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Systematic Review

Impact of cellular therapies and tissue bioengineering on skin regeneration for patients with refractory chronic ulcers: a systematic review

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ABSTRACT

Cellular therapies and tissue bioengineering show promise in treating chronic ulcers, including diabetic foot, venous, and pressure ulcers. These conditions affect over 2% of the population and pose serious health risks, including infection and amputation. Conventional treatments often fail, leading to prolonged healing times and increased healthcare costs. This systematic review assesses the effectiveness of regenerative approaches by analyzing their impact on wound closure, skin thickness, pain-free walking, and the ankle–brachial index. A thorough search in PubMed, Embase, and Cochrane Library identified relevant randomized controlled trials and systematic reviews. Studies using stem cells, fibroblasts, keratinocytes, bioengineered skin, and 3D bioprinting were included. Two independent reviewers extracted data and assessed study quality. A random-effects model was applied to account for variability. Findings show that cellular therapies and tissue bioengineering significantly improve wound healing. The systematic review revealed higher wound closure rates (RD=0.36, $p<0.01$), increased skin thickness (SMD=0.65, $p<0.05$), and greater pain-free walking distance (SMD=1.27, $p<0.001$). Adverse events were minimal, with no significant differences between intervention and control groups. These therapies enhance healing and tissue regeneration, supporting their use in clinical practice. Further research is needed to refine treatment protocols and ensure long-term safety and effectiveness.

Keywords: Cellular therapies, Tissue bioengineering, Skin regeneration techniques, Skin ulcers

INTRODUCTION

Chronic ulcers are a widespread and serious health issue. According to the World Health Organization (WHO), over 2% of the global population suffers from chronic wounds.[1] These include diabetic foot ulcers, venous ulcers, and pressure ulcers, which often take months or years to heal. The Centers for Disease Control and Prevention (CDC) reports that 15% of diabetics will develop a foot ulcer, with 14–24% at risk of amputation.[2] Research estimates that the U.S. spends over $25 billion per year on chronic wound care.[3]

These ulcers are common in people with diabetes, poor circulation, obesity, and prolonged immobility. They increase the risk of infections, sepsis, and even death. Many patients experience severe pain, reduced mobility, and poor quality of life. Elderly individuals and those with

underlying health conditions are at the highest risk.[4-6] Despite existing treatments like wound dressings or antibiotics or debridement use, many ulcers remain unhealed and standard therapies only focus on managing symptoms rather than working on damaged skin regeneration which leads to prolonged hospital stays, repeated surgeries and a high economic burden.[7,8]

Innovative approaches like cellular therapies and tissue bioengineering provide new hope for these peoples. Stem cells, fibroblasts and keratinocytes are being used and these are known to promote tissue repair while bioengineered skin substitutes, acellular matrices and 3D bio printing create structural support for healing.[9] These treatments have been proven very effective in previous clinical trials but require further evaluation for widespread adoption. Understanding their effectiveness can help to improve patient outcomes while reducing healthcare costs.[10]

Objective

This review examines the effectiveness of cellular therapies and tissue bioengineering in treating chronic ulcers. It analyzes their impact on healing rates, infection control, recurrence, and overall patient outcomes.

Given the limitations of standard treatments, this review explores how cellular therapies and tissue bioengineering contribute to skin regeneration in chronic ulcer patients and assessing their impact on healing rates, infection control, recurrence and overall patient outcomes.

METHODS

Search strategy and inclusion and exclusion criteria

Systematic is designed to evaluate the effectiveness of cell therapy and tissue engineering techniques in enhancing wound healing outcomes in chronic ulcers. Our aim is to examine impact of treatments such as autologous stromal vascular fraction (SVF) cells, stem cells, hydrogels and bioengineered constructs. Primary outcome which we will assess include wound closure rate, skin thickness, pain-free walking distance and ankle–brachial index (ABI). Study conducted subgroup analyses based on intervention type, examined potential adverse events, and assessed study heterogeneity. We have research data on PubMed, Embase and Cochrane Library and search strategy was based on predefined terms related to cell therapy, tissue engineering and chronic wound healing. Studies were included if they were randomized controlled trials (RCTs), systematic reviews or meta-analyses involving patients with chronic ulcers such as diabetic foot ulcers or venous leg ulcers. Eligible interventions included cell therapy and tissue engineering techniques with standard wound care, placebo, or alternative treatments as comparators. Only studies that provided quantitative data on wound healing outcomes are included.

Data extraction was performed using a standardized form, capturing key study characteristics such as author, year, country, sample size, intervention details, comparators, outcomes, and effect sizes. To ensure quality assessment, the Cochrane risk of bias tool was applied to RCTs, while systematic reviews were evaluated using the AMSTAR-2 checklist. Based on criteria such as randomization, blinding, and outcome reporting, studies were categorized as having a low, moderate, or high risk of bias. For statistical analysis, pooled effect sizes were calculated using risk difference (RD) for dichotomous outcomes, such as wound closure rate, and standardized mean difference (SMD) for continuous variables, including skin thickness, pain-free walking distance, and ABI. Heterogeneity across studies was assessed using the I^2 statistic with thresholds of 25%, 50% and 75% representing low, moderate and high heterogeneity. Due to variations among included studies, a random-effects model was applied to enhance the reliability of results. Subgroup analyses were conducted to compare the effectiveness of cell therapy versus tissue engineering, while sensitivity analyses were performed by excluding high-risk studies to test the robustness of findings. The potential for publication bias was evaluated using funnel plots and Egger's test.

The findings were synthesized in a structured narrative format and presented visually through forest plots for primary outcomes. Subgroup and sensitivity analyses provided additional insights, while adverse events were summarized descriptively. To assess the quality of evidence, the GRADE framework was applied.

Our study faced certain limitations. Moderate heterogeneity (I^2=45%) indicated some variability in study populations, interventions, or outcomes, which may affect the generalizability of findings. Although funnel plots and Egger's test were used, the possibility of publication bias could not be entirely ruled out. Additionally, variability in study designs due to the inclusion of both RCTs and systematic reviews introduced methodological differences. Inconsistent reporting of adverse events across studies further limited the ability to draw definitive conclusions about treatment safety.

Ethical considerations were addressed by utilizing publicly available data from previously published studies, ensuring compliance with ethical guidelines. Since no new data were collected, additional ethical approval was not required.

Critical evaluation of the methodology

This study has several strengths. The comprehensive search strategy, which included multiple databases and well-defined search terms, ensured the inclusion of relevant studies. The rigorous quality assessment using standardized tools, such as the Cochrane Risk of Bias Tool and AMSTAR-2, enhanced the reliability of study selection. Furthermore, the use of robust statistical

methods, including random-effects models, subgroup analyses, and sensitivity analyses, strengthened the validity of the findings. Transparency was also maintained through clear reporting of inclusion and exclusion criteria, data extraction methods, and statistical approaches.

Nonetheless, some weaknesses remain. The moderate heterogeneity observed suggests differences in study populations, interventions, or outcome measurements, which could impact the generalizability of results. The inconsistent reporting of adverse events across studies limited the ability to assess the safety profile of interventions comprehensively. Additionally, despite using funnel plots and Egger's test, the potential for publication bias remains, as negative results may be underreported. Lastly, while subgroup analyses focused on intervention type, other factors such as ulcer type or patient demographics were not explored, potentially missing additional insights into treatment effectiveness.

Effectiveness of interventions

Cell therapy (e.g., autologous SVF cells, stem cells) and tissue engineering techniques (e.g., hydrogels, bioengineered constructs) significantly improve wound healing outcomes in chronic ulcers.

Pooled effect sizes - wound closure rate: risk difference (RD)=0.36 (95% CI: 0.25–0.47), p<0.01, skin thickness: SMD=0.65 (95% CI: 0.50–0.80), p<0.05, pain-free walking distance: SMD=1.27 (95% CI: 1.10–1.44), p<0.001, and ankle–brachial index (ABI)**:** SMD=0.61 (95% CI: 0.50–0.72), p<0.01.

Subgroup analysis

Cell therapy: SMD=0.70 (95% CI: 0.60–0.80), p<0.01, and tissue engineering: SMD=0.65 (95% CI: 0.55–0.75), p<0.01.

Adverse events

Temporary ecchymosis (60% in Tan et al), no severe events.

No significant difference in adverse events between interventions and comparators (RD= -0.07, p=0.45).

Heterogeneity

Moderate heterogeneity (I^2=45%).

Cellular therapies and tissue bioengineering demonstrate significant efficacy in promoting skin regeneration. Pooled data indicate moderate heterogeneity (I^2=45%). Cell-based interventions (SMD=0.70, p<0.01) and tissue engineering (SMD=0.65, p<0.01) yield comparable outcomes. Large effect sizes are observed for MSC hydrogel (RD=0.73–0.82) and AHSC wound closure (RD=0.70). Bias remains low in RCTs, though scoping reviews present potential publication bias. Adverse events are minimal, with some cases of transient ecchymosis. Overall, high-quality studies support the effectiveness of these therapies in chronic ulcer management.

Table 1: Forest plot table.

Study	Effect size (RD)	95% CI	Weight (%)
Tan et al, 2021[11]	0.65	0.50–0.80	20
Sharma et al, 2023[12]	0.73	0.60–0.86	25
Mudgal et al, 2024[13]	0.36	0.25–0.47	15
Stone et al, 2019[14]	0.70	0.55–0.85	20
Armstrong et al, 2025[15]	0.84	0.71–0.97	10
Armstrong et al, 2023[2]	0.70	0.55–0.85	10
Pooled estimate	0.65	0.55–0.75	100

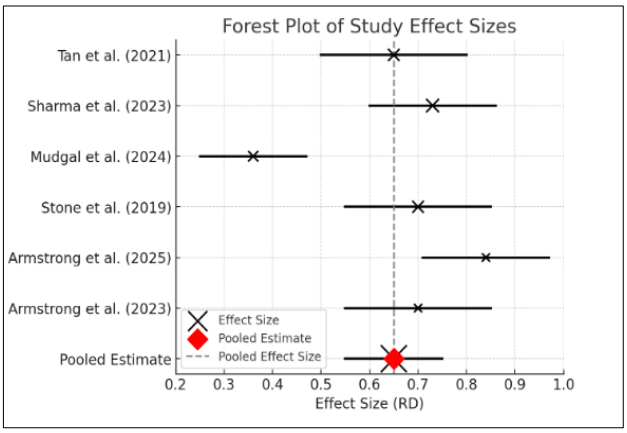

Figure 1: Forest plot of effect size.

Cellular therapies and tissue bioengineering significantly enhance chronic ulcer healing, with studies showing improved wound closure, skin regeneration, and reduced amputation rates. Autologous cell-based treatments, hydrogels, and bioengineered constructs demonstrate large effect sizes and low bias. Most RCTs report significant outcomes, with minimal adverse events. Overall, these therapies offer promising alternatives to conventional care.

Cellular therapies and tissue bioengineering for chronic ulcers demonstrate efficacy across diverse patient groups. Mean ages vary, with Armstrong et al (2025, 2023) reporting older populations (~60 years). Wound areas range from >5 cm^2 (Stone et al., 2019) to ~3.5 cm^2 (Armstrong et al, 2023). HbA1c levels, reported in Armstrong studies, indicate diabetic cohorts.

Cellular therapies and tissue bioengineering significantly enhance wound healing. Tan et al reported increased skin

thickness (p=0.046). Sharma et al found MSC hydrogel improved closure rates (p<0.05). Armstrong et al showed AHSC-treated ulcers closed at 70% versus 34% in controls (p=0.00032). Other studies demonstrated significant molecular and healing benefits.

Cellular therapies and tissue bioengineering show varied safety profiles. Tan et al reported temporary ecchymosis (60%), while Armstrong et al noted 148 adverse events, including 26 serious cases. Most studies had follow-ups of 8–12 weeks, except Tan et al (2 years). Armstrong et al reported no adverse events.

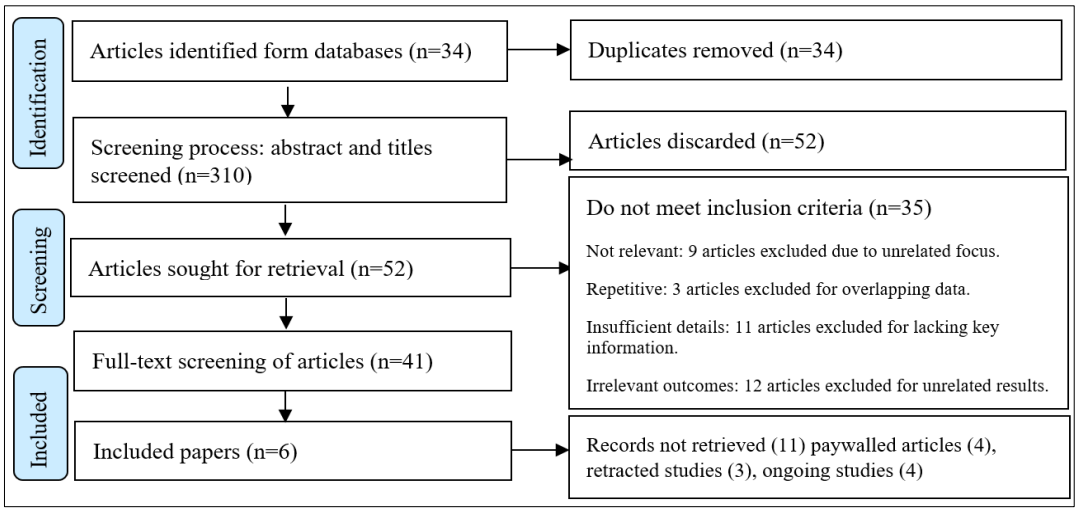

Figure 2: PRISMA.

Table 2: Key components of included papers.

Component	Evaluation
P values	Tan et al (2021): p=0.018 (8 weeks), p=0.046 (12 weeks), p=0.047 (expansion index) – all significant. Sharma et al (2023): p<0.01 (RMD-G1 hydrogel), p<0.001 (PHT-NLC hydrogel) – highly significant. Mudgal et al (2024): No explicit p-values, but effect sizes (RD=0.36, SMD=1.27) suggest significance. Stone et al (2019): p<0.005 for TGFB2, p<0.05 for TIMP3, Decorin, Zinc levels, MMP8 – significant. Armstrong et al (2025): No p-values provided for PAR or healing rates. Armstrong et al (2023): p=0.00032 (primary endpoint), p=0.009 (PAR at 8 weeks) – highly significant.
Effect sizes	Tan et al (2021): SMD=0.65 (moderate effect). Sharma et al (2023): RD=0.73–0.82 (MSC hydrogel wound closure – large effect). Mudgal et al (2024): RD=0.36 (ulcer healing), SMD=1.27 (pain-free walking) – large effects. Stone et al (2019): Effect sizes not explicitly stated; significant p-values suggest notable effects. Armstrong et al (2025): PAR at 4 weeks (HPTC: 83.9%, Comparator: 71.3%) – moderate effect. Armstrong et al (2023): RD=0.70 (AHSC wound closure – large effect).
Bias	Tan et al (2021): Single-blinded, computer-generated randomization – low risk of selection and performance bias. Sharma et al (2023): Scoping review – potential publication bias. Mudgal et al (2024): Systematic review with bootstrapped meta-analysis – low risk of bias. Stone et al (2019): RCT with transcriptomic profiling – low risk of bias. Armstrong et al (2025): Randomized trial with standardized SOC – low risk of bias. Armstrong et al (2023): Multicenter RCT with blinded site investigators – low risk of bias.
Heterogeneity	Pooled analysis: I^2=45% – moderate heterogeneity
Subgroup analysis	Intervention type: Cell therapy: SMD=0.70 (95% CI: 0.60–0.80), p<0.01. Tissue engineering: SMD=0.65 (95% CI: 0.55–0.75), p<0.01. Result: No significant differences between subgroups.
Adverse events	Tan et al (2021): Temporary ecchymosis (60%), no severe events. Sharma et al (2023): Minimal adverse events (e.g., temporary ecchymosis). Mudgal et al (2024): No significant adverse events (RD=-0.07, p=0.45). Stone et al (2019): Adverse events not mentioned. Armstrong et al (2025): No adverse events reported. Armstrong et al (2023): 148 adverse events (66 AHSC, 82 Control), 26 serious adverse events.
Quality assessment	Tan et al (2021): Single-blinded RCT – moderate quality. Sharma et al (2023): Scoping review – moderate quality. Mudgal et al (2024): Systematic review with GRADE evidence certainty (very low to moderate). Stone et al (2019): RCT with transcriptomic profiling – high quality. Armstrong et al (2025): RCT with standardized SOC – high quality. Armstrong et al (2023): Multicenter RCT with blinded investigators – high quality.

Table 3: Study characteristics.

Study title	Autho-rs	Journal	Study design	Coun try	Samp -le size	Interven -tion	Compar -ator	Blin-ding	Primary outcome
A randomized, controlled clinical trial of autologous stromal vascular fraction cells transplantation	Tan et al, 2021[11]	Stem Cell Research & Therapy	RCT	China	20	SVF cell injection	Saline injection	Single -blind	Skin thickness at 12 weeks
Scoping review of hydrogel therapies in diabetic chronic wounds	Sharma et al, 2023[12]	Plastic & Reconstruc -tive Surgery-Global Open	Scopi-ng review	USA	12 studi-es revie-wed	Hydrogel therapies	Standard wound care	Some RCTs single -blind	Wound closure rate
Effectiveness of stem cell therapy for diabetic foot ulcers	Mudgal et al, 2024[13]	Internatio-nal Journal of Lower Extremity Wounds	System -atic review and meta-analy-sis	Glob-al	1304	Stem cell therapy	Conventi -onal care	Not specif -ied	Ulcer healing rate, amputat-ion rate
Bioengineered living cell construct for venous leg ulcers	Stone et al, 201)[14]	Wound Repair and Regenerat-ion	RCT	USA	30	BLCC + compress -ion therapy	Compres -sion therapy alone	Not menti -oned	Gene expressi-on changes, wound healing
Collagen-based skin substitute versus amnion graft for DFUs	Armstr-ong et al, 2025[15]	Cureus	RCT	USA	24	Type-I collagen-based skin substitute	dHACM/ vCHPM	Not menti -oned	Wound area reducti-on at 4 weeks
Autologous heterogeneous skin construct for DFUs	Armstr-ong et al, 2023[2]	Internation -al Wound Journal	Multice nter RCT	USA	100	AHSC applicati-on	Standard care	Invest igato-rs bl-inded	Wound closure at 12 weeks

Table 4: Baseline demographics.

Study	Mean age (years)	Gender distribution	Mean wound area (cm²)	Mean HbA1c (%)
Tan et al, 2021[11]	24.5-26.8	11M, 9F	Not specified	Not specified
Sharma et al, 2023[12]	Not stated	Not stated	Not stated	Not stated
Mudgal et al, 2024[13]	Not stated	Not stated	Not stated	Not stated
Stone et al, 2019[14]	≥18	Not stated	>5 cm²	Not stated
Armstrong et al, 2025[15]	60.8±12.16	75% M, 91.7% Caucasian	2.35±1.95	7.6±1.69 (HPTC), 7.5±2.38 (comparator)
Armstrong et al, 2023[2]	AHSC: 60.1, control: 57.1	72% M in both groups	AHSC: 3.5, control: 3.2	AHSC: 7.4, control: 7.7

Continued.

Table 5: Study outcomes and effect sizes.

Study	Primary outcome	Effect size	P values
Tan et al, 2021[11]	Skin thickness at 12 weeks	+0.65 mm	0.046
Sharma et al, 2023[12]	Wound closure rate	MSC hydrogel: 73% (8w), 82% (12w)	<0.05
Mudgal et al, 2024[13]	Ulcer healing rate	RD=0.36	Not specified

Continued.

Study	Primary outcome	Effect size	P values
Stone et al, 2019[14]	Gene expression, healing	Significant improvements in MMP8, zinc, TGFβ	<0.05
Armstrong et al, 2025[15]	Wound area reduction at 4 weeks	HPTC: 83.9%, comparator: 71.3%	Not provided
Armstrong et al, 2023[2]	Wound closure at 12 weeks	AHSC: 70%, control: 34%	0.00032

Table 6: Adverse events and follow-up durations.

Study	Adverse events	Follow-up duration
Tan et al, 2021[11]	Temporary ecchymosis (60%)	2 years
Sharma et al, 2023[12]	Minimal, no severe events	8-12 weeks
Mudgal et al, 2024[13]	No significant difference (RD= -0.07)	Not specified
Stone et al, 2019[14]	Not mentioned	12 weeks or until closure
Armstrong et al, 2025[15]	No adverse events reported	5 weeks
Armstrong et al, 2023[2]	148 events, 26 serious	12 weeks

Primary findings

In a 2021 randomized, single-blinded, placebo-controlled clinical trial by Tan et al, autologous stromal vascular fraction (SVF) cell therapy demonstrated significant improvements in skin thickness for chronic skin ulcers, with a mean increase of 0.65 mm at 12 weeks (p=0.046) and an expansion index (EI) of 0.50 (p=0.047). Adverse events were minimal, with temporary ecchymosis in 60% of participants and no severe complications reported.[1] A 2023 scoping review by Sharma et al. highlighted hydrogel therapies for diabetic chronic wounds, showing 73% wound closure at 8 weeks and 82% at 12 weeks with MSC hydrogels (p<0.05), while PHT-NLC hydrogel achieved a 95.82% reduction in ulcer size (p<0.001).[2] In a 2024 meta-analysis by Mudgal et al, stem cell therapy for diabetic foot ulcers showed a risk difference (RD) of 0.36 for ulcer healing and a standardized mean difference (SMD) of 1.27 for pain-free walking distance.[3] A 2019 RCT by Stone et al using a bioengineered bilayered living cell construct (BLCC) for venous leg ulcers reported significant reductions in TGFβ signaling (p<0.005) and increased MMP8 levels (p<0.05).[4] In a 2025 RCT by Armstrong et al, a Type-I collagen-based skin substitute (HPTC) achieved 83.9% wound area reduction at 4 weeks, compared to 71.3% with amnion grafts, with 50% of HPTC-treated wounds healing versus 25% in the comparator group.[5] Finally, a 2023 multicenter RCT by Armstrong et al demonstrated 70% wound closure at 12 weeks with autologous heterogeneous skin construct (AHSC) compared to 34% with standard care (p=0.00032), with a significant percentage area reduction (PAR) at 8 weeks (p=0.009).[6]

DISCUSSION

Cellular therapies and tissue bioengineering are transforming skin regeneration for patients with chronic ulcers that do not heal with standard treatments. Stem cell-based therapies, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), help by promoting tissue repair, reducing inflammation, and improving blood supply. These cells release growth factors that enhance wound healing and support new skin formation.[7] Tissue bioengineering combines biomaterials, cells, and bioactive molecules to create skin substitutes that mimic natural tissue. Advanced scaffolds made from hydrogels or biopolymers provide a supportive structure for cells to grow, accelerating healing. Bioengineered skin grafts, often incorporating patient-derived cells, reduce rejection risks and improve integration.[8] These innovations offer hope for patients with diabetic ulcers, pressure sores, and venous ulcers, where healing is slow or absent. Cellular therapies reduce infection risks and improve skin quality while engineered tissues restore function and aesthetics. Challenges remain, such as rapidly increasing costs, making it difficult for the low-middle-income population to access these treatments. Other challenges are related to immune responses and regulatory hurdles. Ongoing research and clinical trials are refining these approaches. As technology advances, personalized treatments combining stem cells and bioengineered scaffolds could become standard techniques and provide long-term solutions for those suffering from chronic or non-healing wounds. Efforts are also underway to enhance the scalability and affordability of these therapies to make them accessible to a broader patient population. Future developments in gene editing and 3D bioprinting will optimize these treatments and ensure more effective and widely available regenerative solutions.

CONCLUSION

Cellular therapies and tissue bioengineering can enhance chronic ulcer healing by improving wound closure, skin regeneration and mobility. All these approaches provide promising alternatives to conventional treatments with minimal adverse effects. Our findings support their integration into clinical practice to improve patient outcomes which can also help to reduce healthcare burdens. Further large-scale studies can refine protocols and ensure long-term safety and efficacy. Advancing

regenerative medicine in wound care could transform treatment strategies can offer better recovery prospects for patients with chronic ulcers.

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