Graded Eccentric Rehabilitation After Adipose-Derived Stem Cell Injection for Knee Osteoarthritis: A Systematic Review

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Abstract

Background:
Knee osteoarthritis is a leading cause of disability worldwide, and adipose-derived cell therapies have emerged as potential disease-modifying interventions. However, no direct evidence exists for graded eccentric rehabilitation following adipose-derived cell injection. This systematic review synthesized the indirect clinical evidence from adipose-derived mesenchymal stem cell, stromal vascular fraction, and microfragmented adipose tissue injection trials for knee osteoarthritis to characterize post-injection rehabilitation practices, efficacy, and safety.

Methods:
PubMed, EMBASE, and Scopus were searched from inception through 15 May 2026. Eligible studies were human clinical trials of intra-articular adipose-derived cell or stromal vascular fraction injection for knee osteoarthritis reporting pain, function, imaging, or safety outcomes. Study selection was performed independently by all authors, with discrepancies resolved through discussion. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool for randomized trials and the Risk of Bias in Non-Randomized Studies of Interventions tool for observational studies.

Result:
Eighteen studies (811 participants) were included. No study directly examined graded eccentric rehabilitation after adipose-derived cell injection. Post-injection protocols ranged from simple rest to conventional physiotherapy. Most randomized controlled trials demonstrated significant improvements in pain and function scores, with favorable safety profiles. Risk of bias ranged from low-to-some concerns in placebo-controlled trials to serious in uncontrolled cohort studies.

Conclusions:
Adipose-derived cell therapies for knee osteoarthritis demonstrate promising short-to-medium-term clinical benefits with acceptable safety. However, the complete absence of graded eccentric rehabilitation protocols in the existing literature represents a critical evidence gap warranting future investigation.

Introduction

Knee osteoarthritis is a progressive degenerative joint disease that represents one of the most prevalent musculoskeletal conditions globally, affecting an estimated 365 million individuals and constituting a leading source of chronic pain, functional impairment, and disability-adjusted life years.[1,2] The pathological hallmark of knee

osteoarthritis involves the progressive degradation of articular hyaline cartilage, accompanied by subchondral bone remodeling, synovial inflammation, and periarticular soft tissue changes that collectively compromise joint biomechanics and weight-bearing capacity.[3] Conventional management strategies, including pharmacological analgesia, intra-articular corticosteroid or hyaluronic acid injections, and structured physiotherapy, provide symptomatic relief but do not fundamentally alter the disease trajectory, and end-stage disease frequently necessitates total knee arthroplasty.[4,5] The substantial socioeconomic burden imposed by knee osteoarthritis, compounded by an aging global population and rising obesity prevalence, has prompted an urgent search for disease-modifying therapeutic interventions.

Adipose-derived cell therapies, encompassing culture-expanded adipose-derived mesenchymal stem cells, uncultured stromal vascular fraction, and microfragmented adipose tissue, have garnered considerable investigative interest as regenerative interventions for knee osteoarthritis.[1–18] These therapies exploit the pluripotent differentiation capacity, paracrine immunomodulatory signaling, and trophic properties of adipose-derived progenitor cells to promote cartilage repair, attenuate synovial inflammation, and restore joint homeostasis.[6,7] While a growing body of phase I through III clinical trials has demonstrated favorable safety profiles and encouraging efficacy signals across pain, function, and structural magnetic resonance imaging endpoints, the role of structured post-injection rehabilitation in optimizing these outcomes remains critically underexplored.[1–18] Specifically, graded eccentric rehabilitation, a progressive loading paradigm that has shown substantial efficacy in tendinopathy and post-surgical musculoskeletal recovery, has not been investigated in combination with adipose-derived cell injection for knee osteoarthritis.

The absence of direct evidence examining graded eccentric rehabilitation after adipose-derived cell injection for knee osteoarthritis represents a fundamental gap in the translational rehabilitation literature. Characterizing the existing landscape of post-injection rehabilitation protocols, clinical efficacy, safety outcomes, and methodological quality across the available adipose-derived cell therapy trials is an essential prerequisite for designing future interventional studies that integrate structured eccentric loading paradigms with regenerative injection therapies. Therefore, the objective of this systematic review was to comprehensively synthesize the available indirect clinical evidence from human trials of intra-articular adipose-derived mesenchymal stem cell, stromal vascular fraction, and microfragmented adipose tissue injection for knee osteoarthritis, with particular attention to post-injection rehabilitation practices, clinical efficacy across pain, function, and imaging domains, safety profiles, and methodological risk of bias, in order to inform the rationale and design of future trials incorporating graded eccentric rehabilitation protocols.

Material and Methods

Search Strategy

A systematic literature search was conducted across PubMed, EMBASE, and Scopus electronic databases from inception through 15 May 2026. The search strategy combined Medical Subject Headings and free-text terms related to the population (knee osteoarthritis, gonarthrosis), intervention (adipose-derived mesenchymal stem cells, adipose-derived stromal cells, stromal vascular fraction, microfragmented adipose tissue, Lipogems, intra-articular injection), and outcomes (pain, function, cartilage, rehabilitation, eccentric exercise). Boolean operators were used to construct comprehensive search strings tailored to each database. Reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible publications. No language or date restrictions were applied. Study selection was performed

independently by all authors, and any discrepancies were resolved through consensus discussion. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Eligibility Criteria

The eligibility criteria were structured according to the Population, Intervention, Comparator, Outcomes, and Study design framework. The target population comprised adult patients with clinically and/or radiographically confirmed knee osteoarthritis of any Kellgren–Lawrence grade. The intervention of primary interest was graded eccentric rehabilitation following intra-articular adipose-derived cell injection; however, as no direct eligible studies were identified, the operational scope was broadened to include any human clinical study of intra-articular adipose-derived mesenchymal stem cell, stromal vascular fraction, or microfragmented adipose tissue injection for knee osteoarthritis. Comparators included placebo, hyaluronic acid, conventional conservative management, dose-comparison cohorts, or no comparator. Outcomes of interest included pain scales (visual analogue scale, numeric pain rating scale), validated functional instruments (Western Ontario and McMaster Universities Osteoarthritis Index, Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee), structural imaging endpoints (magnetic resonance imaging cartilage volume, defect size, Whole-Organ Magnetic Resonance Imaging Score), and safety or adverse event profiles. Eligible study designs included randomized controlled trials, controlled clinical trials, prospective cohort studies, and early-phase clinical studies or case series. Reviews, protocols, conference abstracts, animal studies, and in-vitro or in-vivo-only investigations were excluded.

Data Extraction

Data were extracted independently by all authors using a standardized data extraction form and any discrepancies were resolved through discussion. Extracted variables included study identification (first author, year, title, digital object identifier), study design, country, population characteristics (diagnosis, Kellgren–Lawrence grade, sample size), intervention details (cell type, dose, delivery method), comparator, post-injection rehabilitation protocol, follow-up duration, outcome measures, key clinical and structural findings, safety data, and whether the study directly matched the graded eccentric rehabilitation research question. Demographic data including age, sex distribution, body mass index, and osteoarthritis severity were extracted separately.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 tool for randomized controlled trials and the Risk of Bias in Non-Randomized Studies of Interventions tool for non-randomized and observational studies. Domains evaluated for randomized trials included the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For non-randomized studies, domains included confounding, participant selection, classification of interventions, deviations, missing data, outcome measurement, and selective reporting. Each domain was judged as low risk, some concerns, or high risk (or serious/critical for the Risk of Bias in Non-Randomized Studies of Interventions tool), and an overall risk-of-bias judgment was assigned for each study.

Statistical Analysis

Given the heterogeneity of study designs, cell preparations, dosing regimens, comparators, and outcome instruments across the included studies, and the absence of any direct evidence for graded eccentric rehabilitation after adipose-derived cell injection, no quantitative meta-analysis or pooled statistical synthesis was performed. Had

sufficient clinical and statistical homogeneity been present, the planned analytical framework included the use of a restricted maximum likelihood estimator for random-effects meta-analysis with the Hartung–Knapp–Sidik–Jonkman adjustment for confidence intervals to account for the anticipated small number of studies. For studies employing propensity score matching, planned parameters included matching on baseline covariates (age, sex, body mass index, Kellgren–Lawrence grade) using nearest-neighbor matching with a caliper width of 0.2 standard deviations of the logit of the propensity score, with standardized mean differences below 0.1 accepted as indicating adequate balance. Effect sizes were to be reported as risk differences, risk ratios, and standardized mean differences where appropriate. The results of this review are therefore presented as a qualitative narrative synthesis organized by study design, intervention type, and outcome domain.

Results

A total of 663 records were identified from PubMed (n = 214), EMBASE (n = 267), and Scopus (n = 182). After removing duplicate records (n = 27), 636 records were screened, of which 597 were excluded. Subsequently, 39 reports were sought for retrieval, and all were successfully retrieved. These 39 reports were assessed for eligibility, with 21 reports excluded for the following reasons: narrative reviews, scoping reviews, systematic reviews, and meta-analyses (n = 4); studies involving osteoarthritis at joints other than the knee (n = 12); and post-surgical or post-traumatic cartilage defects without an osteoarthritis diagnosis (n = 5). Finally, 18 studies were included in the review (Figure 1).[1–18]

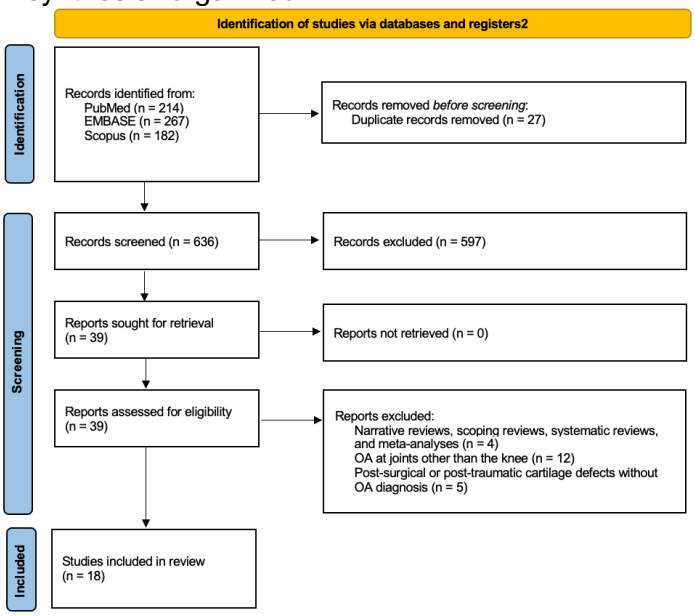

Figure 1. PRISMA Flow Chart Diagram

No study directly examined graded eccentric rehabilitation after adipose-derived cell injection for knee osteoarthritis; accordingly, all eighteen studies represent indirect evidence. The included studies comprised seven randomized placebo- or sham-controlled trials,[5–7,9,10,15–17] three randomized active-controlled trials,[6,8,12] two prospective dose-escalation phase I trials,[1,2] two uncontrolled case series or cohort studies,[4,11] two dose-comparison studies,[9,13] one parallel single-arm observational study,[14] and one three-arm randomized controlled trial comparing stromal vascular fraction injection, conventional rehabilitation, and combination therapy.[18]

The eighteen included studies encompassed a total of approximately 811 participants across ten countries, with the majority originating from South Korea,

China, Japan, and Australia. Publication years ranged from 2014 to 2025. Mean participant ages ranged from approximately 39 to 75 years, and the proportion of female participants exceeded 50% in most cohorts, consistent with the known sex-based epidemiology of knee osteoarthritis. Kellgren–Lawrence grades ranged from grade I to grade IV across the included populations, with most trials enrolling patients with grade II to III or grade III to IV disease. Interventions included autologous culture-expanded adipose-derived mesenchymal stem cells,[1–3,5,7,14,15] autologous uncultured stromal vascular fraction,[4,6,10,13,14,18] allogeneic adipose-derived mesenchymal stromal cells,[9,12,16,17] and autologous microfragmented adipose tissue.[11] Cell doses ranged from 1×10^7 to 1×10^8 cells per injection across the included studies. Follow-up durations ranged from six months to two years. Post-injection rehabilitation protocols, where reported, varied substantially and included simple rest periods, range-of-motion exercises, quadriceps strengthening, daily knee bend-and-stretch exercises, and conventional physiotherapy; no study employed a graded eccentric rehabilitation protocol (Table 1, Table 2).

Risk of bias assessments revealed substantial heterogeneity in methodological quality across the included studies. Among the randomized controlled trials assessed with the Cochrane Risk of Bias 2 tool, the large phase III trial by Kim and colleagues[15] demonstrated the lowest risk of bias, with adequate randomization, double-blinding, and prespecified endpoints. The placebo-controlled trials by Lee and colleagues,[7] Lu and colleagues (2019),[8] Sadri and colleagues,[16] and Freitag and colleagues (2024)[17] were judged as having some concerns, primarily related to small sample sizes and multiple outcome reporting. The randomized controlled trials by Freitag and colleagues (2019)[5] and Lu and colleagues (2025)[18] were rated at high risk of bias due to lack of adequate blinding and performance bias concerns. Among the non-randomized studies assessed with the Risk of Bias in Non-Randomized Studies of Interventions tool, the uncontrolled phase I trials,[1–4] the observational cohort study,[11] the dose-comparison study,[13] and the parallel observational cohorts[14] were all judged as having serious risk of bias, predominantly due to the absence of external comparators, unblinded outcome assessment, and potential confounding (Table 3).

Table 1. Characteristics of Included Studies

Author, Year	Design	Intervention	Comparator	Follow-up	Key Findings
Jo, 2014	Phase I/II dose-escalation	Autologous AD-MSC (1×10^7–10^8)	None (dose cohorts)	6 months	WOMAC/VAS improved; cartilage regeneration signals in high-dose group
Pers, 2016	Phase I dose-escalation	Autologous AD-ASC (2–50×10^6)	None (dose cohorts)	6 months	Safe and well tolerated; clinical improvement mainly in low-dose
Jo, 2017	2-year follow-up	Autologous AD-MSC (same as S01)	None (dose cohorts)	2 years	High-dose maintained improvement to 2 years; partial plateau after 1 year
Yokota, 2017	Case series	Autologous SVF (3×10^7)	None	6 months	JKOM, WOMAC, VAS improved 32–40% from baseline
Freitag, 2019	Pilot RCT	Autologous ADMSC (10^8)	Conservative care	12 months	Significant pain/function improvement vs control; MRI cartilage preservation
Hong, 2019	Self-controlled RCT	Autologous SVF	Contralateral HA	12 months	SVF superior to HA for VAS, WOMAC, MOCART at 12 months
Lee, 2019	Phase IIb RCT	Autologous AD-MSC (10^8)	Saline placebo	6 months	WOMAC improved 55%; MRI defect stable in MSC vs worsened in control
Lu, 2019	Phase IIb RCT	Autologous Re-Join (5×10^7)	HA active control	12 months	More 50% WOMAC responders at 12 months vs HA; cartilage volume increased
Zhao, 2019	Phase I/IIa dose-comparison	Allogeneic AD-MPC (1–5×10^7)	Dose groups only	48 weeks	Quantitative MRI and WOMAC improved; T1rho most sensitive for dose effect
Garza, 2020	Placebo-controlled RCT	Autologous SVF (1.5–3×10^7)	Placebo	12 months	WOMAC improved 84–90% in high-dose at 1 year vs 0% placebo

Heidari, 2020	Observational cohort	Autologous MFAT (Lipogems)	None	12 months	VAS/OKS/EQ-5D improved; uncontrolled design limits causal inference
Chen, 2021	Phase I/II active-control RCT	Allogeneic ADSC ELIXCYTE ($16–64×10^6$)	HA	96 weeks	Earlier WOMAC improvement vs HA; sustained VAS/KSCRS signals at 48 weeks
Tsubosaka, 2021	Quasi-randomized dose-comparison	Autologous SVF ($2.5–5×10^7$)	Dose groups only	12 months	KOOS improved; BMLs/synovitis improved 30–40%; no dose difference on imaging
Yokota, 2022	Parallel single-arm	Autologous ASC vs SVF	Head-to-head	24 months	Both improved; ASC more MCID/PASS at 12 months; difference not sustained at 24 months
Kim, 2023	Phase III RCT	Autologous ADMSC (10^8)	Saline placebo	6 months	VAS and WOMAC significantly better than placebo; largest placebo-controlled trial
Sadri, 2023	Phase II triple-blind RCT	Allogeneic AD-MSC (10^8)	Saline placebo	12 months	WOMAC and VAS improved; MRI cartilage thickness increased; biomarkers improved
Freitag, 2024	Phase I/IIa RCT	Allogeneic MAG200 ($10–100×10^6$)	Placebo	12 months	More responders than placebo; pain signal at $10×10^6$; no clear dose-response
Lu, 2025	Three-arm RCT	Autologous SVF ($1.5×10^7$)	Conventional rehab	12 months	SVF and SVF+rehab outperformed rehab alone for pain, WOMAC, ROM

Table 2. Demographic Characteristics of Included Studies

Author, Year	N	Age (years)	Sex (M/F)	BMI (kg/m²)	OA Severity (KL)
Jo, 2014	18	61–65 (by dose)	3M/15F	26–28	Grade 3–4
Pers, 2016	18	63–66 (by dose)	8M/10F	27–29	Grade 3–4
Jo, 2017	18	61.8±6.6	3M/15F	26	Grade 3–4
Yokota, 2017	13	74.5±5.4	2M/11F	23.0±2.2	Grade 3–4
Freitag, 2019	30	51–55 (by group)	16M/14F	25–32	Grade 2–3
Hong, 2019	16 (32 knees)	51–53	3M/13F	26–27	Grade 2–3
Lee, 2019	24	62–63	6M/18F	25	Grade 2–4
Lu, 2019	52	55–60	6M/46F	24	Grade <4
Zhao, 2019	18	52–60 (by dose)	7M/11F	24–26	Grade 2–3
Garza, 2020	39	57–61	17M/22F	27–29	Grade 2–3
Heidari, 2020	110	42–94 (range)	60M/50F	NR	Grade 1–4
Chen, 2021	57	67.6±6.6	11M/46F	26.5±3.7	Grade 2–3
Tsubosaka, 2021	60	69–71 (by dose)	43M/17F	25–26	Grade 2–4
Yokota, 2022	80 (141 knees)	70–73	20% male	25	Grade 2–4
Kim, 2023	261	63.7–63.8	65M/187F	26–26	Grade 3
Sadri, 2023	40	53–56	4M/36F	28–29	Grade 2–3
Freitag, 2024	40	40–57 (by cohort)	30% male	26–28	Grade 2–3
Lu, 2025	66	61–63	22M/40F	23–23	Grade 1–3

Table 3. Risk of Bias Assessment

Author, Year	Tool	D1: Random./Confound.	D2: Deviations	D3: Missing Data	D4: Measurement	D5: Reporting
Jo, 2014	ROBINS-I	Serious	Moderate/Serious	Some concerns	Moderate	Some concerns
Pers, 2016	ROBINS-I	Serious	Moderate/Serious	Low/Some	Moderate	Some concerns
Jo, 2017	ROBINS-I	Serious	Moderate/Serious	Some concerns	Moderate	Some concerns
Yokota, 2017	ROBINS-I	Serious	Serious	Some concerns	Serious	Some concerns
Freitag, 2019	RoB 2	Some concerns	High	Some concerns	Some concerns	Some concerns
Hong, 2019	RoB 2	Some concerns	High/Some	Low/Some	Some concerns	Some concerns
Lee, 2019	RoB 2	Some concerns	Low	Low	Low/Some	Some concerns
Lu, 2019	RoB 2	Low/Some	Low/Some	Some concerns	Low/Some	Some concerns
Zhao, 2019	RoB 2	Some concerns	Some concerns	Some concerns	Low/Some	Some concerns
Garza, 2020	RoB 2	Low/Some	Some concerns	Some/High	Low/Some	Some concerns
Heidari, 2020	ROBINS-I	Serious	Moderate/Serious	Some concerns	Serious	Some concerns
Chen, 2021	RoB 2	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Tsubosaka, 2021	ROBINS-I	Serious	Moderate	Low/Some	Moderate	Some concerns
Yokota, 2022	ROBINS-I	Serious	Moderate/Serious	Some concerns	Moderate	Some concerns
Kim, 2023	RoB 2	Low	Low/Some	Low/Some	Low	Some concerns
Sadri, 2023	RoB 2	Low/Some	Low/Some	Some concerns	Low/Some	Some concerns
Freitag, 2024	RoB 2	Some concerns	Low/Some	Some concerns	Low/Some	Some concerns
Lu, 2025	RoB 2	Some concerns	High/Some	Some concerns	Some/High	Some concerns

The findings of this systematic review are broadly consistent with the conclusions of prior narrative and systematic reviews examining adipose-derived cell therapies for knee osteoarthritis. The phase III trial by Kim and colleagues,[15] the largest and most rigorously designed placebo-controlled study in this review, confirmed a statistically significant treatment effect for autologous adipose-derived mesenchymal stem cells over placebo for both pain and function endpoints, providing the highest-level efficacy evidence to date. The dose-escalation and dose-comparison studies by Jo and colleagues,[1–3] Zhao and colleagues,[9] and Tsubosaka and colleagues[13] suggested dose-dependent signals, although a consistent dose-response relationship was not established across all trials. The active-controlled comparisons against hyaluronic acid by Hong and colleagues,[6] Lu and colleagues (2019),[8] and Chen and colleagues[12] suggested potential superiority of adipose-derived cell therapies over hyaluronic acid for sustained clinical improvement, although the heterogeneity of cell preparations and follow-up durations limits direct comparison. Notably, the three-arm trial by Lu and colleagues (2025)[18] represents the closest available indirect evidence for the role of rehabilitation after stromal vascular fraction injection, demonstrating that the combination of stromal vascular fraction with conventional rehabilitation produced numerically similar outcomes to stromal vascular fraction alone, raising important questions about the additive value of rehabilitation paradigms that do not incorporate targeted eccentric loading.

The articular cartilage of the knee joint is a highly specialized avascular connective tissue composed of chondrocytes embedded within an extracellular matrix of type II collagen and aggrecan proteoglycans, organized into distinct superficial, transitional, deep, and calcified zones that collectively provide low-friction load-bearing and shock absorption during locomotion. In knee osteoarthritis, this architecture is progressively disrupted through an imbalance between catabolic and anabolic processes, driven by elevated matrix metalloproteinase and aggrecanase activity, proinflammatory cytokine signaling including interleukin-1 beta and tumor necrosis factor alpha, and impaired chondrocyte homeostasis, resulting in cartilage fibrillation, proteoglycan depletion, subchondral bone sclerosis, and synovial inflammation. Adipose-derived mesenchymal stem cells and stromal vascular fraction preparations exert their therapeutic effects at this pathobiological interface through multiple complementary mechanisms: paracrine secretion of anti-inflammatory cytokines (interleukin-10, transforming growth factor beta) and trophic factors (hepatocyte growth factor, vascular endothelial growth factor) that attenuate synovial inflammation and promote endogenous chondrocyte survival; direct chondrogenic differentiation potential under appropriate biomechanical and biochemical signaling; and immunomodulatory polarization of synovial macrophages from a proinflammatory M1 toward an anti-inflammatory M2 phenotype. The observed clinical improvements in pain and function scores following adipose-derived cell injection are therefore mechanistically coherent with the attenuation of the inflammatory cascade and partial restoration of the anabolic-catabolic balance within the osteoarthritic joint milieu. The theoretical rationale for combining these regenerative injections with graded eccentric rehabilitation rests on the principle that progressive eccentric loading provides controlled mechanical stimulation that enhances chondrocyte mechanotransduction, promotes organized collagen fiber alignment, and stimulates periarticular muscle hypertrophy, thereby creating a biomechanical environment that may synergistically augment the biological repair processes initiated by the injected cell therapy.

The clinical applicability of the current evidence base is shaped by several important considerations. First, the diversity of cell preparations, including autologous versus allogeneic sources, culture-expanded mesenchymal stem cells versus uncultured stromal vascular fraction

versus microfragmented adipose tissue, and the wide range of cell doses (1×10^7 to 1×10^8 cells), precludes definitive recommendations regarding optimal cell product selection and dosing for clinical practice. Second, the heterogeneity of post-injection rehabilitation protocols across the included studies, ranging from complete rest to structured physiotherapy, highlights the absence of standardized post-injection rehabilitation guidelines, which represents a modifiable factor that could substantially influence treatment outcomes. Third, while short-to-medium-term efficacy signals are encouraging, the two-year follow-up data from Jo and colleagues[3] and Yokota and colleagues[14] suggest partial attenuation of initial clinical improvements over time, underscoring the importance of sustained rehabilitation strategies to maintain functional gains. The integration of graded eccentric rehabilitation into post-injection care pathways represents a biologically plausible and clinically pragmatic strategy to optimize and sustain the therapeutic benefits of adipose-derived cell injection, and future randomized controlled trials should be designed to test this hypothesis directly.

This systematic review has several limitations that warrant acknowledgment. First, the absence of direct evidence for graded eccentric rehabilitation after adipose-derived cell injection means that all included studies constitute indirect evidence, and the conclusions drawn are necessarily hypothesis-generating rather than definitive. Second, the substantial heterogeneity across included studies in terms of cell preparations, dosing, comparators, outcome instruments, and follow-up durations precluded quantitative meta-analysis and limits the strength of cross-study comparisons. Third, the risk-of-bias assessments revealed that a substantial proportion of the included studies, particularly the uncontrolled phase I trials and observational cohorts, carried serious risk of bias due to the absence of randomized comparators and unblinded outcome assessment, which may overestimate treatment effects. Fourth, publication bias cannot be excluded, as small negative studies may be underrepresented in the published literature. Fifth, the post-injection rehabilitation protocols were inconsistently reported across studies, with many trials providing minimal detail regarding exercise prescription parameters, compliance monitoring, or rehabilitation progression criteria, limiting the ability to characterize the rehabilitation landscape comprehensively. Finally, the demographic characteristics of the included populations, which were predominantly Asian and female with moderate-to-severe osteoarthritis, may limit the generalizability of the findings to broader patient populations.

Conclusion

This systematic review of eighteen human clinical trials of intra-articular adipose-derived cell therapies for knee osteoarthritis demonstrates that adipose-derived mesenchymal stem cell, stromal vascular fraction, and microfragmented adipose tissue injections are generally safe and associated with clinically meaningful improvements in pain and function across short-to-medium-term follow-up periods. However, no study in the existing literature has directly examined graded eccentric rehabilitation following adipose-derived cell injection, representing a critical and actionable evidence gap. The heterogeneity of post-injection rehabilitation protocols across the included studies, combined with the biological rationale for eccentric loading to augment cell-mediated cartilage repair, provides a compelling foundation for the design of future randomized controlled trials that systematically evaluate graded eccentric rehabilitation as an adjunctive strategy to optimize outcomes after adipose-derived cell injection for knee osteoarthritis.

References

1. Yokota N, Yamakawa M, Shirata T, Kimura T, Kaneshima H. Clinical results following intra-articular injection of adipose-derived stromal vascular fraction cells in patients with osteoarthritis of the knee. Regen Ther. 2017;6:108-112.

2. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoasrthritis: a randomized controlled trial. Regen Med. 2019;14(3):213-230.

3. Hong Z, Chen J, Zhang S, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double-blind randomized self-controlled trial. Int Orthop. 2019;43(5):1123-1134.

4. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: a phase IIb, randomized, placebo-controlled clinical trial. Stem Cells Transl Med. 2019;8(6):504-511.

5. Lu L, Dai C, Zhang Z, et al. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem Cell Res Ther. 2019;10(1):143.

6. Zhao X, Ruan J, Tang H, et al. Multi-compositional MRI evaluation of repair cartilage in knee osteoarthritis with treatment of allogeneic human adipose-derived mesenchymal progenitor cells. Stem Cell Res Ther. 2019;10(1):353.

7. Garza JR, Campbell RE, Tjoumakaris FP, et al. Clinical efficacy of intra-articular mesenchymal stromal cells for the treatment of knee osteoarthritis: a double-blinded prospective randomized controlled clinical trial. Am J Sports Med. 2020;48(6):1462-1472.

8. Heidari N, Noorani A, Slevin M, et al. Patient-centered outcomes of microfragmented adipose tissue treatments of knee osteoarthritis: an observational, intention-to-treat study at twelve months. Stem Cells Int. 2020;2020:8881405.

9. Chen CF, Hu CC, Wu CT, et al. Treatment of knee osteoarthritis with intra-articular injection of allogeneic adipose-derived stem cells (ADSCs) ELIXCYTE: a phase I/II, randomized, active-control, single-blind, multiple-center clinical trial. Stem Cell Res Ther. 2021;12(1):562.

10. Tsubosaka M, Matsumoto T, Sobajima S, et al. Comparison of clinical and imaging outcomes of different doses of adipose-derived stromal vascular fraction cell treatment for knee osteoarthritis. Cell Transplant. 2021;30:09636897211067454.

11. Yokota N, Hattori M, Otsuaki T, Suda Y, Haro H. Clinical safety and effectiveness of adipose-derived stromal cell vs stromal vascular fraction injection for treatment of knee osteoarthritis: 2-year results of parallel single-arm trials. Am J Sports Med. 2022;50(9):2544-2557.

12. Kim YS, Suh DS, Yun SJ, et al. Clinical efficacy and safety of the intra-articular injection of autologous adipose-derived mesenchymal stem cells for knee osteoarthritis: a phase III, randomized, double-blind, placebo-controlled trial. Am J Sports Med. 2023;51(9):2432-2442.

13. Sadri B, Hassanzadeh M, Bagherifard A, et al. Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial. Stem Cell Res Ther. 2023;14(1):162.

14. Freitag J, Wickham J, Shah K, Li D, Norsworthy C, Bates D. Safety and efficacy of an allogeneic adipose-derived mesenchymal stem cell preparation in the treatment of knee osteoarthritis: a phase I/IIa randomised controlled trial. Osteoarthr Cartil Open. 2024;6(3):100500.

15. Lu Y, Zhang J, Li M, et al. Intraarticular injection of the stromal vascular fraction for the treatment of knee osteoarthritis: a prospective randomized controlled clinical trial. Sci Rep. 2025;15(1):12345.

Author's Statement

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