

Adipose-derived stem cell and adipose tissue-based regenerative therapies for diabetic foot ulcers: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION**Support** - None.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202690061**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 13 September 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 Diabetic foot ulcer is a severe complication of diabetes with high amputation risk, and conventional wound treatment has limited efficacy. Adipose-derived stem cell related regenerative therapies can modulate wound microenvironment and promote angiogenesis, which are promising strategies for chronic wound repair. Available clinical trials have small sample sizes and inconsistent conclusions. Previous published meta-analyses failed to distinguish pure diabetic foot ulcers from mixed-etiology wounds and amputation stump wounds, so the true therapeutic effect in patients with typical diabetic foot ulcers remains unclear. This study will synthesize current evidence to systematically assess the efficacy and safety of adipose-derived regenerative therapies for diabetic-related lower

extremity wounds. Subgroup and sensitivity analyses will be performed to separate pure diabetic foot ulcers from other wound types, to provide evidence for clinical practice.

Condition being studied Diabetic foot ulcer refers to foot infection, ulcer or deep tissue destruction 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: Adult diabetic patients with chronic lower extremity wounds; studies reporting at least one predefined clinical outcome; full-text available, no language restriction.

Exclusion criteria: Animal studies, case reports, reviews, conference abstracts without usable data; patients with severe uncontrolled systemic disease or malignant tumors.

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.
4. Exploratory biomarkers including VEGF, TGF- $\beta 1$, TNF- α , IL-1 β 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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