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INPLASY

Adipose-derived stem cells for diabetes-related wounds: a meta-analysis and GRADE assessment of the certainty of evidence

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 September 2026 and was last updated on 18 November 2026.

INTRODUCTION

Review question / Objective This systematic review aims to evaluate the efficacy and safety of adipose-derived stem cell and adipose tissue regenerative therapies for diabetic foot ulcers, including diabetic-related mixed-etiology chronic lower extremity wounds and post minor amputation stump wounds of diabetic foot.
Participants(P): Patients diagnosed with diabetes mellitus complicated with chronic lower extremity wounds, and the core population is patients with diabetic foot ulcers.
Interventions(I): Adipose-derived stem cells, stromal vascular fraction (SVF), microfragmented adipose tissue and other adipose-based regenerative therapies.
Comparators(C): Conventional wound care, placebo or other wound repair therapies.
Outcomes(O): Primary outcome is complete wound healing rate. Secondary outcomes include wound healing time, incidence of wound infection and adverse events. Changes in inflammatory and growth factor biomarkers of wounds will be explored.
Study design(S): Randomized controlled trials and non-randomized controlled studies.

Rationale We have revised both the title and eligibility criteria of this protocol before manuscript submission. The title was adjusted to focus on adipose-derived stem-cell therapy and explicitly indicate GRADE evidence-certainty assessment. For eligibility criteria, we specified the threshold of ≥50% diabetic patients for mixed-etiology wounds and added new exclusion criteria to exclude simple non-cellular autologous fat grafting, aiming to improve clinical homogeneity of included studies. All these modifications were NOT driven by the pooled results of meta-analysis. Data analysis has been completed but the manuscript remains unpublished.

Condition being studied Diabetic foot ulcer refers to foot infection, ulcer or deep tissue destruction

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caused by peripheral neuropathy and/or peripheral arterial disease in patients with diabetes. It is a serious chronic diabetic complication with refractory healing and high risk of amputation. Some diabetic patients suffer from mixed-cause chronic lower extremity ulcers and wounds after minor foot amputation, which are also hard to heal. Persistent inflammation and insufficient angiogenesis are core pathological mechanisms of non-healing wounds. Adipose-derived stem cells secrete multiple cytokines to regulate local inflammation and stimulate angiogenesis, which may accelerate wound repair. This review includes diabetic foot ulcers, as well as chronic ulcers and minor amputation stump wounds mainly caused by diabetes. Subgroup analyses will be used to differentiate different wound types.

METHODS

Search strategy Databases including PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang and VIP will be searched. Search terms are divided into three groups: ①diabetic foot / chronic lower extremity ulcer; ②adipose stem cells, stromal vascular fraction, adipose tissue graft; ③randomized controlled trial, non-randomized controlled study. Subject terms combined with free words are used for retrieval with no language restriction. The search cutoff date is May 1, 2026. References of included studies and related systematic reviews will be manually screened to identify additional grey literature.

Participant or population Patients aged ≥18 years with diabetes mellitus and chronic lower extremity wounds, including core population of diabetic foot ulcers, patients with mixed-etiology chronic ulcers mainly caused by diabetes, and patients with diabetic foot minor amputation stump wounds.

Intervention Adipose-derived regenerative therapies, including adipose-derived stem cells (ADSC), stromal vascular fraction (SVF), microfragmented adipose tissue, and other fat-derived cell-based therapies applied locally to wounds.

Comparator Conventional wound care (debridement, dressing change, infection control), placebo, or other non-cell-based wound repair treatments for chronic lower extremity wounds.

Study designs to be included Randomized controlled trials (RCTs) and non-randomized controlled clinical studies comparing adipose-derived regenerative therapies with controlled interventions for diabetes-related chronic wounds.

Eligibility criteria Inclusion Criteria: 1. Study Design: Randomized controlled trial (RCT) or non-randomized controlled study with parallel control groups. 2. Participants: Diabetic patients diagnosed with diabetes who have foot ulcers, wounds following minor diabetic amputations, or chronic lower extremity ulcers of mixed etiology, with ≥50% of participants having diabetes. 3. Intervention: Permissible local application of adipose-derived stem cells (ADSCs), including in vitro expanded ADSCs, newly isolated ADSC/stromal vessel fraction (SVF), and micro-fragmented adipose tissue (MFAT), combined with routine wound management. 4. Comparators: Standard wound care, cell-free local control, or percutaneous transluminal angioplasty (PTA). 5. Outcomes: Studies reporting pre-determined outcomes, such as complete wound healing rate. 6. Language: Publications in Chinese or English.
Exclusion criteria:
1. Participants: Chronic wounds predominantly of non-diabetic etiology.
2. Interventions: Simple autologous fat grafting without cell isolation or mechanical microfragmentation; combined with other cell products where the independent effect of ADSCs cannot be distinguished.
3. Study types: Animal experiments, reviews, case reports, conference abstracts, single-arm studies.
4. Studies without usable extractable outcome data.
5. Duplicate publications; only the most complete report will be used in main analysis.

Information sources We will retrieve electronic databases including PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang and VIP. References of included studies, relevant systematic reviews will be manually screened for additional records. Grey literature will also be identified. No language restriction is applied. Search cutoff date: May 1, 2026.

Main outcome(s) The primary outcome is complete wound healing rate, defined as full epithelialization of the target wound without exudation, assessed at the predefined follow-up time points of original studies.

Additional outcome(s)
1. Wound healing time (time to complete re-epithelialization).
2. Incidence of wound infection.
3. Adverse events and safety outcomes.

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4. Exploratory biomarkers including VEGF, TGF-β1, TNF-α, IL-1β and other inflammatory or growth factors in wound or peripheral blood samples.

Data management Two independent reviewers will screen literatures, extract data and assess risk of bias. Disagreements will be resolved by discussion or arbitration of a third reviewer. Data will be recorded in standardized pre-designed extraction forms. Duplicate publications will be identified and handled properly. All extracted data will be imported into RevMan and R software for quantitative synthesis.

Quality assessment / Risk of bias analysis For randomized controlled trials, the Cochrane Risk of Bias 2.0 tool will be used. For non-randomized controlled studies, the ROBINS-I tool will be applied. Two reviewers will independently assess the risk of bias. Disagreements will be settled by discussion or consultation with a third reviewer.

Strategy of data synthesis RevMan and R software will be used for meta-analysis. Relative risk (RR) with 95% confidence intervals (CI) will be calculated for dichotomous outcomes. Mean difference (MD) or standardized mean difference (SMD) with 95%CI will be adopted for continuous outcomes. Heterogeneity will be assessed by I^2 statistic. If I^2 < 50%, fixed-effect model will be used; otherwise, random-effect model will be selected. Narrative synthesis will be performed when quantitative pooling is not feasible.

Subgroup analysis Subgroup analyses will be conducted according to wound types: pure diabetic foot ulcers versus mixed-etiology ulcers / diabetic foot minor amputation stump wounds. Other subgroups include intervention type (ADSC, SVF, microfragmented adipose tissue) and follow-up duration.

Sensitivity analysis Sensitivity analysis will be performed to test the robustness of pooled results. We will exclude studies with high risk of bias one by one, and repeat the meta-analysis to observe changes in pooled effect estimates. If the pooled result changes obviously after exclusion, the result will be regarded as unstable.

Language restriction There are no language restrictions.

Country(ies) involved China.

Other relevant information This is a retrospective registration of systematic review and meta-analysis.

Keywords Adipose-derived stem cells; diabetic foot ulcers; chronic wounds; regenerative medicine; meta-analysis.

Dissemination plans The results of this systematic review will be submitted for publication in peer-reviewed medical journals, and also used for postgraduate thesis.

Contributions of each author

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