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Literature Review

Stem Cell Therapies in the Management of Diabetic Foot Infections

Kazim Kiratli*

Department of Infectious Diseases and Clinical Microbiology, Katip Celebi University, Izmir, Turkey

ABSTRACT

Diabetes is a chronic illness that affects many people worldwide and its incidence is rising daily. Microvascular dysfunction and prolonged bouts of hyperglycemia lead to several consequences. Among the most significant of these are diabetic foot ulcers, which are linked to a number of morbidities, including death, depression, amputation and a worse quality of life. Numerous factors influence effective treatment approaches, which forces physicians to look for novel alternatives. The stem cell treatments that have been used recently are presented in this review.

Keywords: Neuropathy; Cytokines; Debridement; Endothelial progenitor cells; Angiogenesis

INTRODUCTION

Diabetes Mellitus (DM) ranks ninth globally in terms of causes of death and is one of the most prevalent chronic metabolic disorders. The majority of patients experienced at least one disease-related complication. Data from 2021 show that 536.6 million individuals have diabetes and by 2045, it is expected that this figure will have increased to 783.2 million. A large-scale investigation revealed that 27% of patients with type 2 DM had macrovascular problems and 50% of patients had microvascular problems. A foot with an ulcerated lesion connected to Peripheral Artery Disease (PAD) and/or neuropathy affecting the lower limbs is known as a Diabetic Foot Ulcer (DFU), which is one of the most bothersome consequences of this condition [1].

DFU has an annual incidence of 2%, a lifetime incidence of 19%-34% in patients and an infection affects nearly half of the lesions. Therapy for it is equally challenging because to its extremely complex and multifaceted etiology. These patients are a huge burden on society and the healthcare system because of their repeated natüre patients with DFU are observed to have a limb amputation rate of 14%-24%. Infection and amputation rates are significantly greater in cases of DFU in patients with weakened immune systems. Early deaths are further influenced by the fact that 68% of patients who have an amputation pass away within five years for a variety of reasons (sepsis, etc).

A multitude of complex circumstances, including DFU's propensity to recur, treatment difficulty, high rates of amputation, psychological strain/reduction in patients' quality of life, financial burden on the patient and the healthcare system and other concomitant complications (cardiac disease, PAD, etc.), force clinicians to continually reevaluate their approaches. Significant advancements in imaging and regeneration have occurred in the medical field throughout the past 20 years [2].

In addition to the traditional techniques employed in DFU, this mini-review seeks to give succinct information about the stem cell treatments that have lately been implemented.

LITERATURE REVIEW

Pathogenesis

The physiological reactions of the body to structural tissue injury are what are known as the wound-healing process. Many growth factors, metabolites, cytokines and chemokines interact intimately during this process. There are four overlapping and consecutive stages to the wound healing phase: 1) Hemostasis 2) Inflammation 3) Re-epithelialization (proliferation) and 4) Scar maturation (remodeling). Nonetheless, the hyperglycemic state brought on by DM has an intriguingly detrimental effect on these activities. The pathophysiology of DFU is directly linked to foot injuries, neuropathy, inadequate wound angiogenesis, poor glycemic control and improper care of the extremities [3].

Due to mast cell degranulation, neutrophil infiltration, dysregulation of dendritic cell/T cell and imbalance of macrophages, there is a constant release of inflammatory

Correspondence to: Kazim Kiratli, Department of Infectious Diseases and Clinical Microbiology, Katip Celebi University, Izmir, Turkey; Email: drkazimkiratli@gmail.com

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components in the pathogenesis of DFU. This leads to a prolonged DFU by inhibiting vascular maturation, inducing several inflammatory cascades and reducing collagen deposition. Compared to normal wound healing, DFU is associated with more edema and bleeding for all of these reasons. The aforementioned factors lead to the production of an irregular and loose connective tissue, inhibition of dermal/epidermal tissue formation, decreased granulation tissue formation and lack of matrix formation/remodeling.

Effective glycemic management has been demonstrated in studies to avert neuropathy, which is assumed to be the primary cause of nephropathy, retinopathy and DFUs. Maintaining ideal blood sugar control once the wound forms is crucial for prompt wound healing [4].

Treatment strategies

In the administration of DFU treatment, debridement, revascularization where necessary, ulcer drainage, infection control and glucose control are essential steps. It's unlikely that other modalities will be helpful if these techniques are not used in tandem. The gold standard for wound healing involves repeated debridements in particular. Lifestyle changes (food, patient education, hygienic habits, suitable footwear, etc.) combined with early intervention for minor injuries reduce the risk of DFU development by fifty percent, which in turn lowers the rate of amputations. Only 50% of patients with these treatments recover in 20 weeks and 50% relapse in 18 months, which emphasizes the need for more effective therapies.

An application that has been developed recently is called Vacuum-Assisted Closure (VAC) and it can cure wounds under negative pressure. VAC functions by using a system that includes a vacuum machine to draw tissue fluids (cytokines and different proteolytic enzymes) that inhibit or postpone wound healing into a chamber. With this closed system, the need for dressing changes is decreased, tissue contact with the environment is minimized, infection development is inhibited and the risk of sepsis is decreased [5].

An optimal environment is produced for anaerobic agents that impair local tissue perfusion and cause necrosis and cell death in DFU, which is further worse by infection. Hyperbaric Oxygen Therapy (HBOT) may be used in addition to conventional treatment for certain DFU patients. HBOT promotes angiogenesis, increases collagen synthesis and produces growth factors in the tissue, all of which speed up the healing process of wounds. This approach also contributes to the more sensible use of antibiotics, as it is particularly efficient against anaerobic bacteria.

The process of debridement eliminates non-viable and/or contaminated tissues, creating an environment that is favorable for the regeneration of healthy tissue. Biological, autolytic or surgical agents may be used in this technique.

The federal food and drug administration has also approved becaplermin, a recombinant platelet-derived growth factor, as a therapy for DFUs resulting from diabetic neuropathy. Platelet-derived growth factor is released by keratinocytes, macrophages, endothelial cells, fibroblasts and other cells that are involved in wound healing, in addition to the platelets, which are the source of the factor. This factor promotes the production of granulation tissue, angiogenesis, endothelial migration and fibroblast activity by activating the release of vascular endothelial growth factor. The likelihood of DFU recovery is not sufficiently supported by the available evidence to support the implementation of this therapy modality, which is limited due to the danger of tumor formation.

Another autogenous blood component that is essential for the healing of DFU is Platelet-Rich Plasma (PRP), which is made up of a significant quantity of platelets, fibrin, different growth factors, and other products. By producing more granulation tissue, this technique which is frequently chosen in place of debridement allows wounds to recover. According to research by Angelis et al., PRP helps diabetes patients feel less discomfort in addition to healing the DFU wound. Since DFUs are linked to infection and the creation of bacterial biofilms, the use of PRP and growth factors in wound healing mechanisms actually seems limited, despite their initial promising qualities [6].

DISCUSSION

The various types of “stem cell therapies” for DFU include:

Mesenchymal stem cell

In the healing phase of DFU, immune system cells are essential. Mononuclear cells and Mesenchymal Stem Cells (MSC) are the preferred Stem Cells (SC) in therapeutic practise. Through angiogenesis, MSCs actually accelerate the healing of wounds. MSCs are derived from the bone marrow, umbilical cord, adipose tissue, hair follicles, menstrual blood and gums. With MSCs' anti-inflammatory and immunomodulatory properties, it soothes the immune system and helps eliminate bacterial elements from the surroundings. Maintaining the body's homeostasis at the same time speeds up the healing process for injured tissues [7].

Because stem cells enhance the DFU microenvironment and modulate tissue regeneration in a variety of ways, they appear to be a more favorable alternative than growth factors. It has been shown in certain animal studies that implantation of stem cells improves blood flow in ischemic limbs. MSCs are a good candidate for transplantation due of their low immunogenicity. By secreting several anti-inflammatory agents and growth factors, MSCs aid in the recovery from DFU.

In order to participate in the wound healing process, stem cells differentiate into several cell types, including endothelial progenitor cells, fibroblasts, myofibroblasts and antigen-presenting cells. Revascularization brought on by PAD-induced decreased blood flow and the development of new capillaries in chronic ulcerated lesions are thought to be the primary healing mechanisms in DFU, despite the fact that the exact mechanism of action is still unclear. Furthermore, stem cell therapy has been shown to be able to repair neurons, which were previously believed to be incapable of self-renewal. An injection into an artery, intramuscular injection or direct local application of stem cells are all possible for the patient [8].

Applying MSC is a therapeutic approach that offers benefits in some areas. It can be isolated from bone marrow even in advanced patients and patients with cell lineage commitment, even if it is present in low concentrations in the bone marrow; Lastly, it can be grown *in vitro* without the need for immunosuppressive therapy to prevent graft rejection after application. Due to the relative ease of cell harvesting, MSCs can also be obtained from peripheral blood and umbilical cord. Furthermore, compared to MSCs obtained from bone marrow or peripheral blood, umbilical cord-derived MSCs exhibit higher potential for proliferation and differentiation. The availability of MSCs generated from human umbilical cords, which are less likely to cause immunogenic reactions and cancer, is further facilitated by donor banking.

These cells can also be utilized to provide a perfect match between human leukocyte antigens. These cells can be created in huge quantities because, given the right conditions, they can multiply up to four times their initial number of cells *in vitro* in 3-5 days. The administration of umbilical cord-derived MSCs intravenously to rats suffering from diabetic ulcers was found to dramatically enhance neovascularization in the ulcer area over a 72-hour period in an animal investigation. By the conclusion of the second week, stratified squamous epithelial tissue had developed, while fresh granulation tissue had emerged at the end of the first week. Skin ulcers have dramatically diminished as a result of all these advancements [9].

Adipose tissue-derived stem cell

Adipose tissue serves as an essential source of Stem Cells (SCs) since it can be collected at a lower risk than bone marrow-derived MSCs. Not only may a substantial quantity of cells be obtained with no adverse effects, but cryopreservation allows for up to six months of cell storage, which facilitates quick and simple therapeutic application. The quick proliferation, donor selectivity, decreased chance of cancer, lack of ethical dilemmas and decreased risk of surgical complications are further benefits of MSCs generated from adipose tissue. In a limb ischemia model, MSCs produced from adipose tissue have stronger angiogenic and regenerative potentials when compared to MSCs from bone marrow. The greater paracrine activity of MSCs generated from adipose tissue is responsible for all of these changes. In another study, 66% of patients with lower extremities ischemia-related chronic symptoms reported alleviation after receiving adipose MSCs for six months. There was also a notable increase in collateral circulation.

Hematopoietic stem cells

In a study including diabetic patients with chronic ulcers and end-stage renal failure, the administration of autologously produced and purified CD34+ cells was found to enhance wound closure and tissue perfusion. It was advised to combine CD34+ cells and MSCs obtained from umbilical cords in a different investigation involving five patients. In their investigation, Xu et al. also reported that transplanting SC generated from peripheral blood enhanced vascular perfusion in DFU patient. It has been noted that CD34+ cells, a competent source of endothelial progenitor cells, are a useful therapeutic alternative for DFU.

Bone marrow-derived stem cells

MSCs produced from bone marrow are thought to be a good therapeutic option for DFU patients because they contain multipotent SCs and progenitors of inflammatory cells. It is well recognized that all of these cell types quicken wound healing. In the chronic wound, MSCs have been demonstrated to alter phenotypically and/or undergo senescence, despite their ability to populate the skin dermis.

Leg oxygenation and limb preservation rate significantly increased in a research where bone marrow-derived MSC transplantation was administered to a cohort of PAD patients who did not improve following vascular surgery. An analogous investigation shown that DM patients with lower extremity vascular occlusion benefited significantly from the same treatment approach in terms of both wound healing and pain-free walking distance [10].

Embryonic stem cell

SCs originating from embryos seem to be another alternative in DFUs. They can hasten the initial stage of wound healing by encouraging angiogenesis and fibroblast growth. It assists in to increase the production of substances like fibronectin and cytokines, which are essential for wound healing. Increases in fibronectin and vascular epithelial growth factor were seen following the introduction of embryonic-derived SCs in DFUs. Early healing of the wound is also anticipated to be possible with this type of treatment.

CONCLUSION

By encouraging neovascularization, lowering neuropathy, alleviating inflammation and enhancing collagen accumulation, SC-based uses for DFU provide us greater hope for the future of regenerative medicine. Nevertheless, there aren't many studies involving humans and it's clear that additional clinical work and investigation is still required to fully understand the biological characteristics and mechanisms of action of this medication in order to ensure both safety and effectiveness. Subsequent investigations will provide insight into the ideal dosage and delivery methods for therapies that have not yet been determined upon *via* the regulation of inflammation and revascularization by several cytokines and growth factors, MSC therapies are promising for the treatment of vasculopathy, neuropathy and other problems linked to DM.

REFERENCES

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
3. Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. Diabetol Metab Syndr. 2013;5(1):57.
4. Banu A, Hassan MM, Rajkumar J, Srinivasa S. Spectrum of bacteria associated with diabetic foot ulcer and biofilm formation: A prospective study. Australasian Med J. 2015;8(9):280-285.
5. Lazzarini PA, Jarl G, Gooday C, Viswanathan V, Caravaggi CF, Armstrong DG, et al. Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: A systematic review. Diabetes Metab Res Rev. 2020;36:e3275.
6. Levy N, Gillibrand W. Management of diabetic foot ulcers in the community: an update. Br J Community Nurs. 2019;24(3):S14-S19.
7. Heublein H, Bader A, Giri S. Preclinical and clinical evidence for stem cell therapies as treatment for diabetic wounds. Drug Discov Today. 2015;20(6):703-717.
8. Yu Q, Qiao GH, Wang M, Yu L, Sun Y, Shi H, et al. Stem cell-based therapy for diabetic foot ulcers. Front Cell Dev Biol. 2022;10:812262.
9. Shu X, Shu S, Tang S, Yang L, Liu D, Li K, et al. Efficiency of stem cell based therapy in the treatment of diabetic foot ulcer: A meta-analysis. Endocr J. 2018;65(4):403-413.
10. Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: New insights. Adv Ther. 2014;31(8):817-836.