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NARRATIVE REVIEW

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Mesenchymal stem cell therapy in diabetic foot ulcer: An updated comprehensive review

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Abstract

Background: Diabetes has evolved into a worldwide public health issue. One of the most serious complications of diabetes is diabetic foot ulcer (DFU), which frequently creates a significant financial strain on patients and lowers their quality of life. Up until now, there has been no curative therapy for DFU, only symptomatic relief or an interruption in the disease's progression. Recent studies have focused attention on mesenchymal stem cells (MSCs), which provide innovative and potential treatment candidates for several illnesses as they can differentiate into various cell types. They are mostly extracted from the placenta, adipose tissue, umbilical cord (UC), and bone marrow (BM). Regardless of their origin, they show comparable features and small deviations. Our goal is to investigate MSCs' therapeutic effects, application obstacles, and patient benefit strategies for DFU therapy.

Methodology: A comprehensive search was conducted using specific keywords relating to DFU, MSCs, and connected topics in the databases of Medline, Scopus, Web of Science, and PubMed. The main focus of the selection criteria was on English-language literature that explored the relationship between DFU, MSCs, and related factors.

Results and Discussion: Numerous studies are being conducted and have demonstrated that MSCs can induce re-epithelialization and angiogenesis, decrease inflammation, contribute to immunological modulation, and subsequently promote DFU healing, making them a promising approach to treating DFU. This review article provides a general snapshot of DFU (including clinical presentation, risk factors and etiopathogenesis, and conventional treatment) and discusses the clinical progress of MSCs in the management of DFU, taking into consideration the side effects and challenges during the application of MSCs and how to overcome these challenges to achieve maximum benefits.

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Conclusion: The incorporation of MSCs in the management of DFU highlights their potential as a feasible therapeutic strategy. Establishing a comprehensive understanding of the complex relationship between DFU pathophysiology, MSC therapies, and related obstacles is essential for optimizing therapy outcomes and maximizing patient benefits.

KEYWORDS

cell therapy, diabetes, diabetic foot ulcers (DFU), mesenchymal stem cell, wound healing

1 | INTRODUCTION

Diabetes is a diverse collection of metabolic disorders caused by deficiencies in insulin production, insulin activity, or a combination of the two. Diabetes can be categorized into type 1 and type 2 diabetes. Type 1 is characterized by hyperglycemia caused by the autoimmune attack and damage to the pancreatic β-cells, while type 2 is characterized by insulin resistance mostly caused by obesity, decreased pancreatic production of insulin, and β-cell dysfunction.[1–3] By 2045, 783.2 million people worldwide are expected to have diabetes, up from 536.6 million in 2021.[4] Diabetes-related metabolic abnormalities lead to a wide range of complications, including neuropathy, retinopathy,[5] nephropathy, cardiovascular diseases, and slow wound healing. These issues may cause death or reduce the quality of life.[6] Diabetes patients frequently have significant lower-limb vascular problems, which can lead to DFU, as their condition gets worse and becomes more complicated. According to reports, around 19%–34% of diabetic patients will be complicated with DFU, and 20%–30% of these patients will end with limb amputation.[7,8]

The etiology of DFU is a complex issue, and several intrinsic and extrinsic risk factors are involved in the pathogenesis. Intrinsic factors, like neuropathy and peripheral vascular disorders, on the other hand, extrinsic factors including wound infection, callus development, and increased stress on the ulcer site, all affect how well DFUs heal.[9] Given that conservative medical therapy is currently the only successful clinical strategy for diabetic foot care. Currently, conventional management strategies including wound debridement, wound dressing, treatment of wound infection, revascularization, offloading, hyperbaric oxygen therapy (HBOT), and negative pressure wound therapy (NPWT) can only help patients with their symptoms or slow the progression of the disease. Nevertheless, they are unable to restore injured blood vessels and nerves.[10] DFU seems to be a serious issue that threatens human health on a global scale. Consequently, there is an urgent need for a novel technique that accelerates the healing process in diabetic wounds.

It has been observed that a variety of stem cell types, including mesenchymal stem cells (MSCs), promote and boost the healing process in DFUs.[11–13] These multipotent stem cells can develop into a variety of cell types such as epithelial cells, adipocytes, osteoblasts, fibroblasts, chondrocytes, and vascular endothelial cells.[14,15] MSCs are an efficient method of treating DFU, as evidenced by the growing research that demonstrates their capacity to encourage re-epithelialization and angiogenesis, decrease inflammation and the inflammatory process, take part in immunological control, and subsequently heal DFU.[16,17]

Key messages

- DFU represents a serious threat to global health, leading to a high rate of amputations globally, with one case of an amputation occurring every second and 84% of these occurrences being linked to DFU. This emphasizes the critical need for better treatments and preventative measures.
- MSCs have the ability to improve the healing process when used in concert with other treatments, showing promise as a helpful adjunct to the therapy of DFU.
- Although early results point to the safety and effectiveness of MSC therapy in the treatment of DFU, there are still challenges and potential negative effects related to its application. To make MSCs more useful and efficient in preclinical and clinical settings, future research should concentrate on resolving these limitations and maximizing their utilization.

This review article provides a general snapshot of DFU and discusses in detail MSCs and their role as a novel approach in the treatment of DFU. Moreover, it will take the challenges and general and specific limitations of MSCs into consideration and discuss how to overcome these obstacles.

2 | DIABETIC FOOT ULCER

DFU is a common and serious complication of uncontrolled diabetes.[18] According to International Diabetes Federation, around 19%–34% of the approximately 540 million diabetic patients will experience a DFU over their lifetimes.[8] 10% of those with DFU die within the first year of their initial diagnosis[19,20] and 20%–30% will need lower limb amputations, possibly minor (beneath the ankle), major (above the ankle), or both.[8] According to a study conducted in

TABLE 1 Wanger classification for DFU.[25]

Grade	Clinical presentation
0	Intact skin, no ulcer but high-risk foot
1	Superficial ulcer in the skin or subcutaneous tissue
2	Ulcer extended into joint, tendon, ligament, or capsule without abscess or osteomyelitis
3	Deep ulcer with abscess or osteomyelitis
4	Localized gangrene in the toe or forefoot
5	Extensive gangrene in the whole foot

Abbreviation: DFU, diabetic foot ulcer.

the United States, diabetes mellitus (DM) is responsible for 38% of all amputations. Morbidity and mortality may increase as a result. Neuropathy, ischemia, and infection represent the traditional triad of DFU. The danger of infection and poor wound healing are raised in DFU due to diabetes-related metabolic dysfunction. It occurs because of several factors, including lowered peripheral blood flow, reduced angiogenesis locally, and lowered cell and growth factor responsiveness. Accordingly, peripheral nerve injury, peripheral vascular disorder, deformities, ulcerations, and gangrene all have an impact on the foot.[21]

DFU is clinically presented as a cut in the epidermis and possibly a portion of the dermis. Preulcerative lesions are closed or superficial lesions that are limited to the epidermis (such as blisters, callous, erythema, or warmth), but they are more likely to develop into ulcers.[22] Repeated minor trauma mostly leads to the development of ulcers, frequently as a result of increased pressure at plantar weight-bearing areas, friction, and shearing brought on by abnormal walking patterns, inappropriate footwear, or an undetected injury on an insensate foot (such as ingrown toenails, puncture wounds, or burns).[23] Structural deformities, such as Charcot neuroarthropathy, increase the incidence of DFU.[8] Complex and multiple pathways finally result in ulceration after a modest stressful incident.[23,24] The Wagner method assists in classifying the severity of the ulcer, scoring it on a range of 0–5 (Table 1).[25]

2.1 | Etiopathogenesis

DFU has a complex etiology and several risk factors involved in pathogenesis. The risk factors include peripheral neuropathy (PN), vasculopathy, immunopathy, and the spread of resistant microorganisms.

2.1.1 | Peripheral neuropathy

Diabetic PN is a heterogeneous clinical manifestation that is generally described as any combination of signs or symptoms of peripheral nerve dysfunction that is thought to be a consequence of both metabolic and vascular variables associated with persistent hyperglycemia.[26] Neuropathy affects up to 66% of diabetic patients and is one of the main triggers for DFU.[27] Diabetic PN impairs the functioning of the nerve system's sensory, autonomic, and motor divisions and is responsible for poor wound healing.[28,29] In sensory neuropathy, sensory nerves are damaged and result in loss of pain sensation. Autonomic neuropathy reduces sebaceous and sweat functions in the lower limbs. As a result, the foot dries out, develops cracks, and becomes more susceptible to microbial infection.[30,31] Moreover, motor neuropathy can result in muscle atrophy and anatomical deformities of the foot. This raises the danger of ulceration by causing focally raised pressures at distinct areas of the plantar foot.[32]

2.1.2 | Peripheral vascular diseases

Vasculopathy is a circulatory disorder that is clinically associated with reduced blood flow to the lower extremities as a result of artery stenosis or atherosclerotic occlusion.[33,34] In around 50% of cases, vasculopathy is a major predisposing factor in the development of DFU. It is responsible for 70% of type 2 diabetes-related deaths.[35] Diabetics have insufficient arterial blood flow, hence peripheral ischemia is the underlying trigger for ulceration in 35% of instances. An inadequate blood flow to the extremities results in inadequate wound healing, which aggravates the problem.[36] In turn, this increases the wound site's susceptibility to anaerobic bacterial growth, which leads to fatal side effects including gangrene and amputation.[27,37] Vasculopathy is not regarded as a separate risk factor; rather, it integrates with neuropathy to become the major trigger of non-traumatic amputations.[38]

2.1.3 | Immunopathy and spread of resistant microorganisms

Diabetic patients' immune systems are substantially weaker than those of healthy individuals. Therefore, the presence of infection in diabetic patients is a serious and fatal problem that can potentially result in limb loss.[39] Past research findings reveal that a variety of bacteria, including *S. aureus*,[40] *E. coli*,[41] and *P. aeruginosa*[42] frequently infect diabetic wounds. These microbes cause the progression of sepsis and life-threatening infections by penetrating deeper into the fascia via irritated or poorly perfused skin. Moreover, resistant bacterial strains such as methicillin-resistant *Staphylococcus aureus* commonly infect DFU, increasing the risk of amputation.[43,44]

3 | CONVENTIONAL TREATMENT OF DFU

Effective management and treatment protocol should be started soon after the development of DFU.[45] The gold standard of conventional DFU therapies includes wound debridement, dressing, treating infections, revascularization, off-loading, HBOT, as well as

NPWT.[46] Wound Debridement is the most fundamental approach for managing DFU. Debridement includes removing necrotic or contaminated tissue, blood clots, and unwanted debris from a wound bed. The most prevalent forms are ultrasonic, biological, enzyme, and surgical debridement.[47,48] Furthermore, debridement boosts the healing process by removing dying and infected tissue as well as bacterial biofilms.[46]

Wound dressings are a conventional wound care approach consisting of natural, modified, or synthetic materials and medicinal components.[49] The wound dressing must offer a moist environment that encourages tissue regeneration, keratinocyte migration, revascularization, and granulation and interferes with bacterial growth.[50,51]

Infection is frequently present while wounds heal, particularly in diabetic people.[52] If there are more than two of the typical signs of inflammation (redness, hotness, edema, pain, and loss of function) or purulence, it is considered to be an infection. Aerobic Gram-positive cocci and staphylococci are the most frequently identified microorganisms that are responsible for most DFUs.[53] Narrow-spectrum antibiotics may be used in mild or moderate wound infection, on the other hand, broad-spectrum parenteral antibiotics may be used in severe wound infection.[54,55]

Peripheral artery disease (PAD) is one of the best indicators for the development of chronic wounds and an elevated risk of death from cardiovascular disease.[56,57] According to reports, 40% of people with DFUs develop PAD.[56] DFU patients who suffer from PAD may experience slower healing, greater complication rates, as well a greater risk of amputation. Revascularization might therefore be a potential therapeutic option for individuals who suffer from DFU and chronic limb ischemia.[46,58]

DFU healing is negatively impacted by vertical loads and shear pressure on the plantar. Consequently, Offloading aims to decrease pressure on the DFU's forefoot and plantar surfaces.[59] There are some techniques to reduce foot stress, including orthopedic walking aids and specially designed footwear for DFU therapy.[60] Total contact casting (TCC) bracing is considered an important strategy in the management of DFU. When compared to specifically made footwear, it can reduce the load by itself, and it mechanically aids in lowering and redistributing the stresses on the DFU. It can also promote ulcer healing and is thought to be a vital approach in the management of DFU.[16,61,62] TCC is proven to be significantly superior to common dressing changes and other offloading ways of boosting ulcer healing and minimizing infection.[63,64]

HBOT is a promising approach to overcome local hypoxia. The presence of infection in diabetic ulcer lesions encourages local hypoxia, which in turn encourages the development of anaerobic bacteria, reduces local tissue perfusion, and ultimately results in necrosis and cell death.[65-69] HBOT is a local oxygen delivery to ulcers and systemic oxygen delivery.[16] HBOT is thought to increase local tissue perfusion, which stimulates collagen synthesis, the generation of growth factors, and neovascularization, and reduces oxidative stress, hence improving wound healing.[70,71] Additionally, HBOT creates a bactericidal action against anaerobic microorganisms, hence minimizing the need for antibacterial medications.[72] It's still debatable if HBOT has therapeutic significance, as determined by clinical research.[73,74] According to certain studies, HBOT may improve DFU's short-term, but not permanent ulcer healing power and does not reduce DUF amputation rates.[74] Despite its apparent advantages, HBOT possesses a few adverse consequences, such as toxicity and noncompliance.[68]

Recent developments in medical technology in wound dressing and treatment have led to the development of NPWT. Following debridement, negative pressure wound care involves applying a vacuum device to the ulcer region. This suction device may collect significant volumes of exudate, maintain the wound dry and clean, minimize dressing change frequency, and enhance blood flow to the ulcer region. Sustained negative pressure drainage may additionally provide a kind of irrigation to boost and accelerate the healing process.[16,75] NPWT causes two forms of tissue deformation: macro deformation, which can be detected by wound contraction, and micro deformation, which appears at microscopic levels. Both deformations increase blood flow and enhance the cascade of wound-healing processes, such as tissue granulation, vessel growth, neoangiogenesis, epithelialization, and the elimination of extracellular fluid.[76,77]

Previous studies have completely investigated additional factors such as glycemic management, use of sensitive antibiotics, vascular evaluation, and psychotherapy in DFU patients.[78,79] If the patient's condition deteriorates to the point that maintaining a limb is no longer an option, amputation could be a life-saving alternative. Despite the availability of several treatment options, managing DFU remains one of the most challenging complications associated with diabetes.[80,81]

4 | STEM CELL THERAPY

4.1 | Mesenchymal stem cells

MSCs are a form of multipotent stem cell that Friedenstein et al.[82] originally identified When discussing the genesis of cells, the word “mesenchymal” is used to indicate an embryonic origin. MSCs are cells that can change into different mesodermal tissues. They are also called FCUs, which stand for “fibroblast colony-forming units,” or stromal cells, which are found in bone marrow (BM).[83] The mesoderm is the middle layer of three major layers that arise very early in embryogenesis. It is responsible for the development of a variety of connective tissues, including bones, muscles, cartilage, and fatty tissue, as well as the cells that create blood vessels, cells of the blood, and the urogenital system.[84] MSCs may also be employed to create endoderm and ectoderm-derived cells, including hepatocytes and neural cells.[85] The capacity for MSC differentiation is influenced by the origin of these cells, the circumstances under which they are amplified, and the milieu in which they are cultured. The differentiation process may be sped up by the use of certain growth factors, hormonal substances, or particular differentiation molecules.[86]

Stem cells' self-renewing and differentiating-to-many-types abilities and wide-ranging genetic background make them unique.

Furthermore, MSCs support tissue healing through the release of growth factors and cytokines, which aid in the recruitment of additional cells to the injured location.[87] These cytokines and growth factors also encourage the development of new blood vessels, which is essential for the healing of damaged tissue. MSCs are also capable of regulating the activity of the immune system, reducing inflammation, and suppressing immunological responses, which makes MSC treatment a novel alternative for healing and rebuilding damaged tissues.[88] The majority of MSCs are found in BM, and they can self-renew and display multilineage differentiation.[89–91] They might be derived from a wide range of bodily tissues and organs, including the BM, adipose tissue, blood from the peripheral circulation, Wharton's jelly, dental pulp, placenta, amniotic fluid, and the umbilical cord (UC).[92–94]

MSCs may display a range of surface molecules and cellular cytokines according to where they originated from. CD45, CD34, CD19, CD14, CD11b, CD79, and HLA-DR are not expressed, making CD90, CD73, and CD105 the most common markers that identify MSCs.[95–98] Several studies show that MSCs may be new way to treat DFU by improving angiogenesis and re-epithelialization, helping to control the immune system, reducing inflammatory processes, and repairing DFU.[17]

4.2 | Types of MSCs used in DFU

MSCs can be obtained from a wide variety of sources. They can be produced from BM (BM-MSCs), human umbilical cords (hUC-MSCs), adipose tissue (AMSCs), and placenta (PD-MSCs) and have been the subject of an increasing number of research investigations.[16] Table 2 summarizes the previously documented studies of MSC therapy in DFU in animal studies and preclinical human studies.

4.2.1 | BM-derived MSC therapy in DFU

BM-derived cells such as inflammatory cell progenitors, MSCs, and multipotent stem cells represent intriguing therapeutic potential for healing chronic wounds.[120,121] The plasticity of BM cells raises the possibility that they may generate fresh cells in the skin.[122] BM-MSCs are the most widely employed kind of cells in both preliminary and clinical investigations.[123] MSCs can regenerate the dermis of the skin, and it has been noted that in chronic wounds, they may exhibit phenotypical changes or become senescent.[123] Several studies have shown that the use of BM-MSCs is effective in the healing process of chronic wounds. For example, the topical administration of BM-MSCs has been shown to promote the regeneration of chronic wounds within 2–4 weeks after treatment.[99] Furthermore, there was a link between the number of cells delivered and the proportional reduction in lesion diameter, suggesting that bigger wounds require more MSCs to heal adequately.[100] According to the findings of Badiavas et al.,[122] immediately applying BM-MSCs led to skin regeneration and resulted in the full healing of chronic wounds in every one of the individuals who participated in the research.In a different investigation, Dash et al.[101] showed that therapies with autologous BM-MSCs were a simple, risk-free, and successful approach for the management of chronic wounds that were nonresolving.This treatment proved successful in reducing ulcer size, controlling pain, and increasing the distance that patients were able to walk without experiencing discomfort. After therapy, all biochemical markers were found to have remained within normal limits, showing that the medication had no adverse effects on the body.[101]

MSCs, which originated in BM, are showing promise as an effective supplementary treatment that may hasten the healing of wounds and increase the likelihood of limb salvage. BM cell transplantation was shown to be safe for those with end-stage serious limb ischemia caused by PADs. This procedure was also effective in enhancing leg perfusion, drastically decreasing the number of major amputations, and allowing for the long-term salvage of limbs.[102] According to the findings of Matoba et al.,[103] BM-MSCs have the potential to bring about a long-term reduction in limb ischemia, resulting in an extension of the time until amputation is required. The effectiveness of BM-MSCs and BM-derived mononuclear cells (BM-MNCs) for the management of ongoing wounds among individuals with diabetic serious limb ischemia and DFU were evaluated and compared via the use of intramuscular injections of both cell types.[104] The ankle-brachial index (ABI) and transcutaneous partial pressure of oxygen (TcO2) measurements of the study's findings show that both types of cells have the capacity to improve blood circulation and reduce pain. Results from the group that was injected with BM-MSCs show that the wound's healing rates were much greater 6 weeks after the administration, and complete healing was achieved a month earlier compared with the BM-MNC group.[104] Furthermore, tCO2 (total carbon dioxide), ABI, magnetic resonance angiography, and painless walking time analyses all showed significantly better outcomes in those undergoing treatment with BM-MSCs relative to those who were administered BM-MNCs 24 weeks after therapy. These findings suggest that, in diabetic individuals suffering from critical limb ischemia, BM-MSCs may be well tolerated as well as more efficient than BM-MNCs in improving limb oxygenation and speeding up the healing process of foot ulcers[104] Also, Xu et al.[105] demonstrated that BM-MSC-CM is an excellent therapy for DFU in rats with type 2 diabetes. Inflammation may be reduced, autophagy can be enhanced, and pyroptosis can be reduced with the use of BM-MSC-CM, which can aid the healing of DFUs. These results bring to light a potentially life-saving therapeutic use of BM-MSC-CM for the management of DFUs that sidesteps the potential hazards of live cell therapy.[105]

4.2.2 | hUC-MSC in DFU

As a part of therapeutic angiogenesis, BM-MSC implantation has been used to treat diseases like cerebral infarction[124,125] heart attack[126,127] and ischemia of the limb.[125,127] The capacity to get stem cells from BM depends on the recipient's general health.[127] Hence,

TABLE 2 Documented previous studies that reported the effect of MSCs from different origins in DFU ASCs (adipose-derived mesenchymal stem cells), HUVECs (human umbilical vein endothelial cells), PRF (Platelet-Rich Fibrin), PD-MSCs (placental-derived mesenchymal stem cells), PRP (platelet rich plasma), vCPM (cryopreserved placental membrane containing viable cells), CTP (cellular- and tissue-based products).

Origin of MSCs	Authors	Study group	Method of application	Outcome
Bone marrow-derived	Jain et al.[99]	Human	Topical spray and local injection	In the initial weeks of treatment, a single application of autologous bone marrow-derived cells accelerates the pace of healing chronic lower extremities wounds.
	Falanga et al.[100]	Human and murine model	Topical application through fibrin polymer spray system	Proportional decrease in chronic wound size with the number of cells applied, closure of full-thickness wounds in diabetic mice, and blood vessel formation
	Dash et al.[101]	Human	Implant	Reduction in ulcer size from 7.26 to 2 cm and a remarkable improvement in pain-free walking distance
	Amann et al.[102]	Human	Intramuscular transplantation into the ischemic leg	Significant increase in leg perfusion, sufficient to minimize major amputations and allow for long-term limb salvage
	Matoba et al.[103]	Human	Intramuscular injection	A substantial decrease in the leg pain scale, ulcer size, and pain-free walking distance, resulting in a prolongation of the amputation-free period
	Lu et al.[104]	Human	Intramuscular injection	Improvement of blood circulation, pain-free walking distance, complete healing of ulcer after 1 month in BM-MSC group
	Xu et al.[105]	Rat model	Injection around the ulcer	Acceleration of wound closure, promotion of cell proliferation and angiogenesis, augmentation of cell autophagy, and reduction of cell pyroptosis in ulcers
	Badiavas et al.[106]	Human	For BM-MCS aspirate: topical application and local injection For cultured BM-MCS for booster dose: topical application only	Complete healing and dermal reconstruction of nonhealing chronic wounds.
Human umbilical cord-derived	Yan et al.[107]	Mice model and in vitro cell culture	Injection for mice model and coculture for in vitro cell culture	Acceleration of diabetic cutaneous wound healing via reducing oxidative stress and increasing angiogenesis
	Qin et al.[108]	Human	Endovascular infusion and injection around the ulcer	Complete or gradual ulcer healing, improvement in skin temperature, ankle-brachial pressure index, transcutaneous oxygen tension, and claudication distance
	Zhang et al.[109]	Rat model	Tail vein injection	Acceleration of wound closure; scar reduction; improvement in regeneration of skin appendages, nerves, and arteries; and modulation of the natural distribution of collagen fibers in wound healing
Adipose- derived	Kim et al.[110]	Mice model	Topical application	Improvement of wound healing rate, neovascularization, dermal regeneration, keratinocyte formation, and granulation tissue formation in the allogenic AMSCs group rather than the autologous group
	Fromer et al.[111]	Murine model	Injection into the ischemic muscle	Enhancement of wound healing, proliferation, and neovascularization in HUVEC-primed AMSCs group rather than AMSCs group. This is because, under diabetic conditions, HUVECs produce protein factors that markedly enhance the proliferation and endothelial differentiation of AMSCs.

TABLE 2 (Continued)

Origin of MSCs	Authors	Study group	Method of application	Outcome
	Khalil et al.[112]	Human	Topical application with spraypen	PRF enhances ulcer healing and proliferation properties of autologous AMSCs as the platelets act as a reservoir for several growth factors that stimulate healing process
	Cianfarani et al.[113]	Mice	Topical application	Diabetes modifies the fundamental features of AMSCs and reduces their functionality, which may impact their therapeutic efficacy when used in autologous therapy for diabetic ulcers.
	Rennert et al.[114]	Mice	Subcutaneous injection	Diabetic AMSCs are impaired in their capacity to form a vascular network both in vitro and in vivo.
	Moon et al.[115]	Human	Topical application	Significant complete wound closure in study group compared to control after 12 weeks of follow-up
Placental-derived	Zeng et al.[116]	Human	Topical application	Reduction in wound size after 3 weeks, resulting in a shorter healing time as well as the production of dense granulation tissue that aids in wound recovery
	Du et al.[117]	In vitro study	–	PD-MSCs had the potential to speed up the healing process of ulcers via the generation of various cytokines and HGF, in addition to the paracrine activities that encouraged angiogenesis
	Meamar et al.[118]	Human	Topical application	Improvement of wound healing and pain-free walking distance in both the PD-MSCs and PD-MSCs + PRP gel groups compared to control
	DaVanzo et al.[119]	Human	–	Significant reduction in recurrence or occurrence of ulcers and decline in mortality rate in vCPM group compared to CTP group

Abbreviations: DFU, diabetic foot ulcer; HGF, hepatocyte growth factor; MSC, mesenchymal stem cell.

UC blood or peripheral blood is more commonly used as it is easier to collect.[128] hUC-MSCs can develop into neuronal, muscle, and blood vessel tissue. High-profile status is given to hUC-MSCs because of their capacity for pluripotency. hUC-MSCs have been used in a number of therapeutic contexts recently to promote wound healing.[107] In certain investigations, hUC-MSCs have been demonstrated to improve angiogenesis and promote the rejuvenation of tissues.[107] Qin et al.[127] employed hUC-MSCs for the management of DFU after angioplasty in two separate investigations. Better healing of wounds was seen in individuals administered hUC-MSCs relative to those who received merely angioplasty. In patients with advanced diabetes, the combined effect of the two therapies increased blood flow, decreased the incidence of amputations, accelerated the healing of ulcers, and enhanced quality of life. This suggests that the implantation of hUC-MSCs with angioplasty is a feasible and successful therapeutic therapy for the management of advanced DFU.[127]

Studies of how hUC-MSCs work have also shown that the exosomes made by these cells are stable and immune-stimulating. They may also carry protein molecules and growth factors that have different roles and have different effects.[129] Exosomes made by hUC-MSCs have been shown to control both the growth and differentiation of BM-MSCs.[130] Yan et al.[107] investigated the impact that hUC-MSCs and hUC-Exos (exosomes released by hUC-MSCs) on the healing process of diabetic wounds. They demonstrated that hUC-MSCs regulate the expansion and activity of endothelial cells, as well as promote the healing of injuries by releasing exosomes. Through the promotion of angiogenesis and the alleviation of oxidative stresses, hUC-Exos was able to hasten the process of wound repair. The results of this research suggested that the treatment of diabetic cutaneous wounds may be accomplished via the use of a mixed injection, which could lessen the burden that diabetes places on both the medical system and the economy. Additionally, the application of this therapeutic strategy in the management of diabetic wounds in the future may hold great promise.[107] CORLICYTE® is a novel hUC-MSCs therapy that just passed phase I clinical trial.[131] CORLICYTE® was tested on nine patients with chronic DFU, and all patients experienced a marked reduction in wound size without any adverse effects.[132]

4.2.3 | Adipose-derived MSC therapy in DFU

In comparison to BM-MSCs, AMSCs have emerged as a viable option for cell treatment since they are easy to access and may be obtained from the subcutaneous region. They also originate from several locations and have more time to grow and change. When compared to the method of extracting BM-MSCs, the process of harvesting AMSCs is less invasive, causes less discomfort, and requires less invasive surgery. AMSCs derived either from the patient's own body, from a donor, or from a xenograft may be used. Furthermore, the immunosuppressive effect of these cells is roughly amplified by a factor of three.[133] In addition, compared to BM-MSCs, AMSCs have a higher ability for cell proliferation, which makes them an excellent candidate for use in cell-based therapies intended to treat persistent diseases.[134,135] Minimal ethical debates are necessary due to the fact that AMSCs may be isolated from adult fat obtained from the patients themselves.[136] Numerous investigations also demonstrate that AMSCs speed up the healing process by releasing angiogenic cytokines, inhibiting inflammation and apoptosis, and boosting the production of epithelization and granulation tissue development.[137,138] According to research by Cianfarani et al.,[139] DM inhibits the activity of AMSCs and alters their intrinsic characteristics, which in turn limits the ability of these cells to heal DFU in diabetic rat models. Also, AMSCs from diabetic mice were less able to release vascular endothelial growth factor A (VEGF-A), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF).[140] Kim et al.[140] examined the level of wound repair in mice that had been handled with either ordinary AMSCs or AMSCs produced from diabetic mice. They found that the regular AMSCs group had a higher percentage of dermal renewal, granulation tissue development, keratinocyte expansion, reepithelization, and overall wound healing. Nevertheless, the diabetic AMSCs were still able to maintain their ability to cause angiogenesis and neovascularization.[140] On the other hand, Rennert et al.[114] found that diabetic AMSCs are unable to effectively promote neovascularization and wound recovery. Based on the results of this study, there is a limited role for autologous AMSCs in cellular therapies for diabetic patients, and pretreatment steps to enhance the activity of cells are required.[114] Fromer et al.[111] investigated the potential of the secretome of human endothelial cells to counteract the detrimental impact of elevated glucose levels on AMSCs. This was achieved through a process known as priming, which enhances the regenerative and angiogenic capabilities of AMSCs in murine models. However, it is important to note that further investigation is required to simulate these findings in clinical trials.[111] In addition, research that evaluated the healing process has shown that adding platelet-rich plasma (PRP) to AMSCs has favorable benefits. PRP particularly acts as a strong paracrine effector and cellular carrier, which increases the potency of transferred cells to be utilized in treatments.[141] Moon et al.[115] reported that the allogenic AMSC-hydrogel complex is an effective and safe treatment option for DFU, as this complex can promote a significant complete wound closure after 12 weeks in the study group compared to a control group. Interestingly, this complex is now on phase III clinical trial and registered with ID (NCT04569409), but this trial is not completed.[142] So, it can be concluded that the use of allogeneic normal AMSCs instead of autologous diabetic and damaged AMSCs is a better way to treat wounds in people with diabetes.[140] In another study, the effects of implanting AMSCs in autologous platelet-rich fibrin (PRF) were compared to the effects of using PRF alone to treat chronic DFU healing. They followed this regimen since it is thought to be a more effective and efficient healing method than standard persistent wound care.[112] According to Khalil et al.,[112] individuals who received AMSCs in addition to PRF showed better wound healing than those who just received PRF. Their findings are in line with previous research suggesting that MSCs release significant amounts of VEGF

and HGF and have a higher proportion of transforming growth factor-3 to TGF-1, which leads to cell growth, migration, matrix deposition, and enhancement of vascular angiogenesis.[112]

4.2.4 | Placental-derived MSC therapy in DFU

PD-MSCs have been used in a limited number of clinical trials involving humans for the management of DFU. Although BM-MSCs are the most common source of mesenchymal cells, PD-MSCs are a better option for several reasons. It is simple to get PD-MSCs, and doing so does not give rise to any ethical concerns and the human placenta is less immunogenic than BM. Finally, a greater quantity of stem cells may be separated from the placenta than from BM.[143,144] Along with their capability to secrete substances that may speed up the healing process of wounds, it has been shown that PD-MSCs have an impressive ability to transform into a wide variety of cell kinds.[143–146] In a clinical trial, Zeng et al.[116] investigated the effect of PD-MSCs hydrogel on the healing process of DFU. According to the findings of their study, the use of PDMSC hydrogels led to a reduction in wound size after 3 weeks, resulting in a shorter healing time as well as the production of dense granulation tissue that aids in wound recovery.[116] PD-MSCs secrete paracrine factors, stimulate vascular development, and modulate the immune system, all of which contribute to their potent healing impact in DFU. However, Zeng et al.[116] argued that larger patient samples are required for future research. Further research by Du et al.[147] revealed that PD-MSCs had the potential to speed up the healing process of ulcers via the generation of various cytokines and HGF, in addition to the paracrine activities that encouraged angiogenesis, which is a process that is involved in wound repair.

In another study, Meamar et al.[118] investigated the efficacy of nanofibers infused with PD-MSCs and PRP for the treatment of DFU. In this trial, PD-MSCs coated with PRP gel, and a control group receiving routine wound care were used to treat ulcers over 12 weeks. Additionally, Meamar et al.[118] found that the size of wounds decreased by 66% and 71% in the PD-MSCs-treated and PD-MSCs + PRP gel-treated groups, respectively, but only by 36% in the control group. Both the PD-MSCs and PD-MSCs + PRP gel groups outperformed the control group in terms of wound healing and pain-free walking distance. Biopsies taken from patients in both the PD-MSCs and PD-MSCs + PRP gel treatment groups revealed the growth of new blood vessels.[118] In a more recent investigation, DaVanzo et al.[119] compared the results of individuals with DFU who underwent therapy with a cryopreserved placental membrane containing viable cells (vCPM) to those of individuals managed with other cellular- and tissue-based products (CTPs). The success of the therapy was evaluated based on two different metrics: the decrease in the incidence of after-treatment ulcers and the decrease in mortality after 1 year. The results showed that vCPM had a significant reduction in ulcers when compared to CTP treatment, and it was able to cut mortality by 2.3 percentage points (13%–13.8% change) after 1 year when compared to other CTPs. The decline in mortality was due to the fact that vCPM was effective in reducing the number of ulcers that were present.[119]

5 | MECHANISMS OF MSCs IN THE TREATMENT OF DFU

The physiological mechanisms of DFU wound healing and growth include cellular expansion, differentiation, and relocation. Damage to living tissues results in wounds, and the process of coordinating wound healing begins as soon as the tissue surface is compromised. Throughout the process of repair, cytokines and growth factors work to enhance cell differentiation, expansion, movement, and protein synthesis by stimulating signal regulation and coordinating intracellular and intercellular signaling processes. Recent research has shown the critical role played by numerous growth regulators and molecular pathways in the emergence and progression of DFU.[148,149]

5.1 | MSCs induce angiogenesis by releasing several growth factors and regulators

Vascular destruction and lesions of the vessels are major causes of DFU. The regrowth and formation of new blood vessels in the ulcer zone supply nutrients for the growth of granulation tissue. Therefore, it is crucial for reducing ulcer size and encouraging healing. Extensive research has shown that MSCs release many different types of cytokines, such as epidermal growth factor (EGF), VEGF, IGF-1, keratinocyte growth factor 2, basic fibroblast growth factor, stromal cell-derived factor-1 (SDF-1), and placental growth factor-2. Wound healing, vascular development, and improved microhemodynamics are all aided by the presence of these substances.[150,151] Additionally, another study showed that MSCs derived from the mouse's liver stimulate local growth factor production. These growth factors include SDF-1, EGF, and VEGF. As a result, the formation of new blood vessels is promoted, cell recruitment to the wound is improved, and the contraction of wounds is enhanced (Figure 1).[152–154] Furthermore, BM-MSCs can greatly boost the production of important growth factors like VEGF and EGF, which are necessary for the repair and regeneration of damaged tissues. They have been shown to improve the healing of wounds in diabetic rats by elevating collagen levels (types I–V).[155] Shen et al.[156] have demonstrated that BM-MSCs can accelerate the healing of DFU in mice models by enhancing vascular endothelial cell activation and enhancing angiogenesis through paracrine VEGF and other vasoactive factors. Wan et al.[157] discovered that foot ulcers in diabetic rats healed more quickly after BM-MSC transplantation because VEGF production in the injured area was enhanced and angiogenesis was stimulated. Diao et al.[158] demonstrated that VEGF may enhance transcription factors for controlling endothelial progenitor cells (EPCs), recruit EPCs to the BM, inhibit EPC death, and assist wound healing, in addition to directly stimulating angiogenesis. According to the findings of these investigations, MSCs can promote angiogenesis in the ulcer region

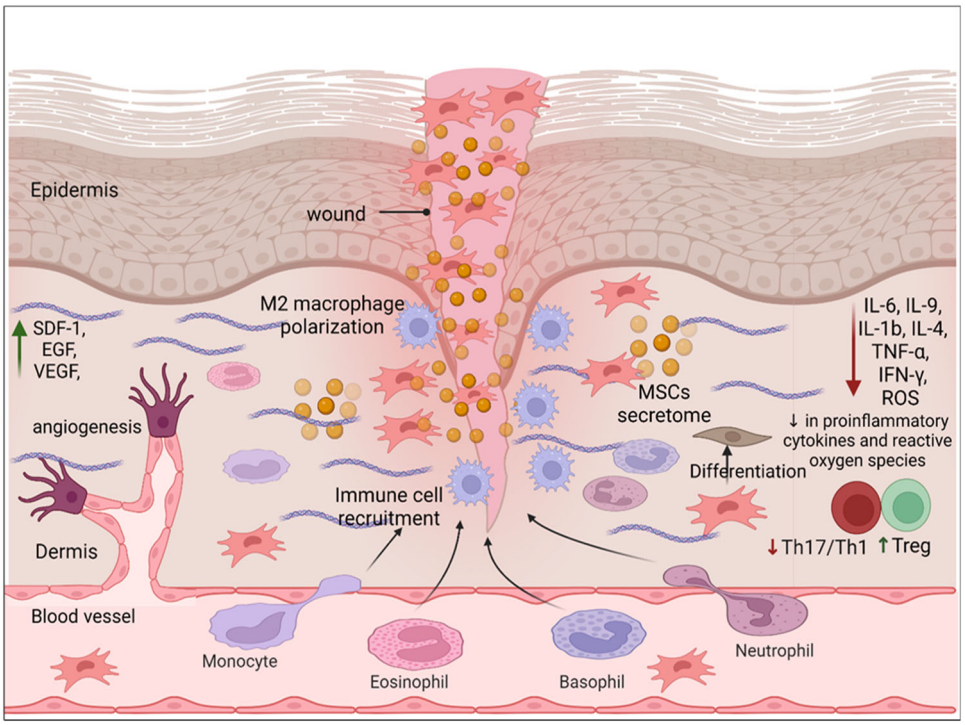

FIGURE 1 Role of MSCs and their secretome in promoting wound healing in DFU. MSCs and their secretome can promote DFU healing through release of growth factors like EGF, VEGF, and SDF-1 that promote angiogenesis, induce cell migration and regulation of wound tissue microenvironment, enhance epithelialization through differentiation and proliferation of fibroblast and keratinocytes, immunomodulatory effect through M2 macrophage polarization, increase Treg activation and inhibition of Th1 and Th17, and reduce inflammation and oxidative stress through inhibition of proinflammatory cytokines and ROS. Adapted from Yu et al.,[152] El Hage et al.,[153] Badillo et al.[154] DFU, diabetic foot ulcer; EGF, epidermal growth factor; MSCs, mesenchymal stem cell; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

directly or indirectly by releasing paracrine growth factors. This increases blood flow and accelerates DFU repair.[16]

5.2 | MSCs inhibit inflammatory T cells and activate regulatory T cells

MSCs not only have the potential to develop into a variety of different kinds of cells, but they also have a regulatory function in the immunological and inflammatory processes that the body has. Many research investigations demonstrate that following damage to a tissue or cells, MSCs can be triggered by inflammation-related cytokines to regulate the process of tissue repair. They do this by launching several substances that can increase the growth and differentiation of progenitor cells while also playing a role in immune system regulation and preventing inflammatory reactions. This is the case after a cell or tissue has been damaged.[159–161]

Inflammation can be mediated by both T helper 1 (Th1) and T helper 17 (Th17) cells[162] (Figure 1). T regulatory cells (Treg) are a subset of specialized immune-suppressive T cells that express CTLA-4 and CD25 on their surfaces and FoxP3 in their nucleus, therefore, preserving immunological self-tolerance and homeostasis.[163,164] In a study by Li et al.,[165] 15 DFU patients who were receiving insulin treatment also received hUC-MSC transplants. Following the transplantation, levels of blood sugar and insulin dosage fell in all 15 individuals. After 4 weeks following the transplantation, there was a considerable rise in the ratios of CD4 + CD25 (hi) FoxP3 + Treg/Th17 and CD4 + CD25 (hi) FoxP3 + Treg/Th1 cells. However, the ratios of Th17/Th1 cells remained stable, and there was a peak in blood levels of VEGF.[165]

5.3 | MSCs reduce proinflammatory M1 macrophages and enhance anti-inflammatory M2

M1 macrophages are characterized by the release of proinflammatory molecules that boost immunity against infections and have significant bactericidal properties, as well as trigger tissue death and inhibit angiogenesis.[166,167] M1 macrophages are distinguished from other types of macrophages by their heightened capacity to release IL-18, IL-1b, reactive oxygen species (ROS), tumor necrosis factor (TNF), and IL-12.[168] M2 macrophages, on the other hand, are thought to fight inflammation and aid in cell regeneration. M2 macrophages express IL-10, Arginase 1, CD206, and chitinase 3-like 3, resistin-like-α.[169] Molecular analysis suggests a role for these substances in angiogenic promotion, parasite infections, tumor immunomodulation, and tissue remodeling.[170] Proinflammatory M1 macrophages penetrate the ulcer in the early stages of healing and clear out any germs, cell debris, or

unwanted objects they find.[171] As the tissue begins the healing process for an acute ulcer, the M1 macrophage pool transforms into an M2 type. M2 cells immediately begin the process of fighting inflammation and repairing damaged cells.[172] When proinflammatory macrophages with the M1 pattern fail to switch to the anti-inflammatory M2 type, tissue healing in chronic wounds is stunted.[173,174] Macrophages are stimulated to generate proinflammatory mediators in response to a chronically excessive glucose situation in vivo. These cytokines include IL-1b, ROS, IL-6, and TNF-α. This leads to a downward spiral of permanent M1 macrophage populations and a consistently elevated degree of inflammation in DFU.[175] Dayan et al.[176] thought that co-culturing human BM-MSCs and hUC-MSCs with macrophages might reduce the number of macrophages and monocytes in the body as a whole. This reduction would include a reduction in the number of macrophages with the M1 phenotype that contribute to inflammation. In contrast, there was a considerable increase in the number of M2 anti-inflammatory phenotypes that had undergone alternative activation.[176] To treat diabetic mouse wounds, Chen et al.[177] loaded 3D nanofiber structures with mouse BM-MSCs. They found that there were more M2 macrophages than normally activated M1 phenotypes, which helped diabetic mice heal faster from wounds.[177] Vascular endothelial cells' ability to function properly is dependent on the release of PGE2 by hUC-MSC. This is accomplished by the modification of macrophage phenotypes, which then leads to an improvement in the surrounding microenvironment of the vascular endothelial cells via the production of VEGF and IL-10. Controlling the change from M1 to M2 macrophage phenotypes in diabetic wounds boosts angiogenesis, which helps the wounds heal.[16,178] On the other hand, to help the body fight against infections, M1 macrophages release cytokines that trigger an inflammatory response. These macrophages are also quite effective in killing bacteria. Thus, the shift from an M1 to an M2 phenotype in mice may reduce their resistance to disease and make them more vulnerable to certain infections.

5.4 | MSCs reduce inflammation and oxidative stress

ROS at high concentrations cause oxidative stress and immune system reactions that damage and impair cells, while low ROS levels are favorable for sustaining survival, proliferation, and differentiation.[179] Phagocytes digest microorganisms, cell debris, or apoptotic inflammatory cells after tissue injury. Long-lived neutrophils produce a significant amount of ROS following phagocytosis, leading to a respiratory burst that damages tissue. MSCs may function as antioxidants by paracrine inhibition of protein oxidation and lipid peroxidation or through direct cell interaction, according to numerous publications.[16,180,181] MSCs have been shown to lower inflammation and oxidative stress in a variety of disorders. These effects include a decrease in the production of enzymes that make ROS, like inducible nitric oxide synthase, myeloperoxidase, and nitrogen oxides, as well as a decrease in the production of cytokines that cause inflammation, like IL-6, IL-9, IL-1b, IL-4, TNF-α, and interferon-γ.[182,183] MSCs have the ability to directly lower ROS as well as myeloperoxidase in activated macrophages and monocytes, which in turn inhibits the proinflammatory phenotypes of these cell types.[184,185] The presence of MSCs significantly reduced the formation of ROS in macrophages. This was accomplished by boosting the release and expression of stanniocalcin (STC)-1 as well as suppressing caspase-1 activation, the NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome, TNF-α, and IL-6 transcription, and IL-1b production.[184] Additionally, it has been demonstrated that PD-MSC transplantation can speed up the healing of diabetic wounds by reducing cytokine levels such as TNF-α, IL-1, and IL-6, and by slowing down the signaling of nuclear factor kappa B.[146] Raffaghello et al.[186] found that BM-MSCs had the potential to inhibit ROS production without compromising neutrophil phagocytic activity. This was accomplished by inhibiting apoptosis in neutrophils, activating them, and preventing them from engaging in inappropriate or excessive oxidative metabolism.[186] Exosomes that are released by human AMSCs have the ability to slow the progress of DFU by suppressing the aging of EPCs and reducing the generation of ROS and cytokines that trigger inflammation.[187]

5.5 | MSCs induce cell migration and regulate the wound tissue microenvironment

Recent research has demonstrated that several different molecular pathways, such as cell signaling processes, perform essential functions in the pathogenesis and DFU healing mechanisms.[188–190] A protein-serine-threonine kinase (AKT) serves as a crucial hub for cellular signaling involved in many different processes. MSC survival, expansion, movement, and angiogenesis are all further influenced by PI13-dependent AKT activation; this pathway has a fundamentally important regulatory function.[190] According to the findings of Hou et al.,[191] the conditioned medium of BM-MSCs prompted human umbilical vein endothelial cells to migrate and proliferate more quickly. These activities were reliant on the extracellular signal-regulated kinases (ERK) signaling pathway but had a tight relationship with the AKT signaling system.[191] Jun et al.[192] showed that hypoxia causes an increase in the release of paracrine substances by amniotic fluid-derived MSCs (AF-MSCs) and that hypoxic-conditioned medium from AF-MSCs (AF-MSC-hypoCM) enhances the healing process through the promotion of the migration of cells and the stimulation of the TGF-β/SMAD2 and PI3K/AKT pathways. This suggests that AF-MSC-hypoCM might be employed for the management of wound regeneration and marks left after operations. In addition, AF-MSC-hypoCM has the potential to provide a different pharmaceutical option for use in the medical and aesthetic industries, which would increase the efficiency of tissue repair.[192] According to the findings of Liu et al., chemokine receptor-4 and SDF-1 both play significant roles in the regulation of BM-MSCs to enhance the healing of DFU.[193] It is interesting to note that combination therapy with PRP and rat ADSCs enhances angiogenesis, activates epidermal stem cell

expansion and recruitment through regulation of the Notch system, and greatly speeds up the repair process of diabetic lesions induced in rats in an experimental setting.[194] These observations provide credence to the hypothesis that the Notch signaling system represents a novel and potentially promising targeted therapy for diabetic wounds.[195,196]

MSCs have been proven to be able to discriminate into epidermal cells and function as epidermal cells in vitro investigations using a variety of different induction techniques.[197,198] Kato et al.[199] used BM-MSCs to heal foot lesions in both diabetic and normal rats. They observed that the levels of phosphorylated focal adhesion kinase went back up once human keratinocytes were grown in BM-MSC-conditioned media with higher glucose concentrations. Also, levels of IGF-1, EGF, and matrix metalloproteinase-2 were found to be higher. This suggests that BM-MSCs may be able to help diabetic foot model mice heal wounds faster by making keratinocytes work better.[199] Also, wounds treated with BM-MSCs encourage the growth of keratinocytes and endothelial cells and the movement of macrophages, keratinocytes, and endothelial cells into the injuries of model animals, which speeds up the repair mechanisms.[200] Considering the findings of another investigation, BM-SCs greatly increased the number of keratinocytes in the injury site, increased the production of new blood vessels, sped up the rejuvenation of epithelial cells in the injured area, and made wounds heal faster.[201] In addition, hUC-MSCs can precisely localize to the specific wound tissues in a rat model of DFU, boost the release of cytokeratin 19, encourage the creation of keratinocytes and extracellular matrix (ECM), and enhance the renewal of epithelial cells in wounded areas.[202] Even though MSCs have been shown in a plethora of studies to be able to differentiate into endothelial cells and keratinocytes, the consequences of their engraftment are still up for debate. It has been hypothesized that MSCs have the capacity to differentiate into keratinocytes under certain conditions; however, MSCs do not possess the full complement of keratinocyte-specific expression markers.[203]

6 | ROUTS OF ADMINISTRATION OF MSCs IN DFU

Stem cell therapy used for treating DFU can be given in one of two ways. Research shows that each of the local and systemic approaches is beneficial in resolving DFU. Among the several methods of cell administration, local injection is by far the most common. Clinical trials typically employ intramuscular administration. The most common routes of administration in preclinical research are intradermal and subcutaneously administered injections.[17]

Systemic cell administration may be carried out endovascularly, for example, through intravenous or intraarterial injections. During angioplasty, it is possible to provide the drug systemically, where it can have an immune-modulating function and enhance the physiological balance of glucose. However, there is a substantial potential for surgical risks, poor engraftment, and high costs associated with this mode of administration.[17]

Topical uses have been more prevalent in preliminary studies than in clinical settings. Hydrogels, sprays, drops, and scaffolds are examples of topical administration methods, and ECM scaffolds have attracted scientific attention. The ECM is regarded as the primary regulator of cell regeneration, expansion, and differentiation.[17] The ability of hydrogel and collagen scaffolds to simulate the in vivo conditions for stem cells results in an increase in cell functionality,[204] engraftment, and retention.[205–208] In topical administration, there is minimal risk involved; it is simple, and in most circumstances, other than those involving hydrogels and scaffolds, it is believed to be quite affordable. However, before treating the wound, local cell administration might require debridement of the wound area.[17]

Chiang et al.[209] conducted research in which they assessed the effectiveness of medically employing autologous stem cells in several transplantation techniques, including intramuscular injection, topical application, and intraarterial injection. The researchers found that the group that received stem cell injections through the intramuscular route had a considerably better rate of full healing compared to the group that received treatment via the intraarterial route. According to Chiang et al.,[209] the findings might be connected to the fact that people who suffer from DM face microvascular difficulties or arterial occlusion, both of which result in significant ischemia of the limb, which in turn leads to peripheral perfusion. Considering that cells are carried closer to the wound area when intramuscular delivery is used, this problem might be eliminated.[209] Also, muscular tissues are able to provide infused cells with nutrients and oxygen, which contributes to the improvement of their function as well as their chances of survival.[210] According to several investigations, the intravascular infusion of stem cells may cause the cells to get lodged in the lungs, which can result in a pulmonary embolism. As a consequence of this, the injection of stem cells through the intramuscular route seems to be the method that is both safer and more successful.[209] Regarding the topically applied treatment of autologous stem cells, Chiang et al.[209] observed that it was successful in the wound repair process, as indicated in earlier research. They also reported that topically applied medication helps with cellular metabolism, cell differentiation, and migration.[209] By increasing ECM production and regeneration of tissues, topical application may also reduce the length of the therapy time, which in turn enhances the rate of survival of the transplant.[211,212] According to these findings, administration through intramuscular and topical routes is more efficient than treatment via intraarterial routes.[209]

7 | BIOMATERIALS AS MSC DELIVERY SYSTEMS

There are some drawbacks related to the topical delivery of MSCs through direct injection. Two of these drawbacks include limited cell survival and reduced cell adaptation at the wound site. As a result of this, many biomaterial conformations have evolved as vehicles for the transport of MSCs, to enhance cell survival and persistence at the site of implantation.[4,213] Scaffolds have been proposed as a solution to

these issues because they offer a three-dimensional framework for the movement of cells, their proliferation, and differentiation while also increasing cell survivability and retention at the wound site (Figure 2).[213,214]

7.1 | Scaffold-based delivery system

7.1.1 | MSC distribution through hydrogel scaffolds in diabetic models

Hydrogel scaffolds evolved as vehicles for the transport of MSCs to enhance cell survival and persistence at the site of implantation.[4] Scaffolds have been proposed as a solution to these issues because they offer a three-dimensional framework for the movement of cells, their proliferation, and differentiation while also increasing cell survivability and retention at the wound site.[214]

Hydrogels are 3-dimensional structures that can expand and retain a substantial amount of water inside their framework. These networks may be made of natural, synthetic, or mixed polymers. Because of their potential to preserve the viability of cells at the site of implantation and their versatility in terms of manufacture, hydrogels have gained a lot of attention in the discipline of treatments related to wound repair in the past few years.[215,216] The hydrogels that are naturally produced have shown a number of beneficial properties, including biocompatibility, biodegradability, inherent biological interactions, and structural resemblance to genuine human tissue.[217] Natural hydrogels, on the other hand, have several drawbacks, such as a restricted range of mechanical characteristics and variable results from batch to batch.[218] Composite hydrogels that blend natural and synthetic materials to achieve the desired form and function are becoming more popular.[219]

Hydrogel-mediated human MSC administration enhanced wound repair in db/db mice, with microhydrogels generated from human

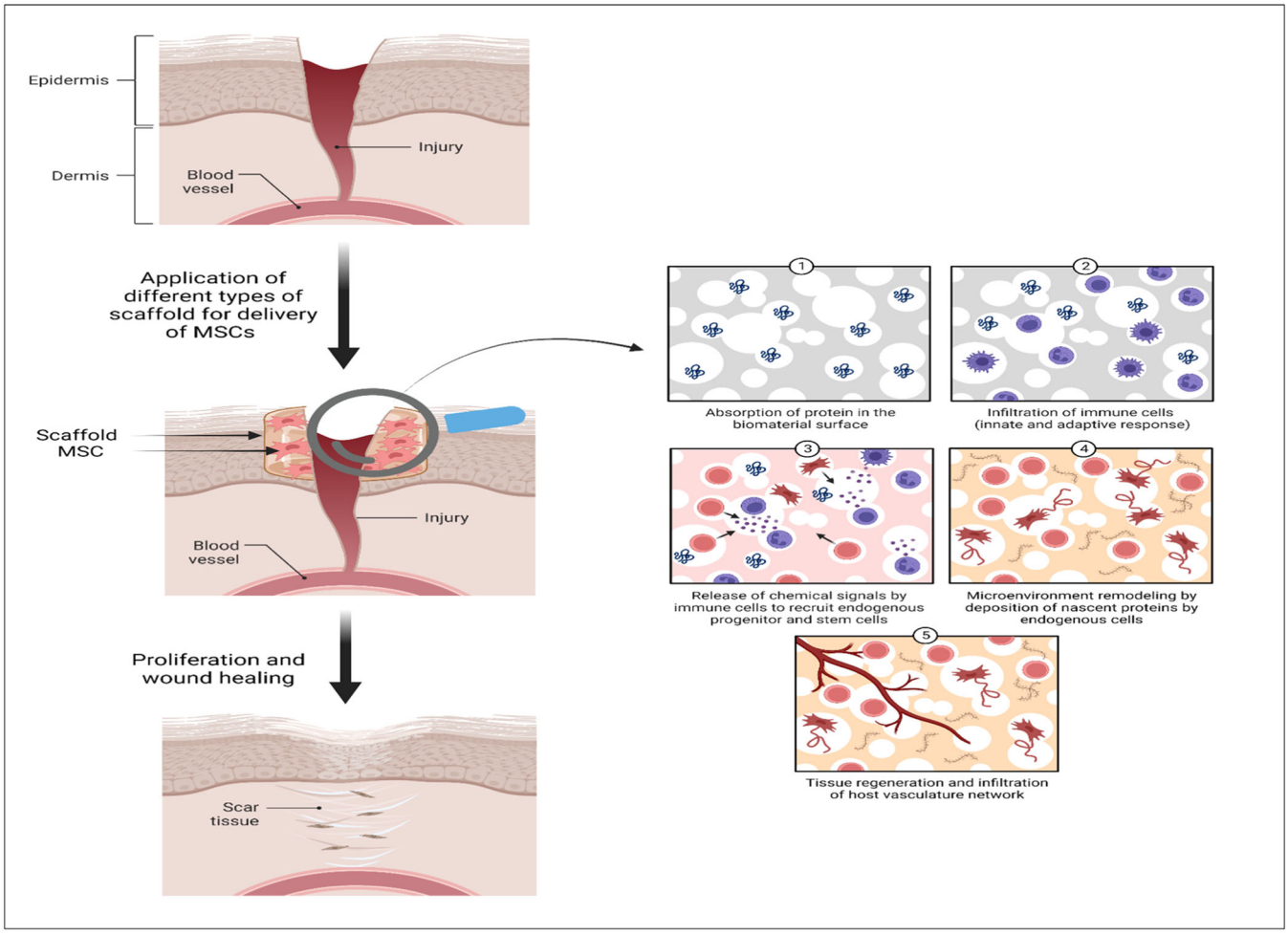

FIGURE 2 Role of a scaffold-based delivery system in delivering MSCs and promoting their wound healing action. MSC delivery can be improved by employing scaffolds and grafts that simulate or preserve the architecture of human tissue, creating a favorable milieu for MSCs to adhere, proliferate, and retain their secretome in addition to directing host cell migration. The secretome of MSCs encourages the migration and infiltration of immune cells (lymphocytes, macrophages, and neutrophils) that will control the inflammatory and immunological response in the wound area, boosting angiogenesis and enhancing wound healing. MSCs, mesenchymal stem cell.

AD-MSCs showing faster wound epithelial growth and thicker dermal development compared to control and hydrogel-alone groups.[220] For treating wounds related to diabetes in mice, human AD-MSCs have also been administered in the form of a hydrogel composed of hyaluronic acid and gellan gum. In this research, an enhanced influence on the neovascularization of diabetes wounds was seen, and the epidermis of the cured diabetic lesion was revealed to be thicker as well as more discriminated than the epidermis of the diabetic lesion that had received no therapy.[221] An additional investigation found that using a PEGDA hydrogel to encapsulate a combination of human BM-MSCs and rat insulin-secreting cells enhanced diabetic wound repair approximately three times quicker than in the control groups.[222]

7.1.2 | MSC delivery through sponge scaffolds in diabetic models

Sponge scaffolds could be prepared from synthetic or natural polymers by various techniques, such as gas foaming, porogen leaching, and freeze-drying. They are very porous and have a consistent network of pores that are linked together.[223,224] Sponge scaffolds are excellent for directing cell migration to an injury site because their porous structures are identical to those of the ECM.[225] Because of their capacity for absorption and storage of water, sponge scaffolds afford a model environment for the proliferation and migration of cells in the wound site.[226] The majority of MSC carriers used for diabetic wound repair are collagen- and chitosan-based sponge scaffolds. O'Loughlin et al.[227] created collagen sponge scaffolds by using the freeze-drying technique. Seven days after delivery, allogeneic BM-MSCs supplied topically through a collagen sponge scaffold facilitated faster wound repair and increased angiogenesis in diabetic rabbit wounds compared to the no-treatment control group.[227] This sponge scaffold created an environment where hypoxia-pretreated rat BM-MSCs could survive while secreting more angiogenic factors like platelet-derived growth factor and VEGF and upregulating the expression of essential transcription factors like HIF-1α. Additionally, the researchers constructed a chitosan-collagen scaffold that included simvastatin. This scaffold had great porosity, adequate mechanical strength, and elasticity comparable to that of human skin, and simvastatin was released in a regulated manner from the scaffold.[228]

The delivery of MSCs derived from rat epidermis via this scaffold led to an improved wound healing rate, boosted vascularization, increased viability, and expanded MSCs in diabetic rat wounds in comparison with a control group that received no therapy and a group that received just the scaffold.[229] In an additional investigation, a sponge scaffold made of polyurethane and glycol chitosan was used to insert rat-derived AD-MSCs into STZ-induced diabetic rat injuries. This method, when utilized together with acupuncture, generated complementary immune-modulating outcomes, which led to better wound healing with full re-epithelialization in a span of 8 days compared to what the AD-MSC alone group experienced.[230] Additionally, sponge scaffolds may couple with growth factors to function as a means of delivery for cells. When BM-MSCs from BALB/c mice were delivered via alginate-chitosan-sponge scaffolds conjugated with EGF, wound healing in diabetic rats was significantly better than in the no-treatment control and MSC-alone groups. This was because more granulation tissue developed, more collagen accumulated, and more blood vessels grew.[231]

7.1.3 | MSC delivery through fibrous scaffolds in diabetic models

Fibrous scaffolds are primarily created using an electrospinning technique to produce 3D constructions made of fibers at the micro- or nanoscale level to imitate the structure of normal human cells.[232–234] Vascular, cartilage, bone, skin, and neurological tissue engineering are a few examples of the many applications of fibrous scaffolds.[235] Because of their potential to operate as a structural model, enhance cell-to-cell and cellular-matrix communications, and influence cellular behavior and function, fibrous scaffolds have been the subject of an increasing body of research in the discipline of wound healing in recent years.[235]

When it comes to diabetic wound healing, fibrous scaffolds have been employed to transport MSCs for diabetic wound repair. Using gelatin, pluronic-F-127, and polycaprolactone, Chen et al.[177] have created a 3-dimensional scaffold for the delivery of mouse BM-MSC. In the wound site of diabetic mice, this fibrous scaffold-MSC composite improved granulation tissue development, blood vessel formation, and the accumulation of collagen in comparison to no-treatment and scaffold-alone controls.[177] To enhance the development of new vessels and healing of wounds in diabetic mice, an integrated electrospinning nanofiber scaffold composed of 10% collagen, 10% silk, and 80% polylactic acid has been created as a cell transporter for supplying HO-1-overexpressing human BM-MSCs to the injury site.[191] In addition, a polycaprolactone and aloe vera-based fibrous scaffold was developed for injecting human UC-MSCs or their conditioned media into the site of damage in db/db mice. After 28 days of implantation into the ulcers, both therapies showed rapid wound healing, re-epithelialization, and a rise in the number of sebaceous glands and hair follicles, with no substantial distinction seen between the two medications.[236] After receiving both medications, the wound showed signs of healthy keratinocytes and increased production of ICAM-1, VEGF-A, and tissue inhibitor matrix metalloproteinase 1 at days 14 and 28. Interestingly, in a wound model using db/db mice, a silk fibroin scaffold loaded with human AD-MSCs accelerated wound healing from 15 to 17 days to just 10 days.[237]

7.1.4 | MSC delivery through decellularized grafts in diabetic models

Decellularized transplants are often obtained from organs or tissues by undergoing decellularization processes that are either enzymatic (for instance, trypsin and pepsin), mechanical (e.g., force and

freezing), or chemical (such as acid and Triton) to eliminate the cellular components of the donor material.[238] Organs and tissues that are frequently utilized include adipose tissue,[239] skin,[240] Wharton's jelly,[241] and in vitro cultivated cells.[242] Unlike other synthetic scaffolds, decellularized transplants still have their original ECM constituents, such as fibronectin, collagen, elastin, and laminin, and their original anatomical structure. They also do not stimulate the immune system.[239,242] These benefits are very necessary in the process of identifying and constructing scaffolds that may be implanted in diabetes-related wounds. Decellularized grafts can restore the damaged ECM of diabetic ulcers by supplying ECM proteins like proteoglycans, collagen, glycoproteins, and glycosaminoglycans, thereby facilitating infiltration of host cells, modulation of the immune system reaction, promotion of new blood vessel formation, and granulation tissue development.[243,244]

Decellularized grafts have been extensively studied as a potential MSC transport system. Among these investigations, one found that diabetic rat AD-MSCs implanted on a decellularized transplant released cytokines (such as VEGF, TGF-β, HGF, and bFGF) that increased the movement and development of fibroblasts, leading to better wound healing.[245] In a different investigation, a graft made from decellularized mouse skin was utilized to transfer mouse BM-MSCs. In comparison to untreated controls, a full-thickness cutaneous wound area in diabetic mice treated with this bio complex showed higher rates of wound closure and dramatically faster angiogenesis and re-epithelialization. The use of a modern multiphoton microscope revealed an enhanced production of collagen type I fibers throughout diabetic wound repair, suggesting a potential pathway for wound recovery.[240] High levels of stability and robust mechanical qualities have been shown in a decellularized dermal matrix that incorporates reduced graphene oxide as a scaffold for cell administration. Mice BM-MSCs have been effectively transferred into a wound model of a diabetic mouse using this decellularized graft. This creates an ideal environment for stem cells to stick together, move around, and multiply, as well as strong blood vessel growth and collagen buildup.[246] In addition, the delivery of human UC-MSCs by a decellularized dermal differentiation matrix to diabetes-related rat lesions demonstrated that the growth and discrimination of human UC-MSCs on the decellularized dermal matrix were controlled by triggered Wnt signaling pathways.[247]

7.2 | MSC delivery through bionanomaterials in diabetic models

Nanomaterials are distinguished by their exceptional physicochemical and biological characteristics. When compared to other types of wound healing materials, it has been demonstrated that nanomaterials can promote quicker wound repair. They have antioxidant and antimicrobial properties, exhibit specific anti- and proinflammatory effects, and promote angiogenesis. They can be used by direct application to the wound or assimilated into scaffolds to generate hydrogel matrices or nanocomposites. All these properties make them useful for promoting wound healing in a variety of ways. Due to their higher surface-to-volume ratio, nanomaterials can be employed for more than just drug transfer. They have been used in stem cell treatments to speed up wound recovery.[248]

It is possible to enhance the development of skin stem cells into fibroblasts and keratinocytes through the application of therapeutic nanomaterials during the wound-healing process.[249] In their in vitro trials, Danková et al.[250] succeeded in promoting the growth of MSCs by mixing polycaprolactone nanofibers with integrated magnetic nanoparticles. In another investigation, it was shown that polycaprolactone nanofibers, when mixed with plant-derived extracts from Myrtus communis, exhibited a protective effect on skin MSCs that had been aged by UV rays. Regarding the various alternatives for skin regeneration, this knowledge might be extremely valuable.[248]

Başaran et al.[251] created a bionanomaterial with the potential for regeneration of the skin by encapsulating heparin in poly (lactic-co-glycolic acid) (PLGA) nanoparticles and incorporating it into sericin and gelatin nanofibers. This method demonstrated controlled medication release as well as a high capacity to retain water and minimal degradation rates. As a consequence of combining this system with the biopolymers gelatin and sericin, a potent medication delivery system was created for topical application in skin regeneration.[251] However, at this time, no therapeutic application of nanofibers for accelerating the healing of wounds in humans has yet been reported. To this day, it has not been able to achieve complete rejuvenation of the structural and functional qualities of the skin. Despite this, there is still a significant amount of work to be done on the research and enhancement of nanofibers for use in tissue engineering. This is because nanofibers offer a potentially effective therapeutic method.[252]

8 | ADVANTAGES OF MSC-BASED THERAPY

The benefits of MSCs in comparison to those of other kinds of stem cells are outlined in the following paragraphs: unlike ESCs, which must be derived from human embryos, MSCs may be produced from adult cells and, hence, do not create ethical concerns when used for therapeutic purposes.[253–256] ESCs produced from embryos are allogeneic cells for the recipient and hence susceptible to immunological rejection.[257] However, MSCs display an immune privileged condition with little immunogenicity.[258–260] Because they express extremely low numbers of MHC class I antigens and lack the expression of MHC class II antigens or T cell costimulatory molecules.[261,262] MSCs are recognized for their capability to suppress immune system reactions, which may explain why they have been effective in treating graft-versus-host reactions and other immunological-mediated diseases.[263] MSCs are common and may be simply isolated from a diversity of tissues, like BM, adipose tissue, Wharton's jelly, and UCs, through a simple extraction method.[264,265] MSCs have a tendency to migrate to locations of tissue damage or tumors, regardless of whether they are supplied locally or

systemically.[266–272] Since MSCs are capable of being genetically modified in vitro, they have the potential to act as carrier cells for the transfer of genes.[259] Because of their capabilities for chemotrophic migration and the release of cytokines, MSCs facilitate the transport of a wide range of therapeutic medicines to cancerous, inflamed, or wounded tissues with minimal adverse consequences.[259,271,273,274] There was no substantial increase in toxicity associated with multiple administrations of fresh or cryopreserved MSCs.[275,276] Even with allogeneic MSC transplants, clinical studies haven't found any major side effects like organ system problems (such as cardiovascular and respiratory insufficiencies, etc.) or death right away or during follow-up procedures after MSC infusions.[276–281] Short-term investigations show that MSC therapy is harmless and tolerated properly, although the long-term effects of this therapy are unclear.[282,283] When compared to ESCs and iPSCs, the likelihood of malignancy or teratoma development upon administration of MSCs is much lower.[284–286] Also, it has been revealed that MSCs can cross the blood-brain boundary in a laboratory animal model of encephalopathy.[287]

9 | OBSTACLES AND CHALLENGES WITH MSCs TRANSPLANTATION THERAPY

MSC transplantation therapy is a relatively new approach that has shown substantial potential for the medical management of a number of illnesses, such as DFU. Unfortunately, there are still multiple significant challenges that need to be conquered before it can be used on patients in a clinical context.

The identification of the donors and tissues that would provide the MSCs of the greatest possible quality for usage in the treatment of certain patients is one of these challenges. The quality of MSCs might vary significantly from one donor to another.[288,289] Secondly, the absence of standardized protocols for dealing with MSCs.[290] There is a substantial level of variation in the quality of the cells, which is the principal obstacle in the way of standardizing the procedures for MSC.[291–293] In addition, aggressive separation procedures and a tedious cell culture approach.[294] MSCs have a poor rate of proliferation in vitro, which makes it difficult to scale up. For MSC therapy to be effective, it often needs a substantial number of cells to be administered.[295] There was evidence of the short-term survival of MSCs that had been injected exogenously in vivo.[296–298] After receiving systematic therapy, there was either ineffective recruitment or adherence to the desired cells, as well as a decline in the efficiency of the transplantation.[278,296,299–301] MSC treatment has been found to be safe in several investigations,[302,303] but MSCs should not be used widely in healthcare settings until serious safety issues, like genetic abnormalities, unintended growth of transplanted MSCs, and the possibility of cancer formation in vivo, have been thoroughly investigated.[304,305] Although preclinical and clinical investigations of MSC-based treatment have revealed promising results, these results are sometimes inconsistent and even contradictory.[306,307]

9.1 | General limitations and side effects of MSC-based therapy

Several studies on MSCs' therapeutic value have shown encouraging findings. However, in recent years, there have been several reports of unfavorable results and adverse effects after MSC therapy.[308] Before the use of allogeneic MSCs, patients are screened regularly to look for any signs of viruses, like the human immunodeficiency virus. However, transferred MSCs have the possibility of containing genes from other types of viruses.[309] According to research that was conducted by Sundin et al.,[310] MSCs from various kinds of organs have the potential to host persistent viruses. It was discovered that the healthy participants' MSCs carried viral genetic information from the B19 parvovirus. In addition to this, viral DNA was found in samples taken from human BM.[311] The most widespread viruses that infect MSCs are B19V, Merkel cell polyomavirus, human herpesvirus 7, Tornado tenovirus, and Epstein-Barr virus.[308,311] Additionally, a number of viruses, such as the avian influenza A H5N1 strain and the respiratory syncytial virus, may infect MSCs.[312,313] A further dangerous concern for cultured cells is contamination with mycoplasma. Numerous things, such as interruptions in laminar flow, insufficient sterilization cycles, inappropriate lab attire, and higher antibiotic doses in culture, might lead to mycoplasma infection.[314] Although the probability of xenocontamination is very remote, it is often linked to the presence of supportive xenogenic chemicals in cell products. Cryopreservation[315,316] and expanding media that contain human serum albumin, the patient's plasma, or fetal bovine serum are the most common causes of contamination.[317,318]

There is a large amount of variation in culture-expanded MSCs concerning the shape of cells, physiological functions, and activities; this variation is a key contributor to MSC heterogeneity.[319] As a consequence of this, cell-derived compounds and experimental models that can be duplicated under the same conditions may have affinities that are difficult to anticipate.[308] Røsland et al.[320] found that following a cultural period of a month, around 46% of human MSCs experienced a spontaneous transition into malignant cells. Several investigations have shown that extended cell culture is linked to a rise in chromosomal anomalies. Froelich et al.[321] found that the incidence of chromosomal abnormalities in AD-MSCs increased dramatically at passage 5.

A meta-analysis of prospective controlled studies found a substantial link between MSCs and short-term fever after intravascular injection.[276] Within 48–72 h of receiving an MSC intra-articular injection, patients experienced minor effusion and increased local discomfort.[322] Multiple animals and in vitro investigations have demonstrated that MSC injections promote tumor growth through a variety of mechanisms, such as the release of proangiogenic mediators and the suppression of the immune system.[323,324] Microthrombosis may manifest itself after MSC injections. Preliminary investigations have revealed that the majority of MSCs that are injected intravenously get stuck in the tiny capillaries of the lung parenchyma.[325–328] In treated individuals, this condition may cause multifocal pulmonary atelectasis and thrombus formation.[325,329,330]

The glomeruli and tubules of the kidney are more likely to be damaged when an excessive amount of cell therapy is administered.[331] Interstitial cell fibrosis and tubule atrophy were seen in a patient with chronic renal disease who had received an injection of autologous MSCs derived from adipose tissue.[332] Experiments have revealed that MSCs may differentiate into cells called myofibroblasts, which may result in the development of fibrous tissue.[333] Further systemic administration of these cells triggered the onset of serious negative consequences owing to the immunosuppressive characteristics of the MSCs. For instance, after an allogeneic HSC transplant, MSC therapy is linked to a higher likelihood of mortality from pneumonia.[334] The safety and effectiveness of MSC therapy for treating COVID-19 have been challenged due to the impact that MSCs have on blood coagulation.[335,336] In general, the unfavorable effects that were observed also included heart failure, allergic dermatitis, and reduced liver function, all of which are common aftereffects of life-threatening pneumonia.[337,338]

9.2 | Specific limitations and side effects of MSCs as a treatment for DFU

MSCs have shown promising effectiveness in treating DFU in both human and animal investigations.[104,115,339] However, recent clinical investigations have shown that MSCs in DFU may cause some unwanted side effects, including diarrhea, urticaria, elevated blood creatinine levels, nausea, high body temperature, and vomiting.[340,341] The therapeutic impact of stem cells may decrease with repeated passage in vitro because of a loss of multidirectional differentiation capacity and paracrine function.[152] Embryonic stem cells (ESCs) have a powerful capacity for proliferation but only a limited capacity for differentiation. The insertion of these cells may provoke a rejection response from the immune system and accelerate the growth of tumors. As a result, ESCs need to be kept as far away from DFU therapy as possible.[342–344] Furthermore, researchers have found that increasing the dose of locally injected stem cells to enhance the effectiveness of the healing process may also raise the likelihood of tumor formation.[345]

10 | CONCLUSION AND FUTURE PROSPECTIVE

The complex etiology of diabetic wounds and decreased wound healing abilities in diabetic persons continue to be an obstacle for the healthcare system and all medical professionals worldwide. DFU is a recent alarm worldwide as it significantly increases the worldwide amputation rate. It was documented that around one amputation occurs each second, and 84% of these amputations are due to DFU.[17] MSCs possess a highly beneficial impact on the management of DFU, and they also have the benefit of being administrated in conjunction with other therapies to more effectively treat resistant DFU. Several studies reported a promising effect of MSCs to boost and enhance the healing process in DFU patients. Although the safety and effectiveness of MSC therapy in managing DFU not clearly provided. Given the information provided in this review, we suggest that future studies are needed to understand the treatment processes, efficacy assessments, and personal selections of stem cell sources. However, there are several challenges and side effects regarding MSCs. So future research should focus on combating these drawbacks and optimizing MSCs to be more applicable in preliminary and clinical studies.

AUTHOR CONTRIBUTIONS

Helal F Hetta: conceptualization; data curation; formal analysis; funding acquisition; validation; writing—review & editing. **Alaa Elsaghir**: conceptualization; data curation; investigation; methodology; resources; supervision; writing—original draft. **Victor Coll Sijercic**: formal analysis; investigation; visualization; writing—original draft. **Mahad S Akhtar**: data curation; investigation; methodology; software; writing—original draft; writing—review & editing. **Sayed A Gad**: data curation; formal analysis; investigation; software; validation; writing—original draft. **Avinash Moses**: investigation; methodology; project administration; supervision; writing—original draft. **Mahlet S Zeleke**: conceptualization; data curation; methodology; project administration; resources; visualization; writing—original draft. **Fawaz E Alanazi**: writing—review & editing. **Abdulrahman K Ahmed**: data curation; formal analysis; investigation; validation; writing—original draft. **Yasmin N Ramadan**: formal analysis; methodology; project administration; resources; software; validation; writing—original draft.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All generated data are included in this manuscript.

TRANSPARENCY STATEMENT

The lead author Mahlet S. Zeleke affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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APPENDIX: List of Abbreviations

ABI: Ankle Brachial Index
AF-MSC-hypoCM: hypoxic-conditioned Medium from AF-MSCs
AF-MSCs: amniotic fluid-derived MSCs
AKT: protein-serine-threonine kinase
AMSCs: adipose tissue mesenchymal stem cells
BM: bone marrow
BM-MSCs: bone marrow mesenchymal stem cells
CTPs: cellular- and tissue-based products
DFU: diabetic foot ulcer
EBV: Epstein-Barr virus
ECM: extracellular matrix
EGF: epidermal growth factor
EPCs: endothelial progenitor cells
ERK: extracellular signal-regulated kinases
ESCs: embryonic stem cells
FBS: fetal bovine syndrome
HA: hyaluronic acid
HBOT: hyperbaric oxygen therapy
HGF: hepatocyte growth factor
HHV-7: human herpesvirus 7
HIV: human immunodeficiency virus
HOT: hyperbaric oxygen therapy
hUC-MSCs: human umbilical cord mesenchymal stem cells
IGF: insulin-like growth factor
ISCs: insulin-secreting cells
KGF: keratinocyte growth factor
MCPyV: Merkel cell polyomavirus
MRA: magnetic resonance angiography

(Continues)

ABI: Ankle Brachial Index

MRSA: Methicillin-Resistant *Staphylococcus Aureus*
MSC: mesenchymal stem cells
NLRP3: NOD-like receptor pyrin domain containing 3 inflammasome
NPWT: negative pressure wound therapy
PAD: peripheral artery disease
PDGF: platelet-derived growth factor
PD-MSCs: placenta mesenchymal stem cells
PGF: placental growth factor
PLGA: poly(lactic-co-glycolic acid)
PN: peripheral neuropathy
PRF: platelet-rich fibrin
PRP: platelet-rich plasma
ROS: reactive oxygen species
RSV: respiratory syncytial virus
SDF: stromal cell-derived factor
SF: silk fibroin
SSCs: skin stem cells
STC: stanniocalcin
TCC: total contact casting
TcO2: transcutaneous partial pressure of oxygen
TGF: transforming growth factor
Th: T helper
TIMP-1: tissue inhibitor matrix metalloproteinase 1
Treg: T regulatory cells
TSG-6: TNF-α-stimulated Gene 6 Protein
TTV: tornado tenovirus
UC: umbilical cord
vCPM: cryopreserved placental membrane containing viable cells
VEGF: vascular endothelial growth factor