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Review Article

The future of diabetic wound healing: unveiling the potential of mesenchymal stem cell and exosomes therapy

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Abstract: Diabetes mellitus (DM) is a significant public health problem and is one of the most challenging medical conditions worldwide. It is the severe complications that make this disease more intricate. A diabetic wound is one of these complications. Patients with diabetes are at higher risk of developing diabetic foot ulcers (DFU). Due to the ineffectiveness of Conventional treatments, growth in limb amputation, morbidity, and mortality have been recognized, which indicates the need for additional treatment. Mesenchymal stem cells (MSCs) can significantly improve wound healing. However, there are some risks related to stem cell therapy. Exosome therapy is a new treatment option for diabetic wounds that has shown promising results. However, an even more advanced form called cell-free therapy using exosomes has emerged. This upgraded version of stem cell therapy offers improved efficacy and eliminates the risk of cancer progression. Exosome therapy promotes wound healing from multiple angles, unlike traditional methods that primarily rely on the body's self-healing ability and only provide wound protection. Therefore, exosome therapy has the potential to replace conventional treatments effectively. However, further research is necessary to distinguish the optimal type of stem cells for therapy, ensure their safety, establish appropriate dosing, and identify the best management trail. The present study focused on the current literature on diabetic wound ulcers, their treatment, and mesenchymal stem cell and exosome therapy potential in DFU.

Keywords: Diabetes mellitus, diabetic foot ulcers, mesenchymal stem cell, exosome therapy

Introduction

The economy has grown noticeably in recent decades, so dietary habits have changed. Thereby, the number of patients dealing with diabetes has increased [1, 2]. Epidemiological calculations projected that there will be approximately 700 million by 2045 [3]. Furthermore, the treatment and care of DM force a significant economic burden on the patients and society [4, 5].

Diabetes can cause much harm, primarily through its complications. One of the most significant complications is diabetic wounds, and it is known that patients who have diabetes are very vulnerable to developing foot ulcers [6]. Statistics show that this disease consumes 20-40% of medical resources yearly [7]. Approximately 15% of diabetic patients are dealing with DFU complications, and this condition is responsible for about 84% of lower limb amputations [8].

Diabetic foot ulcer prognosis is often poor, and the mortality rates are unpromising (60% reduction in their five-year overall survival) [9, 10]. However, the healing of DFUs can be predicted by several factors, some of which can be modified. For instance, better control of diabetes,

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treatment of neuropathy, and early management of ulcers can improve the healing process. Therefore, patients' diagnosis and prompt treatment measures are vital to enhance their chances of healing [6].

There are several traditional treatments for foot ulcers resulting from diabetes, such as offloading the wound, wound dressings to provide a moist wound environment, debridement, and using antibiotics and surgical intervention. Stem cell transplantation has recently become important in curing various diseases, including DFU. Previous investigations have shown that MSCs can significantly improve wound healing [6]. Moreover, in multiple studies, exosome therapy has shown promising results as a new treatment option for DFUs [11]. Regulating recipient cells and managing cellular crosstalk among macrophages, endothelial cells (ECs), and fibroblasts are done by exosomes derived from MSC via genetic material and transcription factors transportation. More importantly, compared to stem cell therapy alone, it has a lower risk of cancer, making it a safer option for diabetic wound treatment [11]. Therefore, it has become a popular choice for diabetic wound healing. This paper reviews the current literature on the Potential of Mesenchymal Stem Cell and Exosomes Therapy in DFU.

The pathogenesis and features of foot ulcers in diabetic patients

The etiology and progression of DFU are intricate and influenced by various intrinsic and extrinsic factors. Considering both aspects is essential to realize responsible mechanisms for raising this issue.

Neuropathy

Neuropathy in DFU cases causes sensory and motor nerve impairment. Likewise, the autonomic nervous system may be damaged. Therefore, an increased risk of skin ulcers, muscle atrophy, and motor dysfunction in the lower extremities may arise [12, 13]. Additionally, abnormalities in sweat gland secretion resulting from neuropathy can cause overheating skin and elevate the danger of foot ulcers. Combining sensory and motor neuropathies can result in rough foot pressure, eventually leading to difficult healing ulcers [14].

Vascular lesions dominated by atherosclerosis

Vascular lesions can cause endothelial damage, inflammation, and blood hypercoagulability. Thus, it promotes the formation of atherosclerotic lesions [15, 16]. This angiopathy is the underlying factor behind DFU, amputation, and death [17]. Atherosclerotic plaque rupture can lead to arterial thrombosis, leading to lower limb ischemia and the formation of DFUs [18].

Wound infections

As a result of poor blood supply and nerve damage, diabetic foot infection can arise in diabetic patients. These chronic infections may result from multiple microorganisms like Candida albicans as fungi [19]. Also, continual diseases are related to immune cellular disorders, impairing resistant characteristics [20].

Numerous growth elements have also been identified to play a pivotal role in developing DM and its complications. Among these elevated factors, Vascular Endothelial Growth Factor (VEGF) has been indicated to be a more potent factor. In diabetic patients with diabetic ulcers, the level of malondialdehyde (MDA) and tumor necrosis aspect-α (TNF-α) are remarkably higher, which might be essential for soluble VEGF1 secretion. These factors contribute to the impairment of wound healing and vascularization [21, 22].

As mentioned above, these are the main reasons for the progression of ulcers in diabetic patients as well. Also, in addition to these factors, other factors are known as the main reasons for poor prognosis in DFUs. Other health issues associated with poor wound healing in diabetics are well assessed as follows: High blood sugar levels can damage blood vessels, leading to poor blood flow. Diabetic patients may also have peripheral vascular disease and neuropathy, which can make it challenging to detect wounds. Diabetic wounds are characterized by excessive inflammation, decreased blood vessel growth, impaired skin cell movement, and decreased cell growth. These changes can make it harder for wounds to heal and increase the risk of complications such as infections, non-closure of wounds, and chronic wounds that do not heal [23].

On the other hand, insufficient angiogenesis is one of the main factors contributing to poor wound healing in diabetic wounds. This happens due to a deficiency of necessary proangiogenic factors, which may be caused by fewer macrophages [24]. Furthermore, diabetic wounds have an increase in antiangiogenic factors and a decrease in capillary maturation factors. This delay in maturation factors can result in a poor healing process, increasing the risk of the wound becoming chronic or recurring [25]. Moreover, Hemoglobin A1C (HbA1c) measures long-term glycemic control in diabetic patients. Studies have shown a strong correlation between high HbA1c levels and poor wound healing outcomes. In a recent retrospective study, it was found that diabetic patients with an HbA1c level of 7.8% or above were at the highest risk of developing postoperative wound complications, including poor healing. Therefore, the American Diabetes Association recommends that people with diabetes maintain their HbA1c levels below 7% to reduce the risk of such complications [26].

Differences in wound healing in DF ulcers and non-DF ulcers

There are four main stages in the regular wound healing process: hemostasis, inflammation, proliferation, and remodeling [14]. When an injury happens, the process of hemostasis is activated as a result of platelet activation. Thus, the damage-associated factors start to release. After releasing these factors, local macrophages activate and damage-associated molecular patterns (DAMPs) discharge. So prolymphocytic neutrophils (PMNs) start the inflammatory phase [27]. Throughout infection progress, particular signaling proteins known as chemokines, such as C-X-C motif chemokine 12 (CXCL12), are discharged, promoting the conversion of macrophages from an M1 (an inflammatory state) to M2 (a non-inflammatory state). Then, non-inflammatory cytokines released by M2 macrophages result in the promotion of tissue healing and restructuring.

As the healing continues, cytokines provoke keratinocytes to elevate epithelial tissue renewal. Eventually, this process involving immune cells and tissue repair mechanisms, as aforementioned, leads to wound healing [28, 29]. Hyperglycemia, chronic inflammation, microcirculation, hypoxia, sensory neuropathy, and damaged blood supply are influential factors that disrupt these four stages and pathways, ultimately leading to delayed healing. Hyperglycemia is crucial in the build-up of Advanced Glycation End (AGEs) products, which affect immune cell function and cytokine levels by deterring the transition from M1 to M2 macrophages [30].

Inflammation is a significant factor in the development of diabetic foot complications. Elevated glucose levels in diabetes activate pro-inflammatory pathways, releasing cytokines such as tumor necrosis factor-alpha and interleukin-6. These cytokines promote inflammation and attract immune cells to the affected tissues. The chronic inflammatory state observed in the diabetic foot has several adverse consequences. It weakens the immune system's ability to fight off infections effectively and may cause immune cells to become less responsive, making it difficult for the body to control infections [31].

Chronic inflammation causes tissue damage, leads to fibrosis, and further impedes tissue repair and regeneration. Unlike standard tissue healing, diabetic foot ulcers display a chronic pro-inflammatory pattern with higher levels of inflammatory cytokines. Studies have found that high levels of cytokines like IL-1β, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) in the blood are linked to poor healing of diabetic foot wounds [32]. Moreover, in type 2 diabetes (T2D), the macrophages, which are immune cells that contribute to the inflammatory response, remain predominantly pro-inflammatory, leading to chronic inflammation followed by more tissue damage [33].

Recent research has shown that neutrophils, another type of immune cell, may also have a detrimental effect on diabetic wound healing by producing neutrophil extracellular traps (NETs) during the healing process. These NETs are generated by a process called "NETosis", which involves the secretion of decondensed chromatin by neutrophils to neutralize microorganisms. Studies have found elevated levels of NET-related biomarkers in people with diabetes [34]. Moreover, hyperglycemia, or high blood sugar, can upregulate the expression of neutrophil PAD4, contributing to the production of NETs that can weaken wound healing. Fur-

thermore, in diabetes, altered macrophage phenotypes fail to promote tissue repair and contribute to chronic wounds [35].

Considering the abovementioned facts, chronic inflammation can worsen an injury and extend the inflammatory response, leading to tissue damage. This can result in impaired function and adverse remodeling of various organs and tissues. The continuous or abnormal activation of repair pathways is responsible for the underlying mechanisms of chronic inflammation, which can cause persistent inflammation and fibrosis. Molecular research focuses on chronic inflammation induction, progression, and resolution. Over time, chronic fibrosis leads to adverse tissue remodeling and impaired function [36].

Vascular disease affects the limb's blood vessels, leading to hypoxia, oxidative stress, and wound healing impairment [37].

In addition, diabetic foot neuropathy hampers the secretion of neuropeptides crucial for recovery, thus adding further complications to the wound-healing procedure for people who have diabetes. Moreover, the extended inflammatory stage in wound healing of individuals with diabetes can result in excessive generation of reactive oxygen species, harming nearby tissues and decelerating the healing process [15]. The imbalance in growth factors and extracellular matrix constituents in wounds of diabetic patients also contributes to impaired healing, causing inadequate creation of fresh blood vessels and the production of collagen, vital components for appropriate wound healing. The modified manifestation of matrix metalloproteinases (MMP) in wounds of diabetic individuals can cause aberrant tissue reconstruction and postponed wound closure [38]. Overall, diabetic wound healing is a complex process influenced by various factors significantly impacting each stage of the typical healing cascade.

Current treatments for DFU

Regarding treating diabetic foot ulcers (DFU), the current strategy involves several measures. These include local wound care with surgical debridement, dressing to keep the wound moist, offloading the wound, assessing the patient's vascular health, controlling any active infections, and maintaining reasonable glycemic control. By following the IWGDF guidelines, clinicians can help most patients heal from foot ulcers [39].

Debridement process promotes wound healing by aiding in granulation tissue formation and re-epithelialization. According to the IWGDF guidelines, sharp debridement is the best standard of care. It is preferred over other methods such as autolytic, bio-surgical, hydro-surgical, chemical, or laser debridement [40].

The choice of antibiotic treatment primarily relies on the results of microbiological tests and antibiotic resistance. Obtaining deep tissue cultures during debridement before starting antibiotic therapy is recommended. As per the IWGDF/IDSA infection guidelines, therapy should begin with empiric and broad-spectrum antibiotics targeting common gram-positive and gram-negative bacteria. The antibiotic regimen should be adjusted based on the clinical response to the initial therapy and the results of both culture and sensitivity tests [41].

During the care of diabetic foot ulcers (DFU), it is essential to conduct regular screening and vascular assessment for Peripheral Arterial Disease (PAD) [42]. The guidelines provided by IWGDF suggest that patients who meet any of the following criteria should receive urgent vascular intervention: ankle pressure less than 50 mmHg, toe pressure less than 30 mmHg, ankle-brachial index less than 0.4, or transcutaneous oxygen pressure less than 25 mmHg [43]. Additionally, offloading the foot and managing any deformity is essential for preventing and treating DFUs. Offloading is essential in treating foot ulcers caused by increased mechanical stress. According to the IWGDF Offloading guidelines, the preferred treatment for a neuropathic plantar ulcer is a non-removable knee-high offloading device [44].

In some cases, amputation may be necessary despite the best efforts to save the foot. Since proximal amputation leads to more energy consumption during activity [45], the preferable amputation is more distal. Moreover, optimizing glycemic control as person-centered care or, if necessary, controlling it by clinicians prescribing insulin is essential [46]. To manage diabetic foot ulcers, clinicians are currently following the IWGDF (International Working Group on the Diabetic Foot) guideline, which is an evidence-based guideline [40].

Stem cells and regenerative medicine

Medical treatment and blood flow reconstruction by surgery (endovascular and open) are the primary traditional therapy for DFUs [47]. However, these standard procedures are inefficient, especially for foot ischemia forced by arterial stenosis and occlusion [48]. Moreover, in some instances of individuals afflicted by cardiovascular and cerebrovascular diseases, the possibility of engaging in arterial bypass interventional treatment becomes implausible, consequently leading to a substantial growth in the probability of limb amputation. Several advanced and efficacious treatments, including cell-based therapies, have been established for repairing chronic wounds. Stem cells improve the microenvironment, leading to tissue regeneration at the wound spot. Therefore, despite some defects in both treatments in DFU healing, stem cell therapy is still more beneficial [1].

A domain of science that centers around the restoration and substitution of impaired tissues and organs, using the potential of stem cells or other innovative methodologies to achieve its goals, called regenerative medicine. Stem cell-based therapy has demonstrated positive therapeutic outcomes mainly due to paracrine effects rather than transplanted cells' long-term survival [49]. MSCs possess distinct properties that can modify the immune response and facilitate regeneration, which makes them an appealing option for enhancing the repair of tissues and angiogenesis in diabetic wounds [50]. The inflammatory response in the wound microenvironment may be regulated by taking advantage of the paracrine effects of MSCs, which will speed up healing and lower the risk of chronicity. Additionally, the regeneration of various tissue types, including skin, blood vessels, and nerves, is the differentiation potential of MSCs, promoting comprehensive wound repair [51]. Two types of stem cells are used in DFU therapy, including autologous and allogeneic cells [52].

Mechanism of exosomes in DFU

Exosomes overview

Exosomes are crucial in transferring diverse particles between cells, including proteins, lipids, and nucleic acids. Furthermore, they are involved in several biological processes, such as the immune system, fibrosis, and the advancement of cancer [53, 54]. Exosome secretion is performed by different cell types, such as immune cells, platelets, cancer cells, epithelial cells, and mesenchymal cells [55, 56].

Research has indicated that exosomes can advance the healing process of chronic skin wounds through multiple mechanisms. These mechanisms encompass reducing the inflammatory response, accelerating the development of new tissue and blood vessels, repairing and substituting damaged cells, and diminishing scar formation. Additionally, previous research has shown that exosomes exhibit natural substance transport properties, which enable them to transfer various important biomolecules between cells. Moreover, since exosomes can be reabsorbed by the cells that secrete them and are rereleased, their effects would be prolonged. Their low immunogenicity feature allows them to transport various therapeutic agents across biological barriers with minimal side effects (**Figure 1**) [57].

Paracrine mechanisms of mesenchymal stem cells through the secretion of exosomes turn this approach into a valuable therapeutic approach. These exosomes may be functionalized to treat various diseases effectively [58].

MSC derived exosome extraction approaches

Isolation and purification of exosomes are critical in their treatment preparation process. The size, shape, density, and surface proteins of the exosomes are crucial factors in choosing proper methods, which can affect the exosome yield and purity [59]. Different ways of exosome isolation are as follows.

Ultracentrifugation

The heterogeneous mixture is sedimented based on density, size, and shape in this method [60]. The estimations have reported applying this method by 56% of all users in exosome research [61]. Many often perceive this approach as user-friendly, needing essential technical expertise. Also, this method is moderately time-consuming, and pretreatments are required for the procedure [61]. Differential ultracentrifugation and density gradient ultracentrifugation are two methods that work according to the density and size of components.

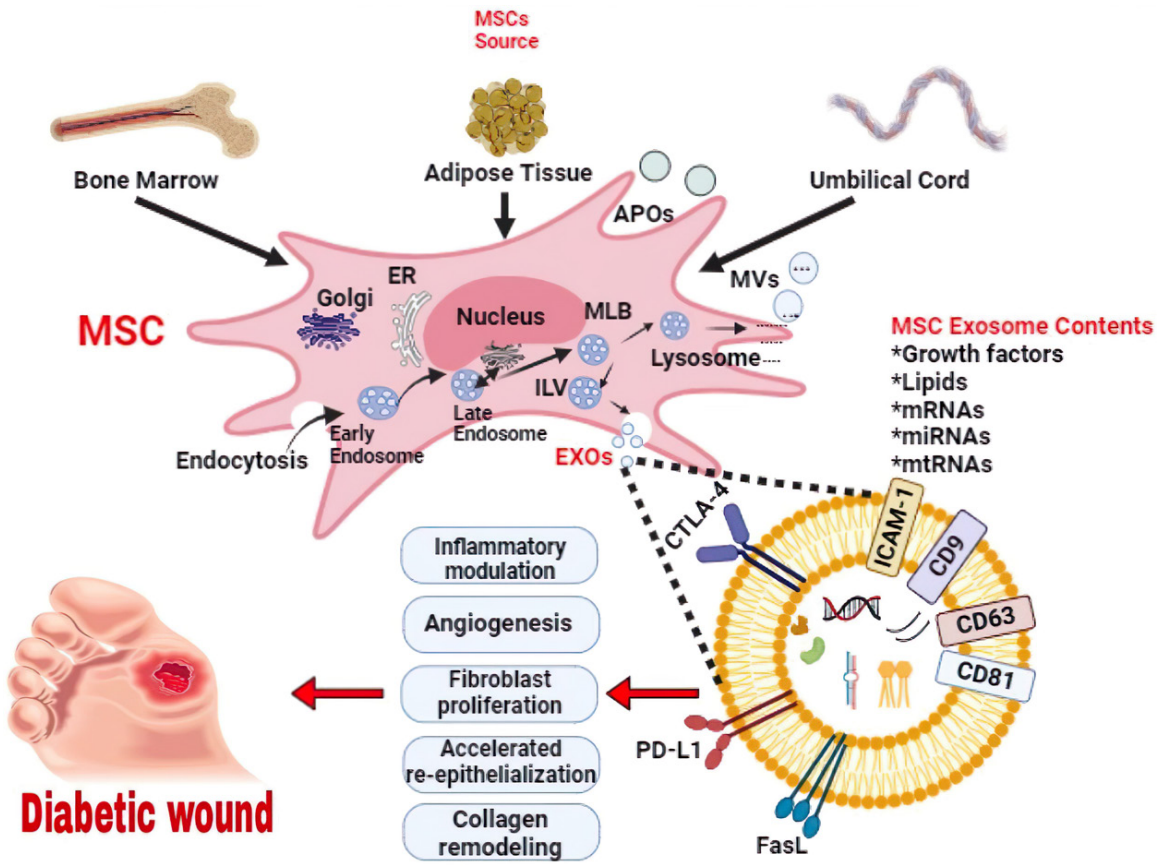

Figure 1. Summary of the MSC-Exos cell sources, contents and utilization in Diabetic Wound Healing.

Exosome separation in isopycnic ultracentrifugation, an ultracentrifugation technique relying on a density gradient, only depends on their density difference. In moving-zone ultracentrifugation, another density gradient technique, the separation is grounded on the size and mass instead of density. Due to the heterogeneity and the similarity in the size of exosomes, some challenges in this process are contamination and exosome losses [61].

Ultrafiltration

It is an exosome isolation technique based on size, in which exosome separation is according to size. Consequently, membrane filters have been utilized to separate exosomes with precise molecular weight or size segregation limits based on their size. However, Ultrafiltration is quicker than ultracentrifugation and does not need specialized equipment; due to applying force, it can generate large vesicles to deform and break apart, which may result in erroneous subsequent analyses [62].

Immunoaffinity

High concentrations of proteins and receptors in the exosomes' membrane make them ideal targets for developing isolation techniques using immunoaffinity. This objective can be achieved by utilizing immunoaffinity interactions between exosomal proteins, specifically antigens, their corresponding antibodies, and the specific relations between receptors and ligands [63].

Enzyme-linked immunosorbent assay (ELISA) based on microplate is a developed example for seizing and measuring exosomes from plasma, serum, and urine. This method presents the results as absorbance values, providing a quick way to compare the surface biomarkers' expression. It also served as an instant measure of the yield and specificity of exosomes [63]. This method yielded comparable results to ultracentrifugation; however, it required much smaller sample volumes, which makes it a more powerful isolation method than ultracen-

trifugation. Furthermore, the specificity of this method can surge by using immunoaffinity capture as an extra purification method for exosomes isolated by other techniques [64].

Precipitation

Exosomes can be isolated from biological fluids using polymers such as polyethylene glycol (PEG), a water-excluding polymer. These polymers bind to water molecules, forcing less soluble components to separate from the solution. In this method, firstly, samples are subjected to overnight incubation at 4°C with a precipitation solution possessing 8000 Da molecular weight. Then, using low-speed centrifugation or filtration, exosomes are isolated from precipitants. Exosome precipitation is a user-friendly and uncomplicated process that does not require specialized equipment, facilitating clinical usage [65].

Microfluidics-based isolation techniques

Ingenious and advanced sorting means such as acoustic, electrophoretic, and electromagnetic manipulations can be executed in addition to size, density, and immunoaffinity as standard approaches. Regarding these facts, it can be expected that by using this, there is no longer a need for high sample volume, and the consumption of reagents decreases as well as time [66]. **Table 1** compares different exosome isolation methods.

Stem cells and wound repair in DFU

Other than the fact that stem cells selectively trigger specific signals and control the development and immune response of donor cells, they are diverse based on their origin [56]. Stem cells involved in DFU therapy, including autologous and allogeneic cells, are recognized as two types of stem cells involved in diabetic wound treatment.

Autologous Stem Cells are proper for healing lower-end chronic lesions. Bone marrow-derived stem cells (BMSCs), peripheral blood stem cells (PBSCs), and adipose-derived stem cells (ASCs) are three autologous stem cells. According to previous investigations, BMSCs are efficient for chronic wound treatment because they have inflammatory cell progenitors and multipotent stem cells. Additionally, the AMSC harvesting procedure is less invasive than BMSC [56, 67].

Allogeneic stem cells, such as placental, amniotic, embryonic, umbilical cord, and umbilical cord blood, are attained from the same sources [68]. Their unique potential for differentiation and easily reachable features make them precious in regenerative medicine. The advantage of using these cells is that they can be obtained non-invasively [69].

Placental stem cells offer several advantages. To explain in detail, they can be easily isolated without ethical concerns. Additionally, larger quantities of these cells can be separated from the placenta compared to bone marrow. Also, the human placenta has lower immunogenicity. Differentiation into various cell types is another remarkable feature of placental-derived mesenchymal stem cells and secretory abilities that enhance wound healing [70].

Umbilical cord blood stem cells (HUCMSCs) are expected to be utilized since they are easier to harvest [71]. These HUCMSCs are highly regarded due to their pluripotency [72]. Recently, they have been utilized for injury repair in various clinical areas. Qin and his colleagues used HUCSC to cure DFU after angioplasty. Their outcomes demonstrated that HUCMSC treatment had better results in wound healing than only angioplasty treatment. It has been shown that using HUCMSCs after angioplasty had better outcomes regarding blood supply improvement, amputation rate reduction, ulcer healing promotion, and progress in the overall quality of life for diabetic patients [73].

Although stem cell therapy for DFU appears to have potential, there are risks and limitations associated with the treatment. One of them is the risk of tumor formation. Exosomes derived from MSC can transport genetic material and transcription factors with lower cancer risk than stem cell therapy alone. As a result, exosome usage in diabetic wound healing has gained considerable attention [1, 74].

Mscs-exosomes (Mscs-Exos) different sources and DFU treatment

BMSC-Exos

Exosomes derived from BMSC have a crucial role in promoting the angiogenesis process, inhibiting inflammation, and regulating the inflammatory microenvironment of the wound [75]. They affect downstream cytokines such as VEGFA and IL-1 by regulating the PTEN/PI3K/

Table 1. Differences between various exosomes isolation

Isolation Technique	Ultracentrifugation	Ultrafiltration	Exosome Precipitation	Immunoaffinity capture-based techniques	Microfluidics-based isolation techniques
Isolation principle	Based on density, size, and shape	Based on size	By varying the solubility or dispersibility of exosomes	Interaction between exosomes membrane-bound antigens (receptors) and immobilized antibodies (ligands)	Various exosomes feature such as size, density, and immunoaffinity
Cost-effective	High equipment cost	Low equipment cost	-	High reagent cost	Low
Risk of contamination	Low	Low (moderate purity)	Co-precipitation of other non-exosomal contaminants	Highly purified	-
Sample capacity	Large	-	Large	Low	-
Yield	Large amounts of exosomes	Lower number of exosomes	-	Low yield	Low
Time-consuming	No (Long run time)	Yes	No (Long run time)	No (Sample pretreatments)	Yes
User friendly	Yes	-	Yes	-	-
Portability	Low	Good	-	-	High
Require dedicated equipment	No	No	No	-	-

Table 2. Comparison of exosomes from different sources

MSCs-derived exosomes from different origins	The Difficulty of Extraction	Mechanisms
BMSCs	Difficult	Stimulation of PI3K/AKT signaling pathway through miRNA-126-mediated PTEN downregulation
ADSCs	Easy	Deters reactive oxygen species (ROS) and inflammatory factors to enhance cellular activity, proliferation and angiogenesis of EPC (Endothelial progenitor cells)
PMSCs	Easy	Promoting angiogenesis and fibroblast function through inducing PI3K-AKT signaling pathway
MenSC-Exos	Easy	Inducing macrophage M1 to M2 polarization

AKT pathway [76]. Moreover, by converting M1 to M2 macrophages, they control the inflammatory microenvironment of the wound [77]. BMSC-Exos can induce HaCaT cell proliferation by suppressing the TGF-β/Smad pathway, enhancing wound healing [76].

ADSC-Exos

Research has indicated that Adipose-derived stem cells (ADSCs) impact wound healing by regulating inflammation, promoting angiogenesis, and enhancing epithelial proliferation [78]. Moreover, ADSC-Exos have been found to accelerate diabetic wound healing by optimizing cellular functions, relieving oxidative stress, and promoting cellular proliferation and migration [79].

PMSC-Exos

Extracting Placenta Mesenchymal Stem Cells (PMSCs) does not require invasive procedures. Due to the highly vascularized nature of the placenta, it is reasonable to assume that PMSCs have more antigenic features [80]. PMSCs consist of stem cells isolated from different parts of the placenta, such as human amniotic epithelial cells (hAECs) and human umbilical cord mesenchymal stem cells (HUCMSCs). The two types of PMSC-Exos affect wound healing in different stages. hAECs-Exos progress angiogenesis and fibroblast function over the PI3K-AKT-mTOR pathway, whereas HUCMSC-Exos regulate macrophage polarization through the TLR4/NF-κB/STAT3/AKT pathway [77].

MenSC-Exos

A recent study investigated the effects of menstrual blood-derived mesenchymal stem cell (MenSCs)-derived exosomes (MenSC-Exos) on diabetic wounds. They found that MenSC-Exos could induce macrophage M1 to M2 polarization during inflammation. While the ARG/iNOS ratio increases, the activity of M1 marker iNOS (induced Nitric oxide synthase) decreases, suggesting that MenSC-Exos may promote diabetic wound healing by modulating the inflammatory response and promoting a more regenerative macrophage phenotype. This research highlights the potential of MenSC-Exos as a novel therapeutic approach for diabetic wound repair [81]. Exosomes from various sources are compared in **Table 2**.

MSCs and MSCs-exosome therapy in wound healing (preclinical studies and clinical trials)

MSC-exosomes are applied in animal models to improve wound healing research in DFU, and their reports have been released in several studies. Moreover, several trials have explored the safety, feasibility, and efficacy of MSC-based therapies for wound healing and skin regeneration in DFU.

The potential therapeutic benefits of UCMSCs transplantation were evaluated in 53 cases with DFU. The study found that the case group experienced significant and sustained improvement in ankle-brachial pressure index, transcutaneous oxygen tension, skin temperature, and claudication distance compared to the control group [73]. Furthermore, another trial outcome showed that implanting autologous graft comprising skin fibroblasts on a collagen membrane, along with BMSCs, reduced wound size and improved dermal vascularity in DFU patients (**Table 3**) [82].

Conclusion

Abnormal wound healing in diabetic patients is a significant issue globally, leading to substantial economic and medical problems. Current

Table 3. The clinical trials of MSCs-based therapy in DFU

Author (Year)	Cell source	Follow up duration	Clinical parameters	Ref
Vojtassak, et al (2006)	Autologous skin fibroblasts + Autologous BM-MSCs	29 days	↓Wound size ↑Vascularity of the dermis	[82]
Amann, et al (2009)	Autologous BM-MSCs	6 months	↓Major amputations ↓Analgesics consumption ↑Pain-free walking distance Improve leg perfusion	[83]
Dash, et al (2009)	Autologous BM-MSCs	12 weeks	↓Wound size ↑Pain-free walking distance Improve leg perfusion sufficiently	[84]
Procházka, et al (2010)	Autologous Bone Marrow Mesenchymal Stromal Cells (BMMSCs)	120 days	↑Limb salvage in patients (79%)	[85]
Lu, et al (2011)	Autologous BMMSCs	24 weeks	↑Pain-free walking distance, Improve leg perfusion	[86]
Li, et al (2013)	Allogeneic Umbilical Cord Blood Mesenchymal Stem Cells (UCBMSCs)	12 weeks	Improvement in weakness, numbness, pain, cold feeling, or intermittent limp, skin temperature	[87]
Qin, et al (2016)	HUCMSCs	3 months	Improvements in skin temperature, ankle-brachial pressure index, transcutaneous oxygen tension, and claudication distance. ↑Neovessels, along with gradual ulcer healing	[73]

treatments are limited in effectiveness, so it is crucial to explore new therapeutic approaches. However, an advanced form of medicine known as cell therapy utilizing exosomes has also emerged. However, an even more advanced form called cell-free therapy using exosomes has emerged. This upgraded version of stem cell therapy offers improved efficacy and eliminates the risk of host rejection. Exosome therapy promotes wound healing from multiple angles, unlike traditional methods that primarily rely on the body's self-healing ability and only provide wound protection. Therefore, exosome therapy has the potential to replace conventional treatments effectively. However, further research is needed to determine the optimal type of stem cells for therapy, ensure their safety, establish appropriate dosing, and identify the best administration trail.

Our viewpoint is shaped by the conviction that understanding the intricate mechanisms underlying MSC and exosome therapy is paramount. By unravelling the complex interplay between these therapeutic agents and the diabetic wound microenvironment, we can unlock new avenues for intervention. We seek to elucidate how MSCs and exosomes exert their therapeutic effects through meticulous research and analysis, from promoting angiogenesis and reducing inflammation to enhancing tissue regeneration. Moreover, discussing the latest clinical trials, we tried to provide insights that resonate with researchers and clinicians. Meaningful advancements in diabetic wound care were elaborated on by bridging the gap between bench-side discoveries and practical applications in this review. By fostering collaboration, innovation, and a deeper understanding of the regenerative capabilities inherent in our biology, we believe that paving the way towards a future where MSC and exosome therapy will be the potential treatment being applied instead of conventional treatments efficiently is not too far.

Disclosure of conflict of interest

None.

Abbreviations

DM, Diabetes Mellitus; DFU, Diabetic Foot Ulcers; MSCs, Mesenchymal Stem Cells; VEGF, Vascular Endothelial Growth Factor; MDA, Malondialdehyde; DAMPs, Damage-Associated Molecular Patterns; PMNs, Prolymphocytic Neutrophils; CXCL12, C-X-C motif chemokine 12; AGEs, Advanced Glycation End products; MMP, Matrix Metalloproteinases; ELISA, Enzyme-linked Immunosorbent Assay; PEG, Polyethylene Glycol; BMSCs, Bone Marrow-Derived Stem Cells; PBSCs, Peripheral Blood Stem Cells; ASCs, Adipose-Derived Stem Cells; UCMSCs, Umbilical Cord Blood Stem Cells; PMSCs, Placenta Mesenchymal Stem Cells; hAECs, human Amniotic Epithelial Cells; HUCMSCs, Human Umbilical Cord Mesenchymal Stem Cells; MenSCs, Menstrual blood-derived mesenchymal Stem Cell; ADSCs, Adipose-

derived stem cells; UCBMSCs, Umbilical Cord Blood Mesenchymal Stem Cells; BMMSCs, Bone Marrow Mesenchymal Stromal Cells.

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