Systematic Review

USE OF EXOSOMES IN DIABETIC FOOT ULCERS HEALING: A SYSTEMATIC REVIEW OF THERAPEUTIC POTENTIAL

.

ABSTRACT

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| **Background:** Diabetic foot ulcers (DFUs) a serious complication of diabetes mellitus, often leads to prolonged hospitalization, infection, and limb amputation. Their multifactorial pathogenesis includes chronic inflammation, impaired angiogenesis, oxidative stress, and defective fibroblast activity In recent years, regenerative medicine has gained attention, particularly the use of exosomes derived from adipose-derived mesenchymal stem cells (ADSCs). These exosomes carry bioactive molecules capable of modulating key processes in wound healing, including inflammation resolution, cellular proliferation, migration, and extracellular matrix remodeling.  **Methodology:** A systematic literature review was conducted using PubMed, Scopus, and Web of Science to identify relevant preclinical and clinical studies published up to April 2025. Search terms included "adipose-derived stem cells," "exosomes," "diabetic foot ulcers," and "wound healing." Studies were selected based on predefined inclusion and exclusion criteria, focusing on mechanistic insights and therapeutic outcomes of ADSC-exos in diabetic wound healing models.  **Results:** From an initial 840 potentially eligible studies, 25 met the predefined inclusion criteria and were incorporated into the final analysis.  **Conclusion:** ADSC-exos improve diabetic fibroblast wound healing by reducing inflammation through macrophage M2 polarization, promoting migration and proliferation of fibroblasts and keratinocytes, and supporting angiogenesis through signaling pathways such as PI3K/AKT, Wnt/β-catenin, and TGF-β/Smad. Together, these actions accelerate epithelial regeneration and granulation tissue formation. Preclinical findings consistently report enhanced healing outcomes, yet translation to human application remains limited. Challenges such as standardization of exosome isolation, dosing, delivery methods, and long-term safety must be addressed prior to clinical implementation. Nonetheless, the current findings support ADSC-Exos as a promising cell-free alternative to stem cell therapy in diabetic wound treatment and may revolutionize treatment strategies for diabetic wounds. |

*Keywords: Adipose-derived mesenchymal stem cells, Diabetic foot ulcers, Wound treatment, exosomes therapy*

1. INTRODUCTION

Diabetic wounds, particularly diabetic foot ulcers (DFUs), represent a significant global health challenge due to their high incidence, associated complications, and significant economic impact. It is estimated that roughly one-third of individuals with diabetes will experience a foot ulcer during their lifetime.[1] These wounds frequently lead to hospital admissions and lower limb amputations, highlighting the pressing need for effective treatment strategies.

DFUs are complex, involving the interaction of vascular dysfunction, decreased immune response, and peripheral neuropathy. A common side effect of diabetes is peripheral neuropathy, which causes problems with the senses, motor skills, and autonomic nervous system. These issues are made worse by hyperglycemia, oxidized low-density lipoproteins, and advanced glycation end products, which disrupt normal tissue homeostasis and delay the healing of wounds.[2]

In this context, exosome therapy has emerged as a promising approach in regenerative medicine. Exosomes are nanoscale extracellular vesicles that carry bioactive substances to recipient cells, such as proteins, lipids, and nucleic acids, facilitating intercellular communication. Exosomes derived from adipose-derived stem cells (ADSCs) hold great promise for controlling inflammatory responses, promoting angiogenesis, and enhancing tissue regeneration. This novel method provides a breakthrough answer for challenging diabetic wound treatment scenarios.

2. material and methods

**2.1 Literature Search**

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We systematically searched relevant studies in PubMed and Scopus databases up to November 31, 2024. The search strategy incorporated the following Medical Subject Headings (MeSH) terms: ((exosomes) OR (extracellular vesicles)) AND diabetic AND foot AND ulcer AND (healing). We limited the search to articles published in English from the past 10 years to ensure the inclusion of recent and relevant findings. Articles were initially evaluated based on their titles and abstracts, followed by a detailed assessment of the full texts.

**2.2 Study Selection and Eligibility Criteria**

The following question was considered to conduct this systematic review: What is the role of exosomes or extracellular vesicles in promoting wound healing in diabetic patients?

● Population: Diabetic patients with chronic wounds or diabetic foot ulcers.

● Intervention: Use of exosome-based treatments

● Comparison: Standard care, other biological therapies

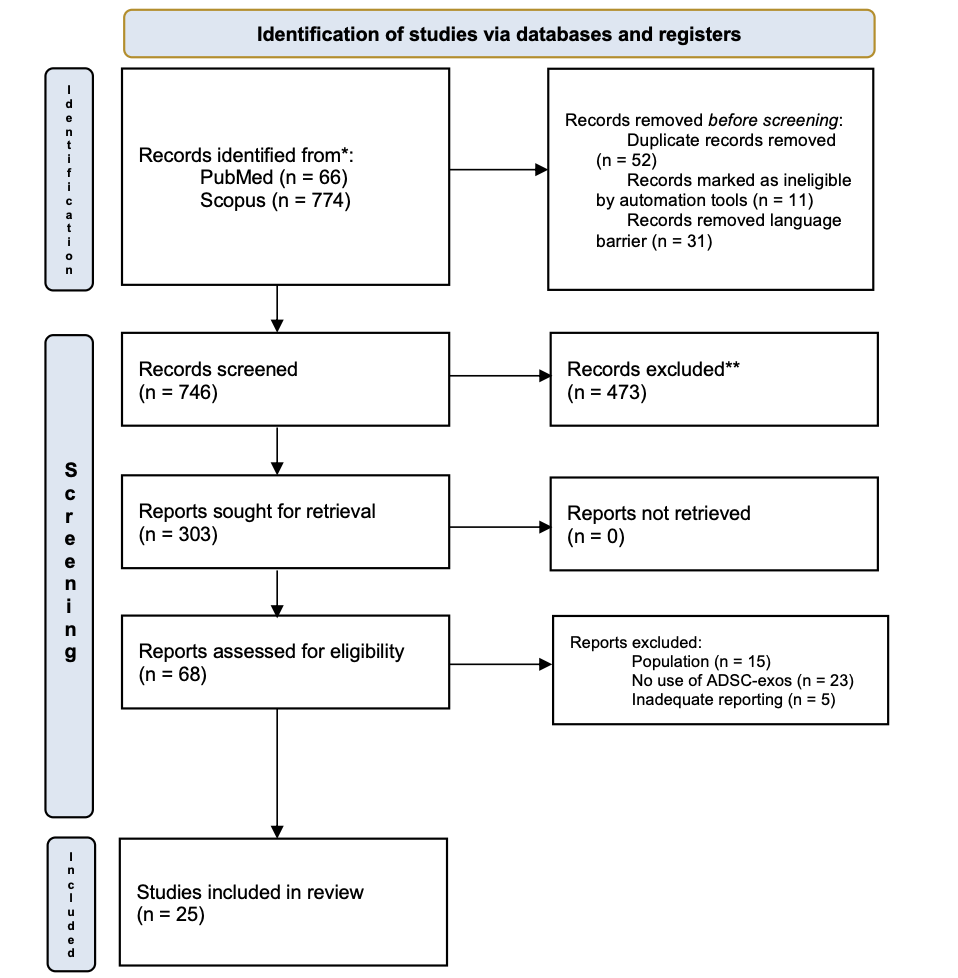
● Outcome: Improvement in wound healing, including molecular mechanisms, clinical endpoints, or surrogate markers such as wound closure or reduced inflammation.

Studies were selected according to: (I) Only clinical and preclinical studies, including randomized controlled trials, cohort studies, and experimental models, were considered. (II) Published from 2014 to 2024 (the last 10 years)

Studies were excluded according to: (I) Studies that did not focus on diabetic foot ulcers, or wound healing in general were excluded. (II) Studies that did not investigate ADSC-derived exosomes or exosome-based therapies were excluded. (III) Studies published in languages other than English were excluded.

3. results and discussion

A total of 840 potentially relevant articles were identified across two databases (PubMed and Scopus). Of these, 52 duplicates were removed, 11 were excluded by automation tools due to ineligibility, and 31 were eliminated for not being in English. This left 746 articles for screening, from which 68 underwent full-text review to determine eligibility. Ultimately, 25 studies met the inclusion criteria and were included in this systematic review. The PRISMA flowchart illustrating the study selection process is shown in Figure 1.



**Fig. 1. Flow diagram of the literature search on the use of Adipose-derived mesenchymal stem cells in Diabetic foot ulcers, on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)**

**3.1 WOUND HEALING**

Hemostasis, inflammation, proliferation, and remodeling are the four overlapping phases of the intricate biological process that is wound healing. Platelet aggregation and fibrin clot formation support the wound site during hemostasis, releasing signaling molecules that are essential for starting the healing process. In order to stop infection, immune cells such as neutrophils and macrophages infiltrate the wound site during the inflammatory phase. Angiogenesis, granulation tissue development, collagen deposition, epithelialization, and wound contraction are characteristics of the proliferation phase. In order to improve tissue integrity, the remodeling phase lastly concentrates on fortifying and rearranging the collagen matrix. [3,4]

Chronic wounds, such as diabetic foot ulcers (DFUs) occur when microbial invasion or underlying disease mechanisms interfere with the normal healing process. Hyperglycemia in diabetes mellitus causes atherosclerosis, peripheral neuropathy, and skin cell dysfunction, all of which substantially delay wound closure. These factors, combined with the recruitment of continuous inflammatory immune cells and overexpression of cytokines like IL-6, IL-1, IL-8, and TNF-α, create a chronic inflammatory environment. This keep the inflammatory phase from ending, delays angiogenesis, and impacts in the production of granulation tissue, which delays the remodeling phase and extends the chronicity of the wound.[5,6]

Conventional treatments for DFUs include glycemic control, debridement, wound dressing, off-loading, vascular evaluation, and infection management.[7] However, these treatments can promote healing, they frequently fail in complicated situations. Exosome-based therapies offer promising alternatives by enhancing cellular communication, promoting angiogenesis, and potentially accelerating tissue regeneration in chronic wounds like DFUs.

**3.2 EXOSOMES**

Exosomes (Exos), as a subtype of extracellular vesicles, are lipid bilayer structures measuring 30–150 nm, formed through endocytosis, membrane fusion, and budding processes. Exosomes can be detected and isolated from the extracellular environment of various cell types, such as stem cells, dendritic cells, epithelial cells, and immune cells. Additionally, they have been found in body fluids, including plasma, saliva, urine, and breast milk.[8] They encapsulate a cell-type-specific combination of biomolecules, including proteins (e.g., cytoskeletal proteins, transmembrane proteins, and heat shock proteins), nucleic acids (DNA, mRNA, miRNA, long and short non-coding RNA), lipids, and enzymes (such as GAPDH, ATPase, and pgk1). These activities provide a system of communication between complex cells, blocking functional components between cells.[9] After being released, exosomes carry their bioactive content and alter cellular functions via interacting with destination cells via endocytosis, receptor-mediated binding, or direct membrane fusion. Their capacity to control angiogenesis, oxidative stress, and inflammation underlies their therapeutic potential.[8,10] This makes them, especially adipose derived stem cells (ADSCs), interesting candidates for therapeutic uses. Because of their extensive distribution in adipose tissue and the relatively simple extraction process by enzymatic digestion, they constitute a valuable and easily accessible resource. ADSCs exhibit a remarkable capacity for multipotency, differentiating into diverse cell types such as osteoblasts, chondrocytes, myocytes, epithelial cells, and neuronal cells. This versatility highlights their potential in regenerative medicine, tissue engineering, and innovative cell-based therapies aimed at restoring tissue function and promoting healing.[11]

**3.3 EVIDENCE IN INFLAMMATION**

Diabetic wound healing is severely restricted by the persistent polarization of pro-inflammatory M1 macrophages, which maintains a maladaptive immunometabolic environment. Under normal conditions, M1 macrophages eliminate pathogens to start the inflammatory phase, which is then followed by M2 macrophages, which stop inflammation and aid in tissue repair. This M1-to-M2 transition is disrupted in diabetes, which results in delayed repair, increased cytokine production, and protracted inflammation.[12,13] As reported by Xiao et al., the use of ADSC-exos along with fibroblasts and endothelial cells decreased inflammation, increased M2 macrophage presence, improved type III collagen deposition, and boosted microvessel density.[14] Shi R. et al. provided additional proof to support this by emphasizing that ADSC-exos decrease pro-inflammatory cytokines such IL-6, IL-1β, and TNF-α while also optimizing angiogenesis and downregulating iNOS (M1 marker) and upregulating CD206 (M2 marker) [15] Yin D. et al. identified circRps5 in ADSC-exos as a critical regulator of M2 polarization, which is essential for reducing inflammation and promoting tissue healing.[16]

Additionally, ADSC-exos modulate inflammatory signaling through TRIM32 upregulation. TRIM32, a ubiquitin ligase, mediates the ubiquitination and subsequent degradation of STING, a key protein in the innate immune response. ADSC-exos lessen chronic inflammation in diabetic wounds by lowering STING-associated inflammation. According to He L. et al., TRIM32 improves the healing environment in hyperglycemic circumstances by promoting vascular repair, maintaining endothelial homeostasis, and lowering oxidative stress.[17]

**3.4 EVIDENCE IN PROLIFERATION**

Cellular activity targeted at tissue regeneration characterizes the proliferation phase, a crucial stage of wound healing. By producing extracellular matrix elements like collagen and elastin, which give the wound vital structural support, fibroblasts play a crucial part in this process. Fibroblasts absorb ADSC-exos during this phase, which promotes fibroblast migration, proliferation, and collagen synthesis. Autophagy is also triggered in epidermal cells to encourage migration and proliferation.[18,19] Wu et al. also showed that exosomal interferon regulatory factor 1 (IRF1) in ADSC-Exos causes overexpression of miR-16-5p, which promotes endothelial cell angiogenesis, fibroblast migration, and proliferation.[20] Additionally, Liu W. et al.[21] and Wang J. et al.[22], both studies emphasize that activation of the PI3K/AKT pathway regulates HIF-1α and VEGF expression, driving angiogenesis and extracellular matrix deposition through increased collagen types I and III. Liang ZH et al. revealed that circ\_0001052 facilitates angiogenesis and cell proliferation by upregulating VEGF (which supports endothelial cell growth) and FGF4 via p38 phosphorylation, a critical pathway modulating tissue repair and regeneration. [23]

**3.5 EVIDENCE IN ANGIOGENESIS**

Diabetes-related microangiopathy, neuropathy, decreased blood flow, hypoxia, inflammation, and endothelial-neural dysfunction all contribute to delayed wound healing.[24] Additionally, excessive hyperglycemia impairs migration, tube formation, nitric oxide bioavailability, oxidative stress, and senescence, all of which impact the function of endothelial progenitor cells (EPCs). Decreased eNOS, FoxO1, and Akt phosphorylation mediate this.[25]

Oiu et al. addressed these effects by showing that ADSC-exos overexpressing linc00511 increases EPC angiogenic ability by suppressing PAQR3 expression, which in consequence causes Twist1 accumulation by blocking BTRC-mediated ubiquitination. Twist1 promotes angiogenesis and is essential for the expression of vascular endothelial growth factor A (VEGFA).[26] Similarly, Shi R. et al. demonstrated that ADSC-exos overexpressing the microRNA "miR-128-3p" increased sirtuin 1 (SIRT1), which promoted angiogenesis and restored EPC function.[27] Additionally, Wang Z. et al. demonstrated that the Forkhead box O1 (FOXO1) signaling pathway causes SIRT1 to be upregulated. [28] FOXO1 acts to restrict vascular expansion and is an essential regulator of endothelial development. FOXO1 translocates to the nucleus in hyperglycemic environments, where it causes apoptosis and aids in the death of microvascular endothelial cells. In addition to increasing SIRT1 levels, inhibiting FOXO1 expression encourages vascularization and tissue regeneration while lowering apoptosis.[29]

Building on our present knowledge of angiogenesis, novel approaches have been developed to maximize this process. These include lowering levels of endogenous angiogenesis inhibitors like Vasohibin-1 (VASH1) and thrombospondin-1 (TSP1) while concurrently raising the mRNA expression of important angiogenic factors such angiopoietin-1 (ANG1) and vascular endothelial growth factor receptor 2 (FLK1).[30] Furthermore, the miR-146a-5p/JAZF1 signaling axis, which is largely controlled by miR-146a-5p, which modifies JAZF1 expression to promote pro-angiogenic activity, is crucial for VEGFA overexpression. These processes are essential for developing treatment strategies that promote vascular regeneration.[31]

**3.6 EVIDENCE IN REMODELING**

As in the proliferative phase, fibroblasts, myofibroblasts, and M2 macrophages become critical in the remodeling phase of wound healing. The main aim of this stage is to restore tissue strength and function by providing an extracellular matrix (ECM). Myofibroblasts cause the wound to constrict while M2 macrophages provide factors that enhance ECM remodeling and stabilize angiogenesis.[32] MicroRNAs like miR-128-1-5p, abundantly present in ADSC-exosomes, control fibrotic events through the inhibition of TGF-β/Smad signaling, which entails reduced activation of fibroblasts and deposition of ECM. This diminishes fibrosis while promoting superior wound healing.[33] Moreover, it was shown by Lv Q et al. that exosomes from modified miR-21-5p-ADSCs enhance diabetic wound healing through activation of the Wnt/β-catenin pathway, therefore critical for re-epithelialization as well as increased keratinocyte migration and proliferation. Also, these exosomes upregulate matrix metalloproteinase-7 (MMP-7) that cleaves extracellular matrix components. [34]

According to Yang C. et al., ADSC-exos induce collagen production and secretion such as α-SMA, collagen I, and collagen III which are applicable to the process of wound healing. Apoptosis of fibroblasts can also be reduced by exosomes through downregulating pro-apoptotic markers such as Bax and cleaved caspase-3.[35] Overexpression of Nrf2 can lead to granulation tissue, angiogenesis, and reduced inflammation.[36]

An essential part of wound healing is ulcer closure which means the maintenance of skin integrity and the avoidance of later problems such as infections or chronicity. Ren S. et al. explored the role of ADSC-exos expressing heat-shock protein 90 (HSP90) on their surface. These exosomes activate the AKT signaling pathway, which is necessary for cell migration and survival, by interacting with the low-density lipoprotein receptor-related protein 1 (LRP1) on recipient cell membranes. Inhibition of either LRP1 or AKT signaling substantially compromised wound healing, which indicates the critical role of the HSP90/LRP1/AKT pathway in prompting diabetic wound repair. [37]

The potential of exosomes generated from ADSCs to promote wound repair has been further validated by clinical investigations. When Moon KC et al. used ADSC-exosome sheets, the wounds closed much more quickly. The treatment group took an average of 40.8 ± 5.3 days to fully close the wound, while the control group took an average of 51.2 ± 3.9 days.[38] Similarly, Kato Y. et al. observed that ADSC-exosome sheets closed wounds in an average of 25.6 days compared to 34.2 days in controls.[39]

In comparing different types of exosomes, Wang J. et al. compared hypoxic ADSC-exosomes (HExos) with normoxic ADSC-exos and found that HExos-treated wounds achieved almost complete closure by day 14. This effect was traced back to regulation in terms of inflammation and secretion of ECM, specifically for fibroblast proliferation and migration which was involved to take place through the PI3K/AKT pathway.[40]

4. Conclusion

Exosomes derived from adipose-derived mesenchymal stem cells have shown to be a promising therapeutic avenue for the treatment of chronic wounds. Their ability to promote macrophage polarization toward a regenerative phenotype, stimulate fibroblast and keratinocyte migration and proliferation, and enhance angiogenesis through activation of key pathways such as PI3K/AKT, Wnt/β-catenin, and TGF-β/Smad. While further studies are needed to fully elucidate their mechanisms of action, optimize delivery systems, and confirm clinical efficacy, the current evidence supports the increasing recognition that exosome-based interventions may significantly advance the therapeutic paradigm for chronic wounds.

DISCLAIMER

The authors declare that generative artificial intelligence technologies were used during the writing and editing of this manuscript. Specifically, ChatGPT (version GPT-4o, developed by OpenAI, accessible at https://chat.openai.com) was employed to assist in improving grammar and language clarity.

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