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Narrative Review of Advancements in Stem Cell Therapy: Adipose-Derived Stem Cells for Diabetic Foot Ulcer Treatment

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ABSTRACT

Diabetic foot ulcers (DFUs) are a severe complication of diabetes, with current standard care often failing to prevent chronic morbidity and amputation. This narrative review examines the therapeutic potential of adipose-derived stem cells (ADSCs) for DFUs treatment. ADSCs promote healing through paracrine secretion of growth factors, immunomodulation, and stimulation of angiogenesis, as demonstrated in promising preclinical and early clinical studies. We outline these mechanisms, discuss the emerging role of ADSC-derived exosomes as a potentially safer alternative, and summarize key clinical findings. However, significant challenges remain, including potential risks of tumorigenicity, donor cell variability, and a lack of standardized protocols. While ADSC therapy represents a highly promising regenerative approach for DFUs, its safety and efficacy must be firmly established through more rigorous preclinical studies and large -scale randomized controlled trails before broad clinical adoption. This review concludes that while ADSC therapy is a highly promising regenerative approach for DFUs, its translation to clinical practice necessitates further rigorous investigations to overcome existing translational barriers.

Keywords: Diabetes; Adipose; Stem cell; Healing, Ulcer; Therapy

INTRODUCTION

Diabetic foot ulcers are among the most severe complications of diabetes, affecting up to 15% of patients during their lifetime[1]. These chronic wounds are caused by neuropathy, inadequate blood circulation, reduced immune defense, and other factors that delay the healing process[2]. Current primary standard medical care including debridement, offloading, and antibiotic therapy often fails to achieve complete healing, leaving patients at risk of chronic morbidity and lower limb amputation[3]. The limitations of conventional care have accelerated the search for the regenerative therapies, with mesenchymal stem cells (MSCs) emerging as a leading candidate. Among MSC types, adipose -derived stem cells (ADSCs) have gained significant traction in recent research due to their high yield from minimally invasive liposuction, multipotent differentiation capacity, and potent paracrine immunomodulatory effects[4, 5]. This article

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provides a narrative review of ADSCs in DFU treatment, focusing on their therapeutic mechanisms, the emerging role of exosomes, clinical trial evidence, and associated challenges and risks.

MATERIALS AND METHODS

This study was conducted as a narrative review, synthesizing current knowledge on the application of ASDCs in DFU treatment. A literature search was performed using the electronic databases Scopus, PubMed, EMBASE, ScienceDirect, EBSCOhost, JSTOR, and Web of Science for English-language articles published between 2015 and 2025. Search terms and combinations included: "adipose-derived stem cells", OR "ADSC", AND "diabetic foot ulcers", OR "DFU''; "stem cell therapy "AND "diabetic ulcer", and "ADSC'' AND "clinical trial". The search focused on identifying original research articles (preclinical and clinical), reviews, meta-analyses, and clinical trial reports. Data extraction was not systematic; instead, relevant studies were selected to provide a comprehensive overview of mechanisms, efficacy, and challenges. Given the narrative design, a formal quality assessment or risk-of-bias analysis (e.g., following PRISMA guidelines) was not performed.

Therapeutic Potential of ADSCs in Diabetic Ulcer Healing

ADSCs, which are multipotent mesenchymal stem cells capable of differentiating into adipocytes, osteoblasts, and endothelial cells, play a vital role in the repair and recovery of damaged tissues[4]. Poor circulation and blood supply characterize diabetic ulcers, and ADSCs can accelerate wound healing through the formation of new blood vessels, inhibition of inflammation, and formation of granulation tissue[5]. Animal research has also shown that ADSCs promote wound healing by increasing the rate of wound restoration, improving the formation of collagen fibers, and collagen deposition in the wounds of diabetic animals[6].

Their regenerative capacity is mediated primarily through paracrine secretion of growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and transforming growth factor-β (TGF-β). These molecules enhance angiogenesis, modulate immune activity, and stimulate fibroblast proliferation[7]. The ability of ADSCs to repair damaged vascular tissues and improve neovascularization is beneficial in patients with diabetes, where perfusion and prolonged hyperglycemia impair wound healing[8]. Additionally, another non-direct autologous differentiation action associated with ADSCs is the secretion of cytokines and growth factors, promoting tissue repair and enhancing the immune reaction that favors the wound healing process[9] as summarized in Table 1.

In Preclinical studies, ADSCs have been shown to accelerate wound closure, promote collagen deposition, and enhance the granulation tissue formation in diabetic models[18] as summarized in Table 2. Similarly, other studies, by Zhang and colleagues, showed that clinical investigations also demonstrated reduced ulcer size, faster re-epithelialization, and improved collagen organization compared with standard care[35,36]. Endothelial cell proliferation and migration are attributed to the promotion of new blood vessel formation in the wound bed[37]. In addition to their paracrine actions, ADSCs can convert into endothelial-like cells that are directly involved in neovascularization and optimization of vascular injury[38]. Consequently, ADSCs promote the re-establishment of structural and dietary requirements for tissue repair and wound healing at tissue sites with impaired blood circulation and oxygen delivery[39] These findings support ADCSs as a promising candidate for DFU therapy.

Table 1: Cellular and molecular biological basis of ADSCs in the healing of diabetic ulcer

Aspect	Mechanism/Function	Impact on Diabetic Ulcer Healing	Reference
IL-10 Secretion	ADSCs release IL-10, which inhibits pro-inflammatory cytokines such as INF-γ and TNF-α.	Reduces chronic inflammation, promotes healing by switching macrophages from M1 to M2.	10
Transforming Growth Factor (TGF-β)	ADSCs secrete TGF-β, facilitating the suppression of inflammation and promoting extracellular matrix remodeling.	Enhances tissue repair and regeneration, aiding wound closure.	11
Macrophage Polarization (M1 to M2)	ADSCs induce the shift of macrophages from a pro-inflammatory M1 phenotype to a reparative M2 phenotype.	Accelerates tissue repair and angiogenesis, critical for wound healing in diabetic ulcers.	10
Extracellular Vesicles (EVs)	ADSCs-derived EVs carry miRNAs and proteins that regulate immune responses by modulating cytokine production.	Improves cellular communication, leading to enhanced immune response regulation.	12
MicroRNA (miRNA-146a)	ADSC-derived exosomes contain miRNA-146a, which downregulates NF-κB signaling pathways.	Reduces inflammation and protects against excessive immune responses in diabetic wounds.	13
Nuclear Factor Kappa B (NF-κB) Pathway	Inhibition of the NF-κB pathway by ADSCs reduces pro-inflammatory gene expression.	Lowers inflammatory responses, enhancing wound healing speed and quality.	12
Heme Oxygenase-1 (HO-1) Expression	ADSCs upregulate HO-1, an enzyme with anti-inflammatory properties that helps in reducing oxidative stress.	Protects tissues from further damage by reducing oxidative stress in chronic diabetic ulcers.	14
Arginase-1 Expression	M2 macrophages, induced by ADSCs, express Arginase-1, which competes with iNOS, reducing nitric oxide production.	Lowers inflammation and promotes wound healing through enhanced tissue regeneration.	15
Fibroblast Growth Factor (FGF)	ADSCs stimulate the production of FGF, enhancing fibroblast proliferation and collagen production.	Promotes tissue regeneration and speeds up wound closure in chronic ulcers.	16
CXCR4 Expression on ADSCs	ADSCs express CXCR4, which enhances homing to injury sites and mediates immune-modulatory effects.	Improves ADSCs' migration to the wound site, contributing to enhanced wound healing outcomes.	17

Table 2: Summary of clinical studies using ADSC

ADSC cell type	Intervention	Study period	Condition	Outcome	Reference
Autologous	SVF (Cell-Assisted)	12 weeks	Diabetic Foot Ulcer	Improved wound closure rates compared to standard care.	19, 20
Allogeneic	Hydrogel	49 days	Ulcer	50% reduction in the wound size in patients who received ADSCs	21
Autologous	3D-AMHAT	12 weeks	Ulcer	All wounds, except one, were fully epithelialized by the ninth week, with a mean time to complete closure of 32 days	22
Autologous	3D-AMHAT	12 weeks	Ulcer	Complete healing was observed in 70% of the patients within 12 weeks	23
Autologous	Injection	9.3 months	Ulcer	Achieved full clinical recovery with no re-ulceration	24
Autologous	Intramuscular injection	4 weeks	Ulcer	Increased mean micro vessel density by + 32% to + 45% at 1 wk (P = 0.035)	25
Allogeneic	Injection	4 years	Ulcer	90% healing, with no adverse reactions	26
Autologous	Subcutaneous injection	12 months	Ulcer	At 6 months, 51 subjects achieved complete closure, and 8 had closure of ≥ 75% out of 63 enrolled patients	27
Autologous	Injection	6 months	Minor amputations	The average hospital length of stay was 16.2 days (P = 0.025)	28
Autologous	Engineered skin graft	21 weeks	Ulcer	There was a significant increase (P ≤ 0.05) in both skin thickness and vascular bed density	29
Autologous	Injection	21 months	Ulcer	There was no difference between any of the groups in terms of clinical outcomes	30
Allogeneic	Hydrogel	12 weeks	Ulcer	Wound closure reached 73% by week 8 and increased to 82% by week 12, with a median closure time of 28.5 days	31
Autologous	Injection	6 months	Minor amputations	At 6 months, 80% of the feet showed healing (P = 0.0064)	32
Autologous	Subcutaneous injection	6 months	Ischemia	After 6 months, all patients demonstrated complete wound healing	33
Autologous	Injection	12 months	Pedal atrophy	Dermal thickness increased significantly post-injection, persisting through 24 months (P < 0.05)	34

ADSC-Derived Exosomes and Extracellular Vesicles (EVs)

Recent research emphasizes the therapeutic potential of ADSC-derived exosomes and extracellular vesicles (EVs) [40]. These nanosized vesicles contain cytokines, growth factors, and microRNAs that reproduce many of the beneficial effects of ADSCs without the risks of uncontrolled proliferation or tumorigenicity [41]. EVs have been shown to enhance angiogenesis, stimulate fibroblast migration, reduce oxidative stress, and promote re-epithelialization in diabetic wound models [42].

Early-phase clinical studies conducted between 2021 and 2024 have reported improved wound healing and reduced inflammatory markers in patients treated with ADSC-derived exosomes [43]. Despite these encouraging findings, large-scale randomized controlled trials are still required to confirm safety, define optimal dosing, and establish standardized protocols for EV production and storage [44].

Modes of ADSCs Activity in the Healing of Diabetic Ulcers

Immunomodulation and Anti-Inflammation

ADSCs exert potent immunomodulatory effects primarily by suppressing the activity of immune cells like macrophages and inhibiting the release of pro-inflammatory cytokines, such as interferon-gamma and tumor necrosis factor-alpha (INF-γ/TNF-α)[45]. Instead, ADSCs secrete anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). This signaling inhibits neutrophil activation and stimulates a crucial switch in macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory, pro-repair M2 phenotype, which is associated with tissue regeneration and resolution of chronic inflammation[46].

Extracellular Matrix (ECM) Remodeling and Re-epithelialization

ADSCs contribute to ECM remodeling by stimulating fibroblasts and supporting collagen and elastin deposition, thereby enhancing tissue integrity[46]. They also secrete chemotactic factors such as stromal cell–derived factor-1 (SDF-1), which recruit endogenous progenitor cells to the wound bed, further supporting tissue regeneration and re-epithelialization[46].

ADSC Therapy on the Radar: An Outline of Concerns and Potential Risks

Formation of Cancer and Uncontrolled Growth

Adipose-derived stem cells have received much interest in regenerative healing due to their multipotent differentiation potential in the human body (Figure 1). Conversely, although incorporating these materials has shown potential for therapeutic applications, there are concerns about the adverse effects of these materials, such as tumorigenicity and uncontrolled cell proliferation. The ability of ADSCs to rapidly proliferate and differentiate augments the possibility of malignancy, particularly in the case of genetic or epigenetic modifications during isolation, expansion, or transplantation[47]. This position is significant in the development of ADSCs applications in patients with a history of cancer or precancerous states, as basic investigations have shown that ADSCs may facilitate tumor growth in specific circumstances[47].

For instance in an animal model, Muehlberg and colleagues showed that ADSCs may stimulate the growth of established tumors; therefore, ADSC therapy might be potentially oncogenic in certain categories of patients[48]. This study suggested that co-transplanted ADSCs could promote tumor growth via the production of pro-angiogenic factors like vascular endothelial growth factor (VEGF), a mechanism that could potentially encourages tumorigenesis and metastasis. Moreover, the same study pointed out that the same ligation of ADSC's tumor-promoting effect is linked to paracrine signaling, which improves the tumor physiologic environment by encouraging the formation of new blood vessels and suppressing the immune system[48]. Such evidence indicates that, although ADSCs have the potential to enhance wound healing and tissue repair, they inherently support tumor formation in patients with asymptomatic cancer or in a precancerous state.

The safety of ADSCs is further challenged by studies that show that these cells might transform into a malignant phenotype during in vitro culture, for instance data have been obtained proving that the extension of PDL for the culture of mesenchymal stem cells, including ADSCs, causes chromosomal changes and increases the probability of cellular senescence and transformation[49]. This underscores the importance of implementing very stringent safety measures to, for example, screen genetically modified cells for any potentially hazardous mutations and/or avoid exposure of the cells to conditions that require them to be in culture for long periods, during which they accumulate further mutations that may lead to tumor formation in humans[49].

To reduce the risk of tumorigenesis, the following measures have been recommended: selection of an appropriate donor, short-term culture, and extensive pre-transplant HLA-matched molecular typing. Furthermore, an intensive examination of the safety profile of ADSCs, including tumorigenicity tests in animal models, is required before the clinical applicability of the cells, particularly for patients who have a history of cancer or high risks of endpoint malignancy[50]. Further studies are also being carried out to study the oncogenic potential of certain genetically modified ADSCs with tumor-suppressive properties or genetically modified ADSCs releasing antitumor factors while maintaining their therapeutic properties[51].

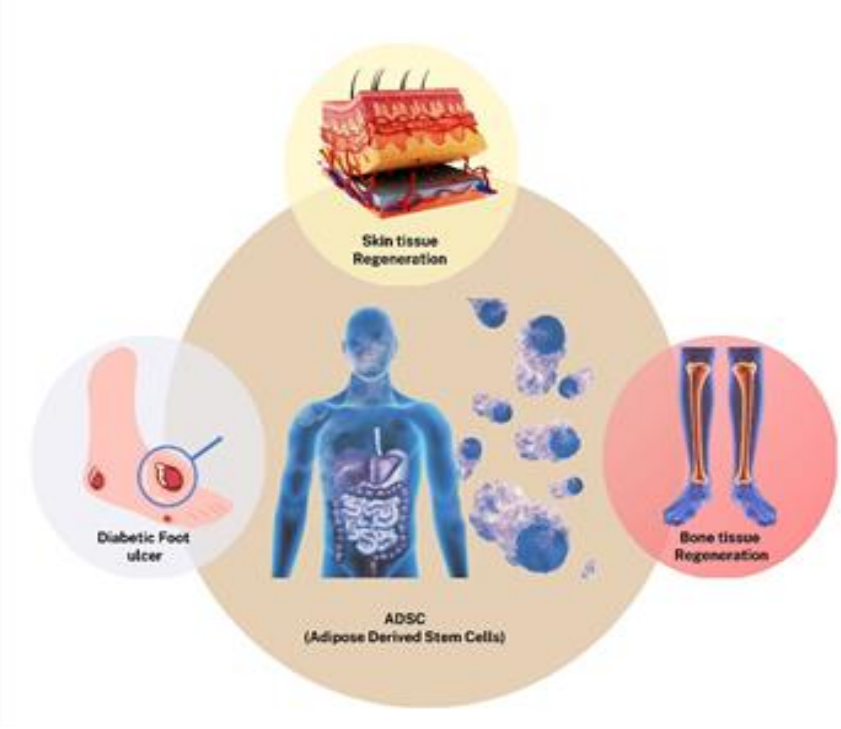

Figure 1. Multilinage Differentiation potential and therapeutic application of Adipose-Derived stem cells (ADSCs); ADSCs can be isolated from lipoaspirates and differentiated into multiple cell lineages, including adipocytes, osteocytes, chondrocytes, and neurons. This multipotency underpins their clinical utility in regenerative therapies for wound healing, nerve repair, cartilage restoration, and other tissue engineering applications, as discussed in this review.

Heterogeneity in Terms of Cellular Quality and Utility

Influencing factors include the quality and functionality of ADSCs, which can be affected by donor characteristics such as age, metabolism status, method of isolation of ADSC, and in vitro culture conditions[50]. For example, Shi's research group observed that the regenerative potential of ADSCs isolated from older volunteers or from subjects with metabolic diseases such as obesity or diabetes is lower than that of ADSCs obtained from young healthy donors[52]. These findings underscore that variability in ADSC quality can have significant implications for the clinical use of ADSC-based therapies because attenuation in the ability of these cells to differentiate or modulate immune responses may prevent the attainment of the desired therapeutic outcomes[52].

Several studies have been dedicated to how donor age and health condition affect the functionality of ADSCs. Chamberlain and colleagues established that ADSCs derived from older persons had lower proliferation rates, lower angiogenic potential, and lower capacity to secrete growth factors, including VEGF and FGF, required for tissue repair and neoangiogenesis, respectively[39]. These results imply that compared with young people, the use of ADSCs in elderly patients may be suboptimal, thus requiring donor screening or methods to restore ADSCs in elderly patients. Similar observations have been made in ADSCs harvested from obese or diabetic subjects, in which sustained metabolic stress impaired stem cell potential and limited its tissue repair capacity[50].

In addition, the method of ADSC isolation and expansion can play a role in the variability in cell quality. These trends necessitated standard operating procedures for the culture, expansion, and cryopreservation of ADSCs to be comparable and to retain the biological functionality of the cell type in different contexts. However, at present, there are no unified protocols that reflect the quality of ADSCs used in research and clinical trials[7]. For instance, variation in the enzymatic procedures for isolating ADSCs from adipose tissue and the traditional media and culture conditions utilized in propagating the cells at times influence cell density, rate of proliferation, and differentiation potency[7]. To this effect, the establishment of highly standardized protocols and rigorous quality control measures, such as functional assays for testing the usability of ADSCs for clinical use, will be of immense importance, since the clinical translation of ADSC therapies remains in progress[53].

The therapeutic promise of ADSCs in diabetic foot ulcer (DFU) repair is rooted in their multifactorial mechanism of action, targeting the core pathological features of these chronic wounds [54]. As this review outlines, ADSCs promote healing through direct differentiation, potent paracrine signaling, immunomodulation, and enhancement of extracellular matrix remodeling[55]. Preclinical data robustly demonstrate accelerated wound closure, improved angiogenesis, and reduced inflammation [56]. Early-phase clinical studies corroborate these findings, showing reduced ulcer size and improved healing rates compared to standard care[57].

However, a critical synthesis of the evidence reveals significant hurdles that must be overcome. The potential for tumorigenicity, even if low, necessitates rigorous long-term safety monitoring, particularly in patients with a history of malignancy[58]. Furthermore, the heterogeneity in ADSC potency–influenced by donor age, health status, and isolation protocols poses a significant challenge for standardizing therapy and ensuring consistent clinical outcomes. These risks underscore the fact that ADSC therapy is not yet a standardized, off the shelf product [59].

A promising avenue to mitigate these risks lies in the use of ADSC-derived exosomes and extracellular vehicles (EVs). These nano vesicles encapsulate the ADSCs' therapeutic cargo (e.g., growth factors, cytokines, miRNAs) responsible for angiogenic and immunomodulatory effects, but without the risks of whole cell transplantation, such as uncontrolled proliferation and immunogenic rejection.[60]. This cell-free approach represents a paradigm shift in regenerative medicine. Nonetheless, the clinical translation of exosome therapies faces its own set of challenges, key among these are the lack of standardized methods for the large–scale production, purification and characterization of EVs[61], as well as unresolved

questions regarding optimal dosing regimens, stability during storage, and targeted delivery to the wound site, resolving these issues is a prerequisite for the widespread clinical application of exosome-based therapies[62].

The translation of these therapies from the bench to bedside is further complicated by the variability in current clinical trial protocols regarding cell dosage, delivery methods (local injection vs. scaffold-based), and treatment frequency[63]. The current body of clinical evidence, while encouraging, remains comprised largely of small-scale studies. Therefore, the findings presented here, while positive, must be interpreted with caution until they are validated by large-scale, randomized, double-blind, placebo-controlled trails[64].

CONCLUSION

Adipose-derived stem cells (ADSCs) represent a promising regenerative therapy for diabetic foot ulcers (DFUs), by simultaneously addressing impaired angiogenesis, chronic inflammation, and defective extracellular matrix (ECM) remodeling. Preclinical and early clinical evidence is promising, demonstrating enhanced wound closure and tissue regeneration. However, significant challenges remain, including potential risks of tumorigenicity, donor variability, and a lack of standardized manufacturing protocols. ADSC-derived exosomes offer a potent cell-free alternative to mitigate these risks but face their own translational challenges. Therefore, the future clinical utility of both ADSCs and their exosomes is contingent upon rigorous, large-scale, randomized, controlled trials that unequivocally establish their safety and efficacy profiles before transitioning from experimental promise to standard clinical care.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

Author contributions

Prithiviraj Nagarajan led the conceptualization, supervision, and writing of the manuscript; Mani Rajarathinam contributed to validation and critical review; Gayathiri Ekambaram handled data curation and visualization; Leena Rajathy Port Louis supported investigation and validation; Ramachandran Kaliaperumal oversaw validation and reviewed the manuscript. All authors reviewed and approved the final manuscript.

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