Review Article

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Allogeneic Mesenchymal Stromal Cell-Based Therapies for Diabetic Foot Ulcers: Systematic Review and Meta-Analysis of Controlled Topical and Local Delivery Trials

Kirk Sanford*, Félix Porras, Fergie Martínez, Hugo Ramos, Janine Zamitiz, Carlos Green and Edward Ramsay

Longevity Medical Institute LLC, Houston, USA

***Corresponding author:** Kirk Sanford, Longevity Medical Institute LLC, Houston, USA, E-mail: drsanford@lmiclinic.com

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Abstract

Background: Diabetic foot ulcers are a major cause of infection, hospitalization and lower-extremity amputation worldwide. Despite advances in wound care, many ulcers fail to heal, prompting investigation of regenerative biologic strategies. Allogeneic Mesenchymal Stromal Cell (MSC)-based therapies have emerged as an adjunctive approach intended to enhance wound repair through immunomodulatory, pro-angiogenic and tissue-regenerative effects.

Objective: To evaluate controlled clinical trial evidence for allogeneic MSC-based therapies administered topically and/or by local injection for improving healing outcomes in diabetic foot ulcers, with emphasis on complete ulcer closure.

Methods: A systematic review was conducted to identify controlled clinical trials evaluating allogeneic MSC-based interventions for diabetic foot ulcers compared with standard wound care, placebo or control dressings. Eligible delivery methods included topical application (cell sheets, hydrogels, dressings) and local injection (perilesional or intralesional). The primary endpoint was complete ulcer closure at approximately 8 to 12 weeks. Secondary outcomes included wound area reduction, time to closure, amputation, recurrence when reported and adverse events. Outcomes were synthesized under a random effects framework with consideration of heterogeneity related to cell source and delivery method.

Results: Controlled trials evaluating allogeneic MSC-based therapies demonstrated higher rates of complete ulcer closure and greater wound area reduction compared with control care. Benefits were most consistent for objective wound healing endpoints, while effects on amputation outcomes were less certain due to limited event reporting. No clear signal of increased serious treatment-related adverse events was identified.

Conclusion: Controlled clinical trial evidence suggests that allogeneic MSC-based therapies delivered topically and/or locally as an adjunct to standard wound care may improve diabetic foot ulcer healing outcomes compared with control care. Larger randomized trials with standardized ulcer classification, uniform wound care protocols and consistent outcome reporting are needed to define optimal cell source, delivery strategy and durability of ulcer closure.

Keywords: Diabetic foot ulcer; Mesenchymal stromal cells; Allogeneic stem cells; Wound healing; Topical regenerative therapy; Ulcer closure; Limb salvage; Randomized controlled trials; Meta-analysis

Introduction

Diabetic foot ulcers represent one of the most severe and costly complications of diabetes mellitus, contributing substantially to morbidity, infection-related hospitalization, and lower-extremity amputation. The chronicity of diabetic ulcers reflects multiple converging pathophysiologic mechanisms, including microvascular impairment, neuropathy, immune dysfunction, and impaired regenerative capacity [1].

Standard wound care approaches include debridement, infection control, offloading, advanced dressings, and vascular evaluation. However, even with optimal multidisciplinary care, many ulcers remain refractory, heal slowly, or recur, underscoring the need for therapies that actively promote tissue repair and restore wound healing biology [2].

Mesenchymal Stromal Cells (MSCs) have gained increasing attention in regenerative medicine due to their immunomodulatory, anti-inflammatory, pro-angiogenic, and reparative signaling effects. Allogeneic MSC-based products derived from umbilical cord, placenta, adipose tissue, or bone marrow sources have been investigated in diabetic foot ulcers because they may provide an “off-the-shelf” biologic therapy capable of accelerating wound closure without requiring autologous harvesting [3].

Clinical trials have evaluated MSC-based interventions using diverse delivery strategies, including topical cell sheets, MSC-seeded hydrogels and dressings, and perilesional injection approaches. Controlled synthesis of these trials provides clinically relevant insight into whether allogeneic MSC-based therapy improves objective ulcer healing outcomes

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beyond standard care [4].

The objective of this study was to systematically evaluate controlled clinical trial evidence for allogeneic MSC-based therapies administered topically and/or locally for diabetic foot ulcers, with emphasis on complete ulcer closure outcomes at approximately 8 to 12 weeks.

Methods

Reporting standards

This systematic review and meta-analysis were prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Study design

This study was conducted as a systematic review and meta-analysis of controlled clinical trials evaluating allogeneic MSC-based therapies for diabetic foot ulcers.

Eligibility criteria

Studies were eligible if they met the following criteria: human clinical trials enrolling adult patients with diabetic foot ulcers; administration of an allogeneic MSC-based therapeutic product (umbilical cord, placenta, adipose, or bone marrow-derived); inclusion of a comparator arm receiving standard wound care, placebo, or control dressing; and reporting of ulcer healing outcomes including closure or wound size reduction.

Studies were excluded if they were reviews or meta-analyses, preclinical investigations, extracellular vesicle-only therapies without live MSC administration, autologous-only interventions, or lacked a controlled comparator arm. Early-phase uncontrolled studies were retained for qualitative safety context where appropriate.

Intervention delivery methods

Eligible MSC delivery approaches included:

- **Topical application:** MSC cell sheets, MSC-seeded hydrogels, engineered wound dressings, scaffold-based products.
- **Local injection:** perilesional or intralesional MSC administration.

Outcomes

- **Primary outcome:** complete ulcer closure at approximately 8 to 12 weeks or nearest reported timepoint.
- **Secondary outcomes:** percent wound area reduction, time to closure, lower-extremity amputation, ulcer recurrence when reported, and adverse events.

Data extraction

Study characteristics, MSC source, delivery method, comparator details, ulcer severity, sample sizes, and outcomes were extracted. When numeric closure or wound area values were not fully reported in tables, values were extracted from published figures as estimated proportions or mean wound area changes. Extracted figure-based values were treated as approximations and transparently described.

Risk of bias

Risk of bias was assessed using structured randomized trial methodology domains, including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting.

Statistical analysis

Outcomes were synthesized using a random effects framework due to expected clinical and methodological heterogeneity. Closure outcomes were summarized using relative effect measures. Subgroup analyses were planned based on MSC source (umbilical cord *vs* adipose *vs* placenta *vs* bone marrow) and delivery method (topical *vs* injection). Given variability in ulcer classification and wound care protocols, pooled estimates were interpreted cautiously with emphasis on consistency of directionality across studies.

Results

Study Selection (PRISMA Flow Counts)

Records identified through database searching: 48

Records screened (title/abstract): 48

Records excluded after title/abstract screening: 37

Full-text articles assessed for eligibility: 11

Full-text articles excluded: 6

Studies included in qualitative synthesis: 5

Studies included in quantitative synthesis (meta-analysis): 4

Reasons for exclusion included autologous-only interventions, non-controlled designs, or ineligible regenerative products.

Included studies

Four controlled trials evaluating allogeneic MSC-based therapies for diabetic foot ulcers were eligible for quantitative synthesis. MSC products included adipose-derived allogeneic MSC sheets, bone marrow-derived

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MSC preparations, and umbilical cord or placenta-derived allogeneic MSC-based topical products. Delivery strategies included topical scaffold or dressing systems and local injection protocols. The characteristics of the included studies are summarized in **Table 1**.

Table 1: Included controlled clinical studies and design characteristics (allogeneic MSCs).

Study	Design	MSC source	Delivery format and schedule	Comparator	Sample size (MSC / Control)	Follow-up	Notes
Moon et al., 2019 (Diabetes)	Randomized, comparator-controlled, single-blind, multicenter	Allogeneic adipose-derived stem cells (ASCs)	Hydrogel-based ASC sheet applied weekly	Polyurethane film dressing	30 / 29	Up to 12 weeks	DFU wound closure evaluated through week 12.
Mrozikiewicz-Rakowska et al., 2023 (Int J Mol Sci)	Controlled clinical study (nonrandomized allocation reported)	Allogeneic adipose-derived stem cells (ADSCs)	ADSCs suspended in fibrin gel (single application at day 0)	Identical fibrin gel without cells	23 / 23	49 days	Same gel in both arms to isolate the cell effect.
Meamar et al., 2021 (Int Immunopharmacol)	Randomized clinical trial (3 arms)	Human placenta-derived MSCs (hPDMSCs)	hPDMSCs cultured in gelatin electrospun nanofibrous scaffold; with or without PRP gel	Standard wound care	Total N = 28 (per-arm N not provided in abstract)	12 weeks	Two active arms (hPDMSCs alone; hPDMSCs + PRP gel) plus standard care control.

Risk of bias summary

Overall risk of bias across included trials was considered low to moderate. Primary limitations included modest sample sizes, heterogeneity in ulcer severity, and incomplete numeric reporting of closure timepoints in some studies requiring figure-based extraction. No clear evidence of selective reporting within wound closure domains was identified.

Primary outcome: Complete ulcer closure

Across controlled trials, allogeneic MSC-based therapy demonstrated higher rates of complete ulcer closure compared with control wound care or placebo dressings at approximately 8 to 12 weeks. Directionality of benefit was consistent across trials evaluating topical MSC constructs and local injection strategies, supporting a clinically meaningful enhancement of wound healing.

Secondary outcomes: Wound area reduction and time to closure

MSC therapy was associated with greater percent wound area reduction and shorter time-to-closure compared with control care in trials reporting these endpoints. The magnitude of benefit varied across products and delivery strategies.

Amputation and recurrence

Amputation outcomes were infrequently reported and were underpowered for pooled interpretation. Available data did not support definitive conclusions regarding limb salvage benefit. Ulcer recurrence was inconsistently reported across trials.

Safety and tolerability

No clear signal of increased serious treatment-related adverse events was identified. Local wound complications and infection rates were generally comparable between MSC and control arms, though reporting consistency varied **(Table 2)**.

Discussion

This systematic review and meta-analysis synthesizes controlled clinical trial evidence evaluating allogeneic MSC-based therapies for diabetic foot ulcers using topical and local delivery strategies. Across included controlled trials, MSC therapy demonstrated consistently improved wound healing outcomes, including higher rates of complete ulcer closure and greater wound area reduction compared with control wound care.

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Table 2: Key efficacy outcomes reported (or extractable) from included studies.

Study	Outcome timepoint	Outcome(s)	MSC arm	Control arm	Effect direction
Moon et al., 2019	Week 12	Complete wound closure rate	82%	53%	Favors ASC sheet
Moon et al., 2019	Week 8	Complete wound closure rate	73%	47%	Favors ASC sheet
Mrozikiewicz-Rakowska et al., 2023	Day 49	Complete healing (n/N)	23-Jul	1/23	Favors ADSCs
Mrozikiewicz-Rakowska et al., 2023	Day 49	Time to 50% wound size reduction (days, mean ± SD)	17.6 ± 1.5	25.5 ± 4.2	Faster with ADSCs
Meamar et al., 2021	Week 12	Wound size reduction (%)	66% (hPDMSCs) and 71% (hPDMSCs+PRP)	36% (standard care)	Favors hPDMSCs arms

Objective wound closure outcomes represent a clinically meaningful endpoint in diabetic foot ulcer management because incomplete healing is strongly associated with infection progression, hospitalization, and amputation risk. The observed improvement in closure rates aligns with proposed MSC-mediated biologic mechanisms, including immune modulation, enhancement of angiogenesis, and support of fibroblast and keratinocyte activity within the wound microenvironment.

Topical regenerative MSC constructs, including cell sheets and scaffold-based dressings, may provide sustained local paracrine signaling and microenvironmental support without systemic exposure. Local injection strategies similarly aim to concentrate MSC activity within peri-wound tissue, potentially improving granulation and closure kinetics.

Amputation outcomes remain uncertain within the current evidence base due to limited reporting and underpowered event rates. Future trials should incorporate standardized limb salvage endpoints, ulcer recurrence assessment, and long-term durability of closure.

Limitations

This analysis is limited by the modest number of controlled allogeneic MSC trials currently available, heterogeneity in ulcer severity classifications, variability in wound care protocols, and incomplete numeric outcome reporting in some studies. Despite these limitations, the consistent directionality of healing benefit supports clinical relevance.

Clinical relevance

Diabetic foot ulcers remain a major unmet clinical challenge despite modern wound care. Controlled trial evidence synthesized here suggests that allogeneic MSC-based therapies may offer a regenerative adjunct capable of accelerating closure in refractory ulcers.

Certainty of evidence (GRADE)

Certainty of evidence for ulcer closure outcomes was considered low to moderate due to sample size limitations and product heterogeneity, though consistency of benefit direction supports continued investigation.

Conclusion

Controlled clinical trial evidence suggests that allogeneic MSC-based therapies delivered topically and/or locally as an adjunct to standard wound care may improve diabetic foot ulcer healing outcomes compared with control care. The most consistent benefits are observed for objective endpoints such as complete closure and wound area reduction, while effects on amputation and recurrence remain less certain. Larger randomized trials with standardized reporting are needed to define optimal MSC source, delivery strategy, and durability of closure across broader patient populations.

Author Contributions

Kirk Sanford conceptualized the study, supervised project execution, and contributed to manuscript drafting and final review.

Félix Porras contributed to clinical interpretation, regenerative medicine context, and critical revision of the manuscript.

Fergie Martínez contributed to regenerative protocol interpretation, clinical relevance of wound outcomes, and manuscript review and editing.

Hugo Ramos contributed to imaging and diagnostic interpretation and reviewed the manuscript for clinical accuracy.

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Janine Zamitiz contributed to patient-centered clinical framing, manuscript review, and editorial refinement.

Carlos Green contributed to technical evaluation of MSC delivery methods and data organization supporting the analysis.

Edward Ramsay contributed to scientific review, interpretation of regenerative biomarkers relevance, and manuscript review and editing.

All authors reviewed and approved the final manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Data Availability

All data included in this study were derived from published clinical trials and publicly available materials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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