trials, stem cell treatment has surfaced as a novel interventional approach for treating DFU and it seems to be both safe and effective. Autologous stem cells and Analogous stem cells are the majorly used cell types. Autologous stem cells are derived from Blood, Bone and Tissue. Analogous stem cells are derived from Embryo, umbilical cord and placenta. The Wound Healing Society (WHS) released treatment guidelines for DFUs in 2006. The WHS DFU recommendations aim to clarify contentious diagnosis and treatment approaches, identify areas in need of more research and conduct a systematic review of the medical literature to support physicians in their decision-making.

KEYWORDS

Diabetic foot ulcer, Wound healing society, Autologous stem cells and Allogenic stem cells.

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INTRODUCTION

A class of illnesses known as diabetes mellitus impact how the body uses glucose, or blood sugar. An essential source of energy for the cells that comprise muscles and tissues is glucose. It is also the primary energy source for the brain. Diabetes has different primary causes. However, diabetes can result in an excess of sugar in the blood regardless of the type you have. A blood sugar level that is too high can cause major health issues. Type 1 and type 2 diabetes are chronic diabetes diseases[1]. Prediabetes and gestational diabetes are two diabetes disorders that may be treated. When blood sugar levels are greater than usual, prediabetes develops. However, the blood sugar isn't elevated

enough to qualify as diabetes[2]. Furthermore, if preventative measures are not implemented, prediabetes might progress to diabetes. Gestational diabetes develops in the course of pregnancy. However, when the baby is born, it can disappear. Diabetes patients frequently have foot issues. They may develop over time as a result of elevated blood sugar harming the feet's blood vessels and nerves. Diabetic neuropathy is a nerve damage condition that can cause pain, tingling, numbness, or loss of feeling in your feet. You might not be aware of a cut, blister, or ulcer (open sore) on your foot if you are painless. That kind of wound could become infected. Because the damaged blood vessels may result in decreased blood flow in your foot, the infection may not heal well. Gangrene can result from an infection and inadequate blood supply. This indicates that the skin, muscle and other tissues begin to deteriorate[3]. You might require an amputation if your foot ulcer or gangrene does not improve with treatment. Your injured toe, foot, or portion of your leg will be amputated during this procedure. It could save your life and stop a dangerous infection from spreading. Foot ulcer is partly caused by too much pressure on one part of your foot[4].

WHAT IS DIABETIC FOOT ULCER?

An open wound or sore that typically appears on the bottom of the foot, diabetic foot ulcers affect about 15% of patients with the disease[2]. Six percent of people who get foot ulcers end up in the hospital asa result of an infection or another ulcer-related problem. In the US, diabetes is the most common cause of nontraumatic lower extremity amputations, accounting for 14-24% of amputations in patients who develop foot ulcers. On the other hand, studies have demonstrated that it is possible to avoid developing a foot ulcer[5].

WHO GETS AFFECTED BY DFU?

An ulcer on the foot can happen to anyone with diabetes. Ulcers are more common in Native Americans, African Americans, Hispanics, and older men. Individuals, who take insulin, as well as those with diabetes-related kidney, eye and heart conditions, are more likely to get a foot ulcer[6]. Foot ulcers can also result from consuming smoke and alcohol, as well as from being overweight[3].

Several causes can lead to the formation of ulcers, including diabetes for an extended period of time, trauma, poor circulation, abnormalities of the foot and irritation from friction or pressure[7]. Long-term diabetes patients may experience neuropathy, which is a diminished or total loss of sensation in the feet as a result of nerve damage brought on by high blood sugar levels over time. Nerve damage frequently happens without any discomfort and the affected person may not even be aware of the issue[5]. Your podiatrist can use a monofilament, a straightforward and painless technique, to examine your feet for neuropathy[8].

COST TO TREAT DFU

It has been estimated that approximately one-third of all resources used to treat diabetes mellitus and its consequences are spent on diabetic foot care. If we take a million diabetic patients and their 2.2% yearly ulcer incidence rate, the entire yearly treatment expenditure for these plantar ulcers comes to €220m[6]. Hospital stays and amputation treatments account for around half of the total expense of ulcer therapy. That suggests that overall treatment costs would drop to €198m (€220m ~ 0.2 x €110m) if appropriate ulcer treatment could prevent 20% of hospitalization and amputation (an effect size commonly observed in wound healing studies)[9]. But if 50% of ulcers may be avoided with appropriate preventive treatment (an average effect size demonstrated in 30 controlled trials on prevention), expenditures can be lowered to €110m (0.5 × €220m) for the same patient group, saving €88 million for every million diabetics[10].

ULCER EXAMINATION

Skin exam

The skin of your feet to look for dryness, cracking, calluses, blisters, ulcers, and other damage or abnormal areas

Your toenails for cracks and fungal infection.

The temperature of your feet to see if they are the same[11].

Nerve exam

Monofilament test

You will close your eyes while your provider brushes a soft strand of nylon (a monofilament) over your foot and toes. You'll tell your provider when you feel the strand touching your foot.

Tuning fork and vibration perception threshold tests (VPT)

Your provider will place a tuning fork or other device that vibrates on different parts of your foot and toes to see if you can feel the vibrations[12].

Pinprick test

Your provider will gently press a small pin against your big toe to see if you can feel it. The pin will not break through your skin.

Ankle reflexes

Your provider will tap a special, small hammer on your Achilles tendon, the thick band of tissue that connects your calf muscle to your heel bone. If your nerves are working properly, your foot will jerk slightly on its own[11].

Musculoskeletal (muscle and bone) exam

Bent or overlapping toes

Bunions

A rocker shape on the bottom of your foot (Charcot Foot)[11]

Vascular (blood vessel) exam

Feel the pulses in your foot and ankle

Compare blood pressure measurements in your ankles and arms. If blood pressure in your ankle is lower than in your arm, you may have reduced blood flow to your foot. This is called an ankle-brachial index test. Your provider may do this test if you have signs and symptoms of a blood flow problem[12].

TREATMENT OF DFU

Remain off your feet to avoid ulcer pain. Off-loading is a technique that helps with diabetic foot ulcers of all kinds[13]. Walking pressure can exacerbate an infection and cause an ulcer to enlarge. Physician could advise you to wear the following products to safeguard your feet,

Diabetic-friendly footwear

Foot braces

Compression wraps

Shoe inserts to avoid calluses and corns

Foot ulcers can be treated by doctors by debridement, which involves removing any dead skin or foreign items that may have contributed to the ulcer. A significant consequence of a foot ulcer is an infection, which has to be treated right away[14]. Different infections require different treatments. To find the best antibiotic, tissue near the ulcer may be sent to a laboratory.

One way to stop a foot ulcer from getting infected is to:

Foot massages

Cleaning the area surrounding an ulcer

Changing the bandage frequently to keep the ulcer dry

Treatments with enzymes

Dressings with calcium alginates to stop the formation of bacteria

FDA approved drugs

Ertapenem Injection

Honey

Empagliflozin

Canagliflozin

Ertugliflozin

Nano-oriented medicine technologies

Microcapsule based nano technology

Nanometrology probes

Nanofilm and closed loop insulin therapy

Artificial nano-pancreas

Insulin nano capsules

Nano sensors

WAGNERS CLASSIFICATION OF DFU

STEM -CELL BASED THERAPY

In diabetic foot ulcers, stem cells can target and bypass faulty healing processes and disordered cell signaling. In this sense, stem cells are thought to be a promising ulcer treatment. Wound healing is a dynamic and extensive process that involves several essential processes that are compromised in diabetes patients, including angiogenesis, neovascularization, and growth factor release[15]. The

diverse potentials of stem cells include anti-inflammatory and neoangiogenic actions, release of numerous growth factors, and differentiation into several cell types that are involved in the wound healing process. Additionally, stem cells have the capacity to differentiate into a variety of cell types, including endothelial, keratinocyte, myofibroblast, and pericytes, which may be involved in wound healing[16]. While early stem cell therapy reports have demonstrated success, the various characteristics utilized in each study make it difficult to easily understand and generalize these data, making it challenging to standardize guidelines for treating DFU using stem cell therapy[15]. According to reports, stem cells can impact numerous pathophysiological processes, including ulcer healing, by inducing angiogenesis in the ischemic tissue, boosting the manufacture of extracellular matrix and driving the activities of tissue repair cells.Stem cell implantation improves blood flow circulation in ischemic limbs, as demonstrated by several animal experiments[16]. There are two types of stem cells used in the treatment of diabetic foot ulcer. They are:

Autologous stem cells

Allogenic stem cells

AUTOLOGOUS STEM CELLS

Autologous stem cell therapy (ASCT) has become a new and promising treatment for ulcer repair and persistent wounds in the lower extremities. In patients with critical limb ischemia, bone marrow mononuclear cell implantation was found to be a safe and effective therapeutic angiogenesis treatment in the first human experiment conducted in 2002. The rate of amputations was lowered, and full ulcer healing was aided by this cell implantation. As a result, additional data was emerging showing that ASCT was superior to conventional treatment for chronic lower extremities wounds. Peripheral blood-derived stem cells (PBSCs), peripheral blood mononuclear cells (PBMNCs), adipose-derived stem cells, and bone marrow-derived stem cells (BMSCs), such as bone marrow mesenchymal stem cells (BMMSCs) and bone marrow mononuclear cells (BMMNCs), are examples of autologous stem cells employed in therapy[15].

ALLOGENIC STEM CELLS

Allogeneic stem cells are those that have been obtained from recipients but not from members of the same species. Pluripotent mesenchymal stem cells are extracted from allogeneic sources, including placental, amniotic, embryonic, umbilical cord (UC) and cord blood. MSCs from placental and amniotic fluid have a special capacity for differentiation and are readily available, making them extremely useful in regenerative medicine. Mesenchymal stem cells derived from umbilical cord blood (UCMSCs) have been utilized to treat ischemic consequences of chronic wounds and to speed up the healing of cutaneous wounds. Placental mesenchymal stem cells have been used in several animal research; human studies utilizing this technique are extremely rare. The convenience of acquiring placental or umbilical cord MSCs is a benefit of using them[15].

Stem cells stimulated macrophage M2 polarization and anti-inflammatory cytokine production. In the wound site, stem cells raised PDGFA, HGF, NGF and bFGF while lowering MMP-2, MMP-9, and proinflammatory cytokines. By interacting with fibroblasts, stem cells increased the deposition of collagen. Elevated local VEGF can attract fibroblast-like cells to the wound site and raise PDGF and FGF-2 levels. TGF-β can control local immunity by raising the number of Treg cells, while EGF can encourage the growth of keratinocytes. TNF-α, tumor necrosis factor-α; MMP-2, matrix metaroprotease-2; MMP-9, matrix metaroprotease-9; FGF-2, fibroblast growth factor; EGF, epidermal growth factor; IL-10, interleukin-10; MSC, mesenchymal stem cell; PDGFA, platelet-derived growth factor A; HGF, hepatocyte growth factor; NGF, nerve growth factor; bFGF, basic fibroblast growth factor; Regulatory T cells, or Tregs; interferon-γ (IFN-γ); transforming growth factor-β (TGF-β)[16].

EXTENDED APPLICATION OF STEM CELL THERAPY

Promote Collagen deposition
Upregulation of Local Growth factors
Improve Inflammatory environment
Improve Survival rate
Promote Angiogenesis
M2 Polarization of Macrophages
Promote Proliferation and Migration
Promote Paracrine

WOUND HEALING SOCIETY (WHS)

The Wound Healing Society (WHS) released treatment guidelines for DFUs in 2006. But in recent years, further evidence has developed that enhances our comprehension of earlier recommendations. The WHS DFU guidelines seek to clarify contentious diagnosis and treatment approaches, identify areas in need of more research, and help doctors make informed decisions about patient care by methodically evaluating the medical literature. To update the 2006 guidelines, an advisory team made up of academics, physicians, researchers, and business representatives was selected[17].

The guideline levels in 2006 are

Level I

Meta-analysis of several randomized controlled trials (RCTs) or at least two RCTs supporting the guideline's intervention was one of the 2006 guidelines' levels. A different approach would be to conduct many animal or laboratory trials using at least two clinical series proving the findings of the tests.

Level II

Less than Level I, but at least two noteworthy clinical series or expert opinion publications with literature evaluations endorsing the intervention, together with at least one RCT. Strong experimental evidence that is not yet backed up by sufficient human experience.

Level III

Insufficient data, such as those from many clinical series, meta-analyses, or RCTs, but suggestive evidence of a proof of principle.

GUIDELINES FOR THE DIAGNOSIS OF DIABETIC ULCERS WITH LOWEREXTREMITY

In order to rule out clinically significant vascular disease, it is necessary to confirm whether pedal pulses can be felt distinctly with the hand or whether the ankle-brachial index (ABI) is greater than 0.9. Noncompressible arteries are suggested by an ABI>1.3.

A normal Doppler-derived waveform, a toe: Brachial index of >0.7, a transcutaneous oxygen pressure of >40 mmHg, and/or hyperspectral imaging analysis may aid to suggest an acceptable arterial flow in elderly individuals or patients with an ABI > 1.2. An ischemic etiology for the leg wound is confirmed by anatomic and physiological data obtained from color duplex ultrasonography scanning. (Level I)

It is possible to test for the existence of substantial neuropathy using a 10 g (5.07) Semmes-Weinstein monofilament. (Level II)[18].

GUIDELINES FOR OFF-LOADINGFOR TREATMENT OF DIABETIC ULCERS

Any patient who has considerable arterial insufficiency, significant neuropathy, a history of amputation or ulcer formation, preulcerative callus, foot deformity, or other risk factors for amputation should be prescribed protective footwear. (Level II). For high-risk individuals who have had a previous foot amputation or ulcer, wearing protective footwear reduces the likelihood of repeat ulcerations. (Level I).

Crutches, walkers, wheelchairs, custom shoes, depth shoes, shoe modifications, custom inserts, and custom shoes are acceptable offloading techniques. Therapeutic orthotic walkers, complete contact casts, diabetic boots, and shoes for the forefoot and heel. (Level I)[18].

GUIDELINES FOR INFECTION CONTROL IN THE TREATMENT OF DIABETIC ULCERS

By using surgical, enzymatic, mechanical, biological, or autolytic debridement, remove all necrotic or devitalized tissue. (Level II).

Determine the kind and level of infection present in a debrided ulcer if there is a suspicion of infection or if the debridement and offloading therapy are not working within two weeks after the beginning of epithelialization from the margin, of infection in a diabetic ulcer that has been debrided using a validated quantitative swab technique or tissue biopsy. (Level II)

After sufficient debridement, topical antimicrobial agents can reduce the amount of bacteria in ulcers if there are more than 105 CFU/g of tissue present. Topical antimicrobial agents should be stopped once the bacterial balance has been reached in order to reduce cytotoxic effects and the appearance of organisms with bacterial resistance. (Level I).

Wound healing cannot be accelerated by topical antibacterial and antiseptic therapy (Level I)

Systemic antibiotics work well for acute diabetic foot infections that are not limited to the granulating wound (Level II)

The area around the ulcer that has cellulitis, which is an infection and inflammation of the skin and subcutaneous tissue most frequently caused by streptococci or staphylococci, should be administered systemic antibiotics that are Gram-positive bactericidal (Level II).

Appropriate diagnostic procedures for osteomyelitis suspicion include radionucleus scans, MRIs, CT scans, bone biopsies, serial x-rays and probing the wound region to the bone using a sterile device. Level Two. Leukocyte screening with PET and WBC tagged SPECT/CT using Tc99m. (level II)[18].

Table No.1: No. of cases reported in different age category in a common study conducted with 50 people

S.No	Age	No. of Cases	Percentage
1	18-25	03	06%
2	26-35	09	18%
3	36-45	08	16%
4	46-55	15	30%
5	56-65	15	30%
6	Total	50	100%

Table No.2: Cost to treat Diabetic Foot Ulcer in various countries

S.No	Country	Cost (USD)	Type of Care
1	US	10.9 billion/yr	Foot care
2	UK	3.93 billion/yr (7539/patient)	Foot care
3	France	1265/yr	DFU
4	Belgium	10572 24965	Per ulcer Per patient without amputation
5	Sweden	47518 42858	Per patient with minor amputation. Per patient with major amputation
6	India	1960	DFU

Table No.3: Grades of Wagner classification

Grade	Lesion
0	No ulcer, but high-risk foot(bony prominences, callus, deformities, etc.)
1	Superficial, full-thickness ulcer
2	Deep ulcer may involve tendons, but without bone involvement
3	Deep ulcer with osteomyelitis
4	Local gangrene (toes or forefoot)
5	Gangrene of whole foot

PATHOPHYSIOLOGY OF DFU

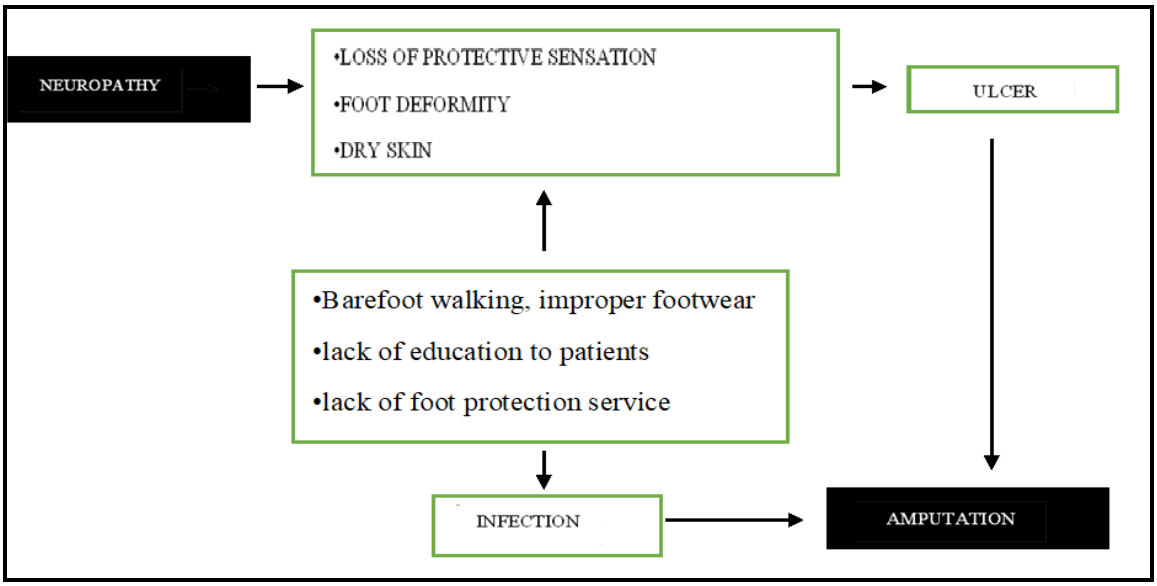

Figure No.1: Pathophysiology of DFU starting from neuropathy to Amputation

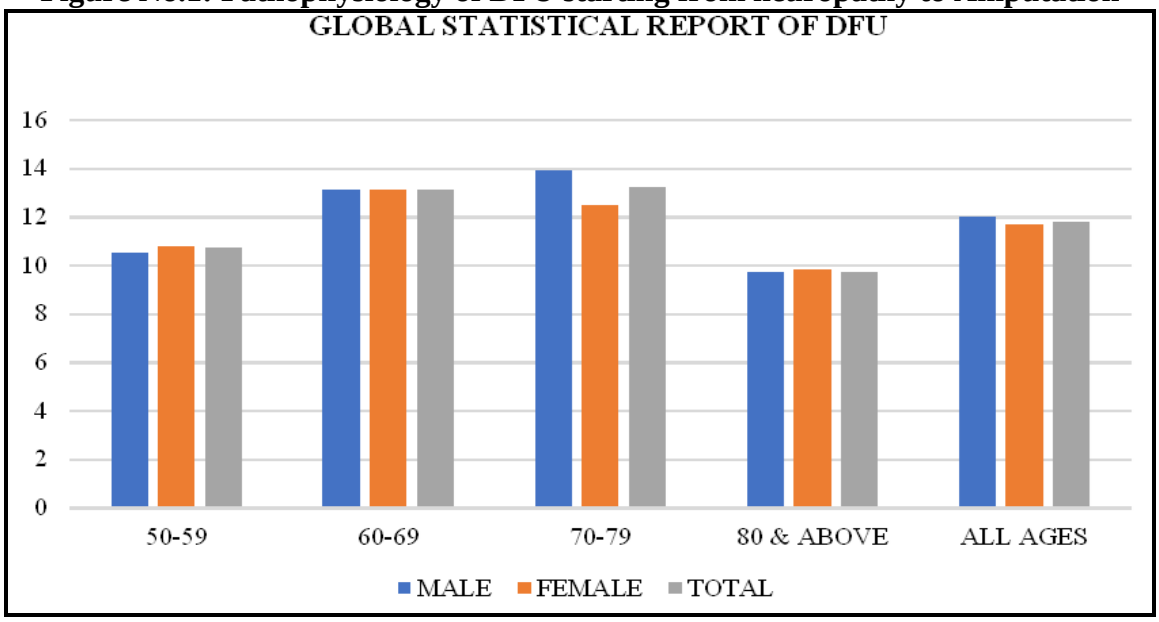

Figure No.2: Global statistical report of DFU compared in a study

WHAT CAUSES DFU?

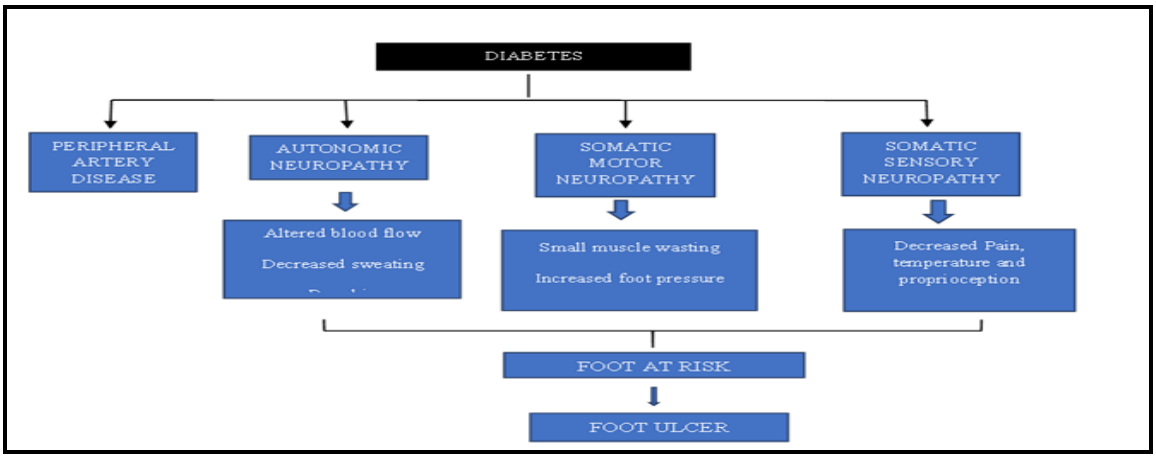

Figure No.3: Causes of occurrence of foot ulcer due to diabetes

CONVENTIONAL DFU TREATMENTS

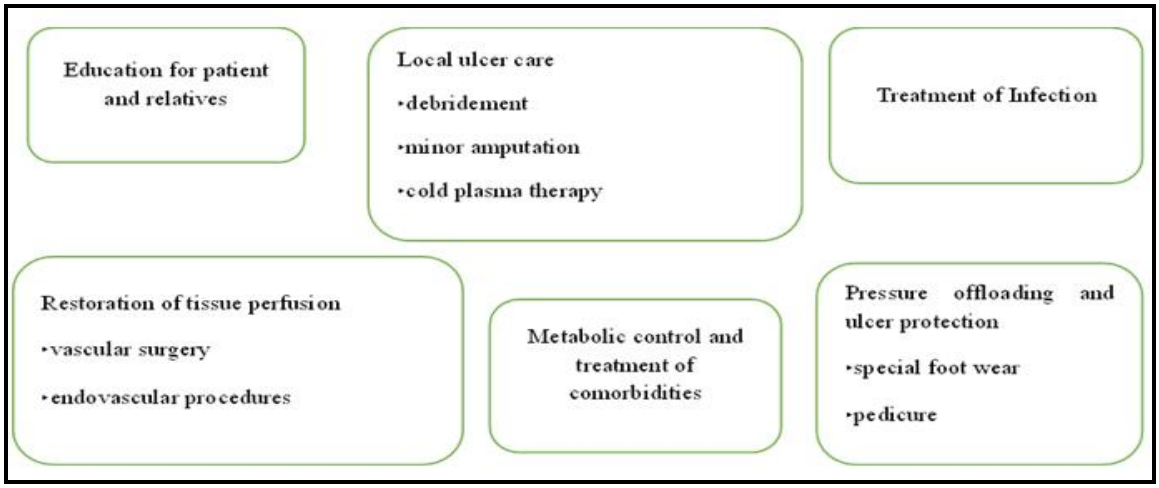

Figure No 4: Alternative conventional treatments for DFU

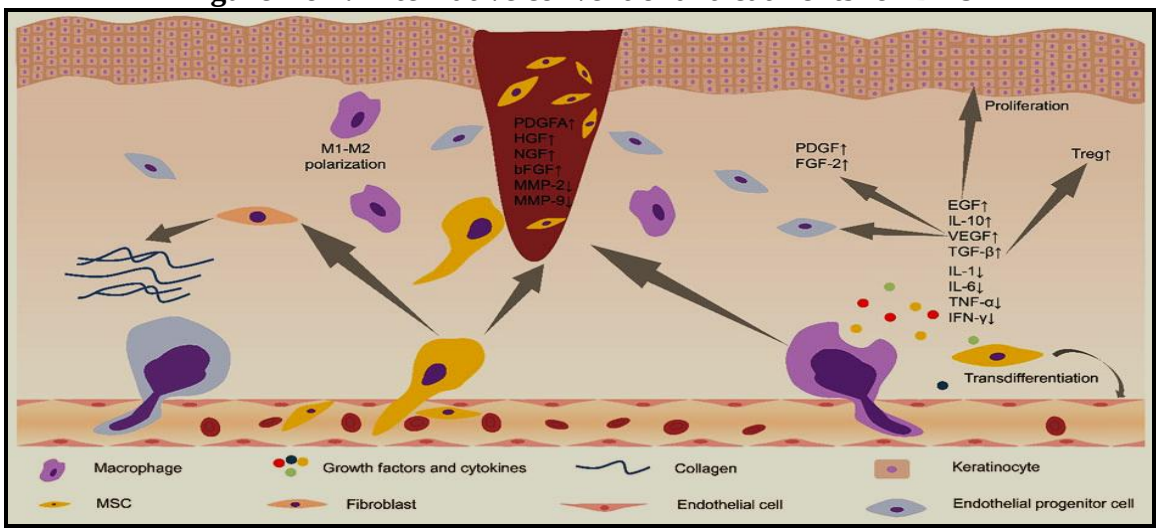

Figure No.5: Changes following the introduction of stem cells to the diabetic foot ulcer microenvironment

CONCLUSION

This article has discussed the possible financial savings from preventative foot care, the knowledge gaps on ulcer prevention, and the differences in emphasis between ulcer prevention and ulcer healing, and the great potential for preventing diabetic foot ulcer recurrence. Diabetes-related foot care and research must now take a backseat to the prevention of foot ulcers. Preventative foot care involves two key steps: 1) doing what we say we should, which is applying information to everyday foot care and 2) enhancing treatment adherence. Based on available data, stem cell therapy appears to be a successful treatment for DFU in humans. Research investigations that are clinical or preclinical do not provide a consensus. Concerning the ideal kind of stem cell to use, as well as the best way to administer stem cells, nothing is known. Variations in preclinical research designs point to the necessity of reaching an agreement on the best animal model for research that can be applied to human subjects. Finally the various WHS Guidelines to treat DFU is been discussed. Majorly it is been classified in three levels where the entire treatment methods will come under these levels.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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