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**Human Clinical Article**

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# Intra-articular allogeneic adipose-derived mesenchymal stromal cell injections for stage III knee osteoarthritis: a double-blind placebo-controlled trial with 60-month follow-up

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## Abstract

**Knee osteoarthritis (KOA) is a progressive degenerative joint disease with limited treatment options that effectively modify disease progression. This study evaluates the safety and efficacy of allogeneic adipose-derived mesenchymal stromal cells (ADMSCs) injected under ultrasound guidance in patients with symptomatic stage III KOA. In this single-site, randomized, double-blind, placebo-controlled trial, patients were assigned to receive either 2 doses of allogeneic expanded ADMSCs, administered 2 weeks apart (Arm A, mean total dose: $69.58 \times 10^6$ ADMSCs), or 2 equal-volume normal saline injections (Arm B). Blinding was maintained for 12 months, after which follow-up of Arm A continued to 60 months. Treatment efficacy was assessed using normalized Knee Injury and Osteoarthritis Outcome Score and Western Ontario and McMaster Universities Osteoarthritis Index at 6, 12, 24, 36, 48, and 60 months, while magnetic resonance imaging (MRI) evaluations were performed at baseline and 12 months. A total of 29 subjects (21 in Arm A, 8 in Arm B) completed the study. Adverse events in Arm A were mild and transient, including localized pain and swelling. Patients in Arm A demonstrated significant improvements in clinical scores compared to baseline, with highly significant differences at 6, 12, 24, and 36 months ($P < .0001$). MRI assessments at 12 months revealed structural improvement ($P < .02$). However, clinical improvements declined steadily after 36 months, with scores nearing baseline at 60 months. These findings suggest that allogeneic ADMSC therapy is safe and provides sustained clinical and structural benefits for up to 3 years. Larger trials are needed to optimize dosing and assess long-term efficacy.**

**Keywords:** knee osteoarthritis, mesenchymal stromal cells, cartilage regeneration, cellular therapy, regenerative medicine



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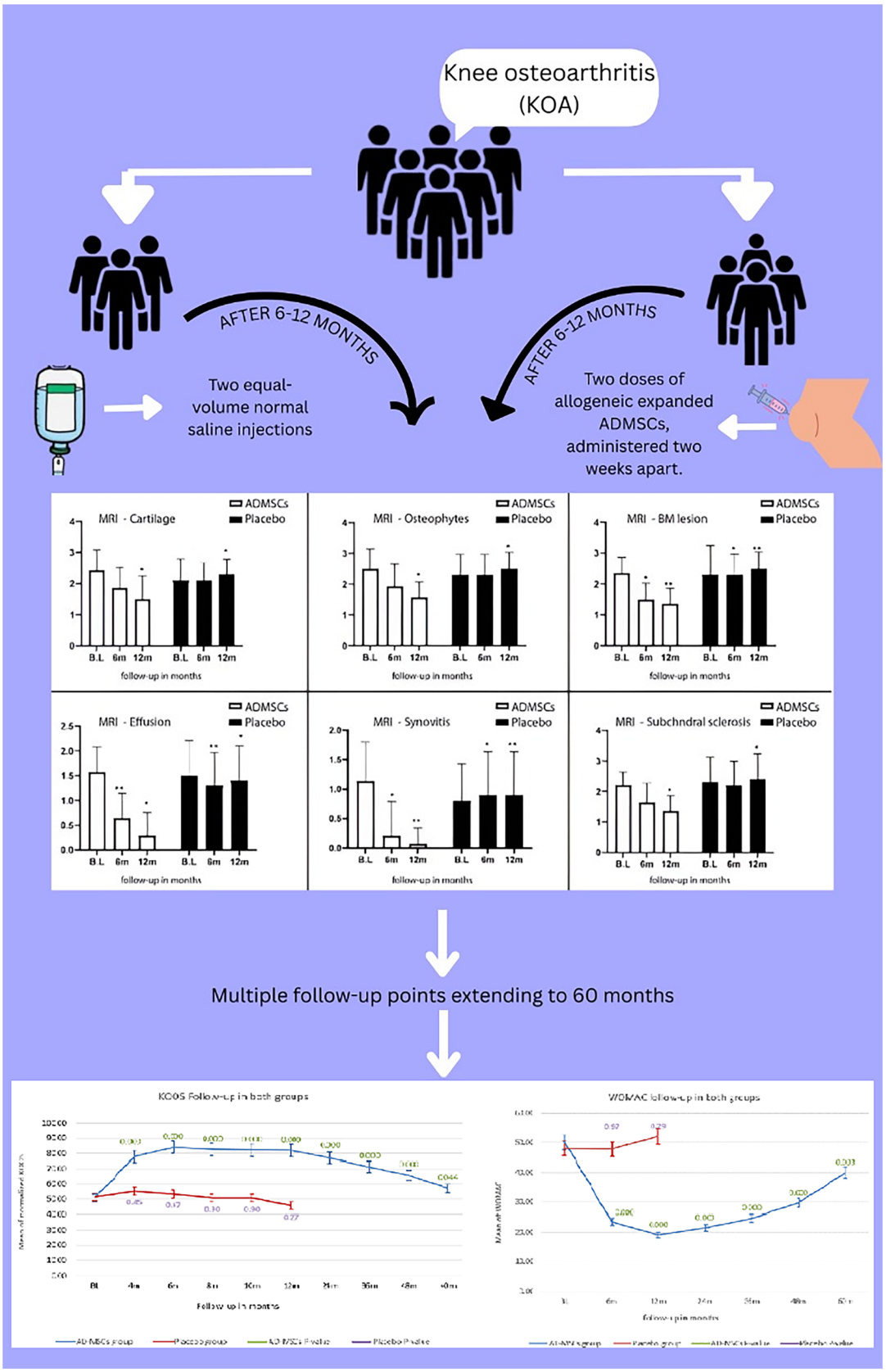
## Graphical abstract



**Significance statement**
Knee osteoarthritis is a leading cause of pain and disability worldwide, with few treatment options capable of altering its course. This study explores a novel cell-based therapy using donor-derived fat tissue cells delivered directly into the knee joint. The findings show that this approach may reduce symptoms and improve joint function for several years without serious side effects. By offering a non–surgical, regenerative option for patients with advanced disease, this research provides important insights into the future of cell-based treatments for degenerative joint conditions.

# Introduction

Knee osteoarthritis (KOA) is a degenerative joint disease characterized by progressive cartilage loss, subchondral bone sclerosis, and osteophyte formation. KOA is a leading cause of chronic pain, physical disability, and decreased quality of life, especially in the elderly population. Non–surgical interventions, such as physical therapy, analgesics, and intra-articular injections, are the first-line treatments for KOA.[1–3] However, they often provide only temporary relief and fail to slow the disease progression.

Recently the use of adipose-derived mesenchymal stromal cells (ADMSCs) has shown promising results.[3,4] ADMSCs are distinguished by their relative ease of isolation, while retaining the hallmark advantages common to other MSC sources, including high proliferative capacity and low immunogenicity.[3–5]

Several preclinical and clinical studies have investigated the safety and efficacy of ADMSC therapy in KOA. In vitro studies have demonstrated that ADMSCs can differentiate into chondrocytes and produce extracellular matrix components, such as type II collagen and aggrecan, essential for cartilage regeneration.[4,5] Animal studies have suggested that intra-articular injection of ADMSCs may reduce cartilage degeneration, decrease synovial inflammation, and improve joint function in a dose-dependent manner.[5,6]

Clinical studies have also shown promising results. A randomized controlled trial of 30 patients with KOA showed that intra-articular injection of autologous ADMSCs led to significant improvements in pain, function, and quality of life compared to saline injection.[7] Additionally, Koh et al.[8] showed that intra-articular injection of autologous MSCs derived from the infrapatellar fat pad significantly reduced pain, improved knee function and enhanced cartilage whole-organ MRI score in KOA patients. Recently, Cao et al.[9] did a systematic review and meta-analysis of 8 clinical studies (502 patients) and found that MSC therapy was safe and effective in improving pain and function in patients with KOA.

Despite these promising results, several questions remain unanswered, such as the optimal dose and frequency of ADMSC injection, the long-term safety and efficacy of ADMSC therapy, and the mechanisms underlying ADMSC-mediated cartilage regeneration. Further research is needed to address these questions and optimize ADMSC therapy for KOA.

Mesenchymal stromal cells (MSCs) have emerged as an innovative, minimally invasive therapeutic option for KOA, with potential benefits in cartilage regeneration and modulation of joint inflammation. These effects are now understood to be mediated primarily through the immunomodulatory and paracrine properties of MSCs, rather than direct differentiation into chondrocytes.[10,11] Preclinical and early clinical studies have suggested that MSCs may improve pain, function, and joint structure in KOA patients.[7,9]

Although early-phase studies have demonstrated the safety and efficacy of MSC therapy in KOA, important gaps remain. Most trials have been limited to short- or mid-term follow-up (≤24 months), leaving the durability of benefit uncertain. Moreover, few studies have focused specifically on patients with advanced (stage III) KOA, who represent a group with particularly limited therapeutic options. Finally, while autologous MSCs have been the focus of most published clinical studies, their use is limited by the need for invasive harvesting, inter-donor variability, and delays associated with individualized cell expansion. Allogeneic ADMSCs, in contrast, can be manufactured under cGMP conditions from healthy donors to provide a standardized, readily available 'off-the-shelf' therapy, which was the motivation for our study design. This work aims to study the safety of allogeneic ADMSCs in advanced-stage KOA and, as a secondary endpoint, to examine the efficacy of this treatment with extended follow-up to 60 months.

# Patients and methods

## Study design and ethical statement

This work is a prospective double-blind placebo-controlled phase I/II study. Informed consent was obtained from each patient as indicated by Helsinki Declaration. Institutional review board approval was obtained from the Cell Therapy Center institutional review board committee. The study was prospectively registered at ClinicalTrials.gov (NCT02966951). The study's primary aim was safety with a follow-up of 60 months. The secondary aim was to evaluate the efficacy by clinical and structural assessments of experimental arm (Arm A) versus placebo (Arm B) using normalized KOOS and WOMAC scores,[12,13] and MRI assessment at 6 and 12 months. Blinding was lifted at 12 months, and patients in Arm A were followed up clinically at 24, 36, 48, and 60 months, while patients in Arm B were offered MSC therapy without further analysis.

## Safety and clinical efficacy follow-up

Patients in both groups underwent follow-up assessments at 2, 4, 6, 8, 10, and 12 months post–injection, which included laboratory evaluations of hematological parameters, inflammatory markers, liver and kidney function, and comprehensive biochemical profiling.

Additionally, patients were assessed by clinical evaluation and follow-up interviews using a questionnaire developed at the CTC (Supplementary Material) as part of the in-house pharmacovigilance program. The questionnaire considers a systemic approach, including cardiovascular, neural, respiratory and local site adverse events.

Adverse events (AEs) were defined as either new symptoms occurring after injection or clinically significant worsening of baseline symptoms, assessed using structured follow-up interviews, questionnaires, and VAS scoring. Swelling and effusion were considered AEs only if they were new or worsened within 7 days post–injection compared to baseline status.

Clinical efficacy was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline and multiple follow-up points extending to 60 months. KOOS is a comprehensive patient-reported outcome measure that evaluates 5 domains: pain, symptoms, activities of daily living, sports/recreation, and quality of life. WOMAC is a widely used osteoarthritis-specific instrument, assessed pain, stiffness, and physical function. KOOS and WOMAC raw scores were normalized to a 0-100 scale, where 0 indicates the worst outcome and 100 the best. In line with the scoring instructions provided in our version of the questionnaires, these normalized values were expressed as percentage of the maximum possible score, and changes over time were analyzed to compare the treatment effect between groups.

## Radiographic assessment

KOA staging was done following the Kellgren and Lawrence classification as previously described[14,15] using standard knee X-ray imaging with the standing anteroposterior and horizontal lateral projection. Two radiologists independently did image interpretation and staging. Patients with grades III were selected. No patient with significant varus or valgus malalignment or significant effusion of either knee or both knees was included.

Baseline and follow-up MRI scans were performed using a 3.0T MRI scanner, with a dedicated 8-channel knee surface coil. The imaging protocol included T1-weighted sagittal, T2-weighted sagittal and coronal fat-suppressed, proton density (PD) sagittal, and T1-weighted fat-suppressed 3D sagittal and axial sequences. Imaging parameters were standardized with a field of view of 140-150 mm, slice thickness of 2 mm, flip angle of 40°, and voxel size of $0.07 \times 0.04 \times 2$ mm. Analysis was done as previously reported by our group[16] developed originally by Meredith et al.[17] Briefly, 6 key pathological features were analyzed: cartilage integrity, bone marrow lesions, osteophytes, subchondral sclerosis, joint effusion, and synovitis. Each parameter was graded on an ordinal scale from 0 (none) to 3 (severe). Cartilage damage was assessed using a validated scoring system,[18] incorporating lesion severity and size across 17 anatomical sub–regions.

## Cellular preparation and expansion

ADMSCs were isolated and cultured as previously described by our group[16,19] under cGMP conditions. Briefly, adipose samples were obtained from lipoaspirate material collected in a sterile syringe from patients undergoing liposuction following a signed informed consent. Lipoaspirates were treated with 0.075% collagenase solution (type I; Worthington) at 37 °C for 30 minutes with shaking every 5 minutes, after which the enzyme activity was neutralized with phosphate-buffered saline (Gibco). The cell suspension was then centrifuged at 1200 × g for 10 minutes to obtain a high-density cell pellet. Then the cells were washed with culture medium (Alpha MEM (Gibco) with 4 mM glutaMax (Gibco), 5% human platelet lysate and 1% Penicillin Streptomycin [Gibco]) at 500× g for 10 minutes. The cell pellet was resuspended and passed through a 70 µm cell strainer (BD). The cells were seeded at a density of $0.2 \times 10^6/cm^2$ and incubated in 5% $CO_2$ at 37 °C. After 24 hours, the culture flasks were washed with PBS to remove non–adherent cells and cultures were maintained until they reached 80%–90% confluence with media being changed every 72 hours. ASCs were harvested using 10X Tryple E (Gibco) and cultures were expanded to reach passage 3 then cryopreserved as a cell bank of individual allogenic doses. Quality control tests were performed to ascertain identity, purity, viability and sterility as per International Council for Harmonisation (ICH) guidelines and as explained further in the following section. For each injection, the cells were thawed and cultured until confluence at passage 4, then collected and suspended in normal saline.

## MSCs characterization and release

Cells were subjected to quality control tests adhering to European Commission Guidelines on Good Clinical Practice specific to advanced therapy medicinal products (ATMPs) before release. This included MSC phenotypical characterization for MSC markers by flow cytometry (BD FACSCanto II; BD Biosciences, USA) using BD Stemflow hMSC Analysis Kit, viability testing using trypan blue exclusion dye on the Countess automated cell counter system (Thermo, USA), mycoplasma using nucleic acid testing (MycoSEQ Mycoplasma Detection Kit, Thermo, USA) by real time PCR, endotoxin using LAL method (Endosafe, Charles river, USA), bacterial contamination using growth method (BactecAlert, Biomeuriex, France), and manual karyotyping by G-banding. All methods and set criteria were described previously by our group.[20,21] Additionally, MSCs were tested for multilineage differentiation potential. For osteogenic and adipogenic differentiation, cells were cultured in Stempro Osteogenesis differentiation media and Stempro Adipogenesis differentiation media, respectively, as per the manufacturer's recommendation. Following osteogenic induction, cultures were stained using Alizarin Red (Sigma-Aldrich), and following adipogenic differentiation, cultures were stained using Oil Red O (Sigma-Aldrich), to assess extracellular deposits.

## Sample size and statistical analysis

Sample size was calculated to detect an expected improvement of 80.35% in the treatment group, based on our previous findings in similar pilot studies.[15,16] A power of 80% and a significance level of 0.05 were used. Calculation was performed using Cohen's *d* formula for continuous outcomes.

Statistical analyses were performed using Mathmatica and Statistical Package for the Social Sciences (SPSS) software. Continuous variables, including KOOS and WOMAC scores, were expressed as mean ± standard deviation (SD). Comparisons between treatment and placebo groups were conducted using Mann-Whitney test. Within-group changes over time were analyzed using Wilcoxon test. The statistical significance of MRI-based changes at 12 months was assessed using Wilcoxon test. A *P*-value of <0.05 was considered statistically significant and <0.01 as highly significant. Responder rate was defined as the proportion of subjects who show at least a 50% improvement in clinical or MRI outcome compared to their baseline measurement.

# Results

## Cell production and release

Adipose tissue was collected from a single donor undergoing routine liposuction after obtaining an informed consent. The donor was screened for absence of transmissible diseases including hepatitis B and C, HIV, and Syphilis. Adipose tissue was transferred to the manufacturing facility at the cell therapy center (CTC)/ University of Jordan. MSCs isolated and expanded under cGMP conditions showed hallmark characteristics of MSCs by being plastic adherent, spindle shaped (Figure 1A), and having the ability of multi–lineage differentiation (Figure 1B-D).

Quality control assessments confirmed the MSC phenotype through flow cytometric analysis (Figure 2), demonstrating positive expression of CD105, CD73, and CD90, while lacking expression of CD45, CD34, CD11b, CD19, and HLA-DR. Additionally, release testing verified sterility, as evidenced by the absence of aerobic and anaerobic bacterial and fungal growth, as well as negative detection of mycoplasma nucleic acids. Endotoxin levels were <0.050 EU/mL, and chromosomal analysis by G-banding showed a normal karyotype. Cell viability was assessed immediately prior to injection and confirmed to be greater than 90%.

## Patient enrollment and randomization

Patients complaining of knee joint pain were interviewed and checked against pre-defined inclusion and exclusion criteria (Table 1), which were similar to our previously published work.[16] The estimated sample size required was 32 in the treatment group and 11 in the placebo group. "Sample" was defined as individual knee joints rather than patients. A total of 47 patients (61 knees) met all inclusion criteria, 43 of whom (55 knees) consented to being enrolled in the study. Patients were randomized at a ratio of 3:1 into arm A (treatment) and arm B (placebo) through assigning random numbers by an independent study coordinator. Of the enrolled patients, 29 (aged 48-75 years) received all doses and completed the full follow-up period (Figure 3). In total, 29 knees in the treatment group and 8 knees in the placebo group were treated and followed through to study completion. The remaining participants were lost to follow-up or relocation. Importantly, no patient discontinued participation due to treatment-related adverse events. In the placebo group, several patients withdrew because their pain did not subside and their function did not improve. However, group allocation remained blinded until the 12-month time point, in accordance with the study protocol.

The first patient was treated on November 7, 2017, and the last patient completed the last dose on November 13, 2018. All patients received 2 doses and were followed for a minimum of 60 months. Patients of both genders were included.

## Demographics and clinical features

Patients showed comparable demographic data, with a mean age of 64.2 years and 63.5 years, a mean body mass index of 27.14 and 28.18, a mean KOOS score[12] of 50.71% and 51.25% and a mean WOMAC score[13] of 50.12% and 47.95% for Arm A and Arm B, respectively (Table 2). The severity of clinical scores indicate advanced symptomatic KOA.

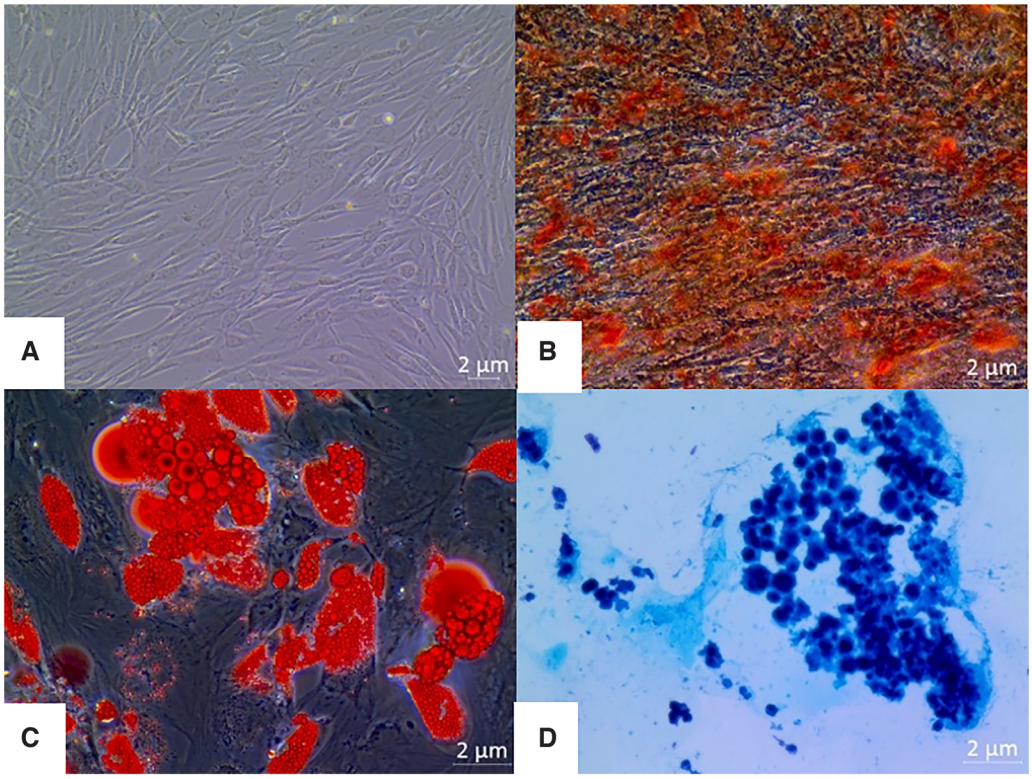
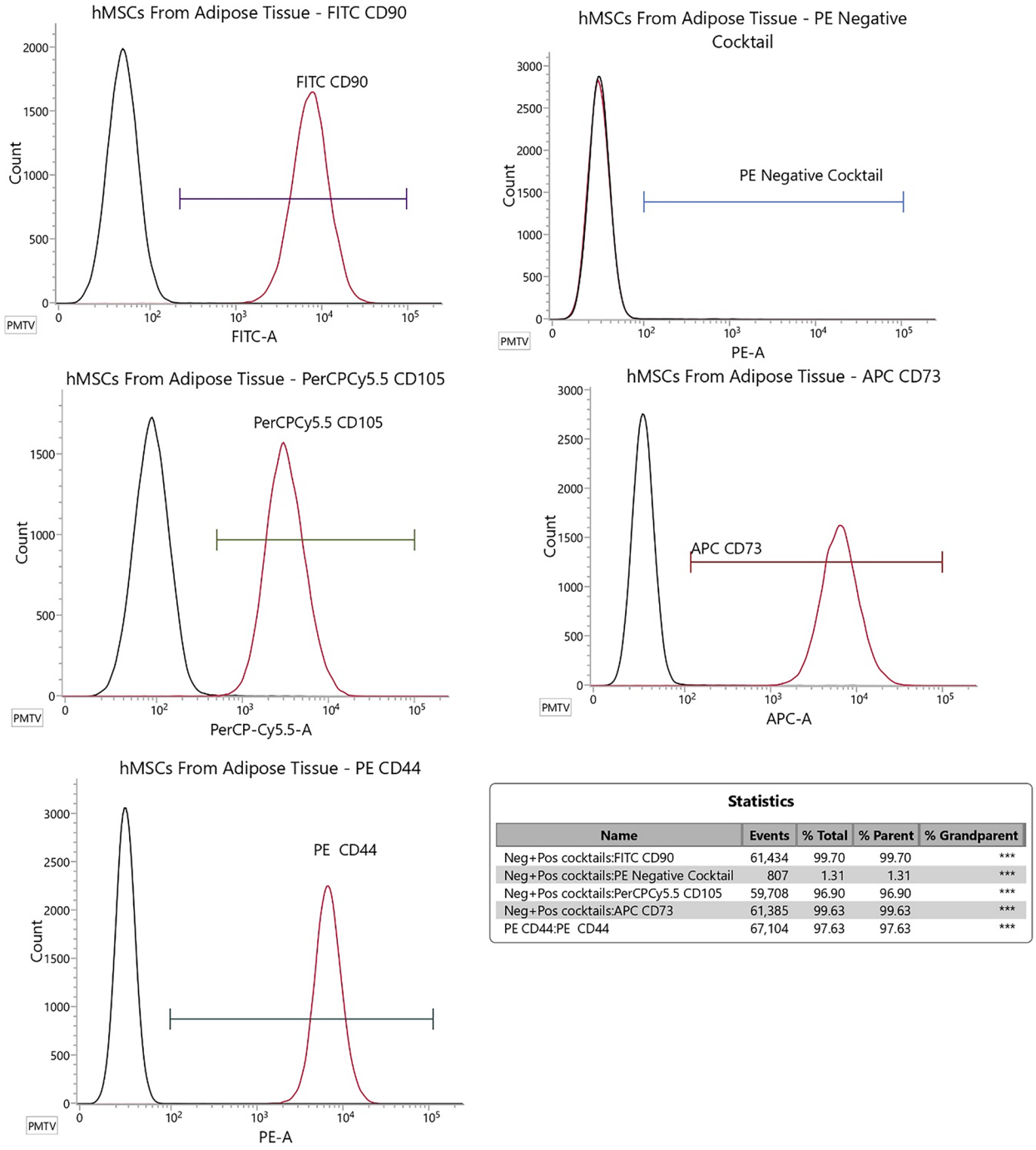



**Figure 1** Culture and tri-lineage differentiation of adipose-derived mesenchymal stromal cells (MSCs). Adipose-derived mesenchymal stromal cells (ADMSCs) showed a typical spindle-shaped, fibroblast-like, plastic-adherent morphology (A), were able to differentiate into osteogenic (B), adipogenic (C), and chondrogenic (D) lineages.




**Statistics**

| Name | Events | % Total | % Parent | % Grandparent | |
|---|---|---|---|---|---|
| Neg+Pos cocktails:FITC CD90 | 61,434 | 99.70 | 99.70 | *** | |
| Neg+Pos cocktails:PE Negative Cocktail | 807 | 1.31 | 1.31 | *** | |
| Neg+Pos cocktails:PerCPCy5.5 CD105 | 59,708 | 96.90 | 96.90 | *** | |
| Neg+Pos cocktails:APC CD73 | 61,385 | 99.63 | 99.63 | *** | |
| PE CD44:PE CD44 | 67,104 | 97.63 | 97.63 | *** | |

**Figure 2** Flow cytometry analysis of adipose-derived mesenchymal stromal cells (ADMSCs). ADMSCs demonstrated positive expression of CD105, CD73, CD44, and CD90, and negative expression of CD45, CD34, CD11b, CD19, and HLA-DR.

## Safety and adverse events

Patients were followed-up for any adverse events for up to 60 months. There were no significant short- or long-term adverse events. Laboratory tests were insignificant. A limited number of patients reported mild to moderate post–injection knee pain, effusion, and swelling, developing within 24 hours and clearing no later than one-week post–injection. Table 3 shows the number of reported adverse events for Arm A and B, compiled for the 2 doses. Data suggests MSC injection might be more painful and might cause more swelling than placebo. No patient discontinued participation or withdrew from follow-up because of adverse events, and all reported events were transient and self-limiting. Participants who did not complete in-person assessments all remained reachable throughout follow-up.

## Efficacy of ADMSC treatment

Efficacy outcomes, as assessed by the KOOS and the WOMAC scores, are summarized in Table 4. Patients on Arm A (ADMSC-treated) demonstrated significant improvements in both KOOS

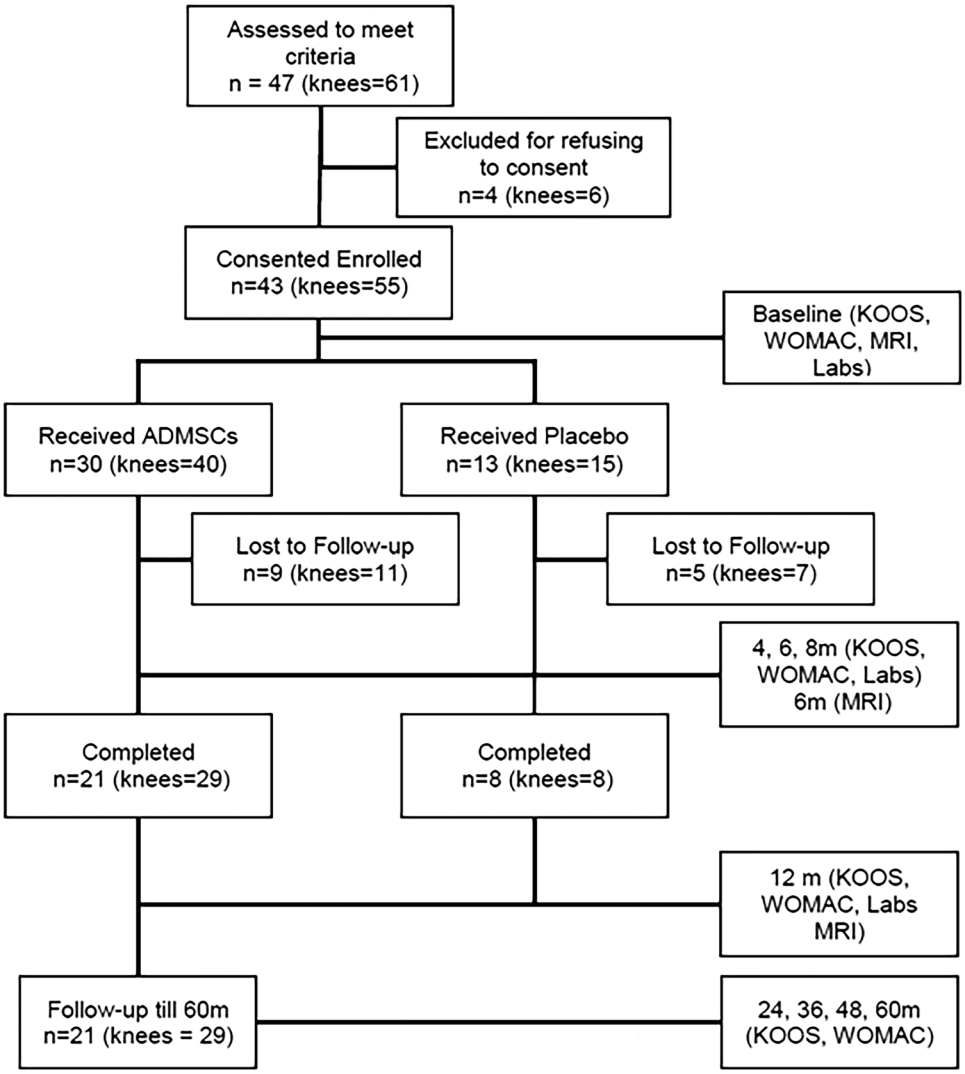



**Figure 3** Flow diagram of patient enrollment, randomization, and procedures.

and WOMAC scores compared to Arm B (placebo). At 6 months, the KOOS score in Arm A increased from a baseline mean of 50.71 ± 11.9 to 83.90 ± 10.83, whereas the placebo group showed minimal change (51.25 ± 10.28 at baseline to 53.38 ± 9.36 at 6 months). This improvement was sustained at 12 months, with KOOS scores remaining significantly higher in the treatment group (81.87 ± 11.3) compared to placebo (45.63 ± 9.43) ($P < .0001$). Similarly, WOMAC scores showed a marked reduction in Arm A, decreasing from a baseline of 50.12 ± 11.94 to 23.47 ± 13.02 at 6 months and further to 19.02 ± 11.42 at 12 months, indicating significant symptom relief. In contrast, WOMAC scores in Arm B remained unchanged over time (47.95 ± 8.71 at baseline vs. 52.00 ± 5.81 at 12 months). The between-group differences were statistically significant ($P < .0001$).

MRI analysis of various components of the degenerative parameters revealed significant structural improvements in Arm 1 at 6, and 12 months compared to Arm 2 (Table 5). In Arm 1, cartilage scores improved significantly over time (baseline: 2.43 ± 0.65; 12 months: 1.50 ± 0.76; $P < .01$). Similar trends were observed in osteophyte burden ($P < .01$), bone marrow lesions ($P < .01$), joint effusion ($P < .01$), and synovitis ($P < .01$). In contrast, Arm 2 exhibited no significant improvements in any parameter.

Figure 4 shows MRI results as a comparison between Arm 1 and Arm 2 at baseline, 6 and 12 months. All parameters in the study arm showed a significant (cartilage, osteophytes, effusion, subchondral sclerosis; $P < .05$) or highly significant (BM lesion, synovitis; $P < .01$) improvement as compared to placebo.

## Long-term decline in efficacy

We observed a rapid improvement within the first 3 months of receiving the treatment, with the maximum improvement at 12 months. The improvement continued for an additional 24 months. After that, we observed a steady decline in WOMAC and KOOS scores despite the fact they were still showing a statistically better score than baseline as shown in Figure 5. The improvement continued to be statistically significant, but the level of statistical significance declined after 36 months post–therapy.

# Discussion

In this randomized, placebo-controlled trial, we demonstrate that intra-articular administration of allogeneic ADMSCs in patients

with stage III KOA is safe and provides significant improvements in pain, function, and MRI-assessed structural parameters. These benefits were sustained for up to 3 years, with gradual decline thereafter, although scores remained above baseline at 60 months. To our knowledge, this is one of the longest follow-up studies of MSC therapy in KOA and among the first to evaluate a 2-dose regimen of allogeneic ADMSCs prepared under cGMP conditions.

Among the different sources of MSCs, ADMSCs offer particular advantages relevant to this trial. Compared with BM-MSCs and UC-MSCs, ADMSCs demonstrate superior proliferative capacity and immunomodulatory effects, while being associated with fewer treatment-related adverse events.[23] In addition, their relative ease of isolation under cGMP conditions makes them especially suitable for development as an "off-the-shelf" allogeneic product. These considerations guided our choice of ADMSCs for this study, in which we demonstrate both safety and sustained clinical benefit in stage III KOA.

Chen et al.[23] conducted a meta-analysis evaluating the efficacy of bone marrow-derived MSCs (BM-MSCs), adipose tissue-derived MSCs (ADMSCs), and umbilical cord-derived MSCs (UC-MSCs) in treating KOA. The analysis included 15 studies involving 585 patients. BM-MSCs demonstrated the most significant improvement in range of motion and pain relief. At the same time, ADMSCs were more effective in enhancing functional outcomes, as evidenced by improvements in WORMS and WOMAC scores. Furthermore, ADMSCs were associated with fewer treatment-related adverse events compared to BM-MSCs. Li et al.[24] conducted a direct comparison of BM-MSCs and ADMSCs under human platelet lysate-supplemented culture conditions, revealing that BM-MSCs exhibited greater osteogenic and chondrogenic differentiation potential, whereas ADMSCs demonstrated superior proliferative capacity and immunomodulatory effects.

Our study investigated the efficacy of intra-articular administration of allogeneic ADMSCs in patients with symptomatic KOA. The treatment significantly improved pain and functional outcomes, as measured by patient-reported outcomes and MRI assessments. We utilized the WOMAC and KOOS scores to evaluate changes in patient health status and treatment effectiveness.[12,13] The WOMAC score in the ADMSC group showed a significant decline from 6 to 48 months post–treatment compared to the control group, though a slight increase was observed at 60 months. Similarly, Lee et al. reported a notable reduction in WOMAC scores and pain at 6 months following autologous ADMSC injection, though long-term data were not provided.[25]

The KOOS assessment, which provides a comprehensive evaluation of knee symptoms, revealed significant improvements across all dimensions from 6 to 48 months post–treatment. However, the level of significance declined at 60 months, suggesting that the long-term benefits of ADMSC therapy may be limited. The early clinical improvements observed may be attributed to

**Table 1** Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| **1. More than 6 months knee joint pain and or swelling** | 1. Subjects less than 18 or older than 75 years |
| **2. Grade III knee osteoarthritis (KOA)[a] confirmed by 2 observers** | 2. Intra–articular injected treatment in the past 6 months |
| **3. No local or systemic infection** | 3. Significant valgus or varus deformity of the knee |
| **4. No significant hematological disease** | 4. Knee ligament injury or ruptured meniscus observed by magnetic resonance imaging (MRI) |
| **5. Absence of significant biochemical or hematological laboratory test abnormalities** | 5. Infection or positive serology for transmissible agents |
| **6. Informed consent form signed by the patient** | 6. BMI greater than 30 |
| | 7. Malignancy |
| | 8. Immunosuppressive drugs |

[a]KOA grading as per Kellgren and Lawrence[14] radiological assessment of osteoarthritis.

**Table 2** Demographical data of enrolled subjects and the baseline severity of clinical score by Knee Injury and Osteoarthritis Outcome Score (KOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and structural severity by magnetic resonance imaging (MRI).

| Group | | ADMSCs (Arm A) | | | | | | | Placebo (Arm B) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gender** | | **Male** | | | **Female** | | | **Total** | **Male** | | | **Female** | | | **Total** |
| **No. of patients** | | 7 | | | 14 | | | **21** | 2 | | | 6 | | | **8** |
| **No. of knees and laterality** | | RT | LT | Total | RT | LT | Total | **29** | RT | LT | Total | RT | LT | Total | **8** |
| | | 6 | 5 | 11 | 9 | 9 | 18 | | 0 | 2 | 2 | 5 | 1 | 6 | |
| **Mean age (range)** | | 65.0 (57-75) | | | 63.4 (55-74) | | | **64.2 (55-72)** | 68.0 (66-70) | | | 62.0 (48-73) | | | **63.5 (48-73)** |
| **Mean BMI (range)** | | **27.14 (23.5-33)** | | | | | | | **28.18 (24-32)** | | | | | | |
| **Baseline KOOS** | | 51.09% | | | 50.00% | | | **50.71%** | 52.5% | | | 50.83% | | | **51.25%** |
| **Baseline WOMAC** | | 46.09% | | | 50.55% | | | **50.12%** | 48.20% | | | 47.86% | | | **47.95%** |
| **Baseline MRI Mean ± SD** | Cartilage | | | | **2.43 ± 0.65** | | | | | | | **2.10 ± 0.70** | | | |
| | Osteophytes | | | | **2.5 ± 0.65** | | | | | | | **2.30 ± 0.67** | | | |
| | Bone marrow lesion | | | | **2.36 ± 0.50** | | | | | | | **2.30 ± 0.67** | | | |
| | Effusion | | | | **1.57 ± 0.51** | | | | | | | **1.50 ± 0.71** | | | |
| | **Synovitis** | | | | **1.14 ± 0.66** | | | | | | | **0.80 ± 0.63** | | | |
| | Subchondral sclerosis | | | | **2.21 ± 0.43** | | | | | | | **2.30 ± 0.82** | | | |

**Table 3** Reported adverse events compiled as a sum of adverse events reported following the 2 doses.

| Adverse event (AE)[a] | Allogeneic/adipose-derived mesenchymal stromal cells (ADMSCs) | | | Placebo group | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| **Pain[b] 1-3** | 6 | 15 | 21 | 1 | 4 | 5 |
| **Pain 4-5** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Pain > 5** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Effusion** | 2 | 1 | 3 | 1 | 1 | 2 |
| **Swelling** | 7 | 16 | 23 | 1 | 4 | 5 |
| **Bruising** | 0 | 0 | 0 | 0 | 1 | 1 |
| **Rigors** | 1 | 0 | 1 | 0 | 0 | 0 |
| **Fever** | 1 | 1 | 2 | 0 | 1 | 1 |

[a]Adverse events represent new symptoms or clinically significant worsening of baseline symptoms following injection. Pain was assessed using VAS, and an increase from baseline was recorded as an AE. Swelling and effusion were considered adverse only if new or aggravated compared to baseline.
[b]As measured by the visual analog scale.[22]

the paracrine effects of MSCs, including the secretion of immunomodulatory cytokines and growth factors.[26]

Freitag et al. administered single and double doses of $100 \times 10^6$ autologous ADMSCs to KOA patients, observing improvements in WOMAC and KOOS scores up to 12 months post–treatment. However, MRI osteoarthritis knee scores (MOAKS) did not show significant changes.[27]

In contrast, our study demonstrated significant improvement in MRI-derived cartilage integrity scores at 1 year ($P < .05$), supporting the short-term efficacy of allogeneic ADMSC in promoting structural joint repair The scoring system was adapted from Meredith et al.[17] and Wu et al.[18] As described by Wu et al., cartilage damage is determined by both the depth and surface area of lesions, while Meredith et al. applied this concept to MRI by dividing the knee into 17 anatomical sub–regions, grading each for lesion severity (0-6) and lesion size (0-4), where lower values indicate greater cartilage preservation. In the ADMSC group, the mean cartilage score improved from 2.43 ± 0.65 at baseline to 1.86 ± 0.66 at 6 months and 1.50 ± 0.76 at 12 months, while the placebo group showed no significant change (2.10 ± 0.70, 2.10 ± 0.57, 2.30 ± 0.48). These results indicate a steady reduction in both the severity and area of cartilage defects following ADMSC therapy.

Furthermore, bone marrow lesion scores declined from 2.36 ± 0.50 to 1.36 ± 0.50, indicating reduced subchondral bone stress and marrow edema. Effusion scores improved from 1.57 ± 0.51 to 0.29 ± 0.47, showing reduced intra–articular fluid accumulation, while synovitis scores decreased from 1.14 ± 0.66 to 0.07 ± 0.27. Using the same semi-quantitative MRI framework, these improvements across cartilage, bone, and synovium demonstrate a joint-wide restorative response to ADMSC therapy, consistent with the whole-organ assessment approach proposed by Meredith et al.

We did not investigate biochemically the repair mechanism of ADMSC in our patients. Potential hypothetical mechanisms include the reduction of serum COMP concentration, a marker of cartilage degeneration,[6] and the inhibition of TNF-α and IL-6 production by OA chondrocytes and synovial cells, creating a favorable environment for cartilage regeneration.[28] Further investigations are warranted to verify these hypotheses.

The primary endpoint of our study was met, with adverse events in the treatment group limited to transient mild-to-moderate pain and swelling at the injection site. A systematic review of intra–articular BM-MSC therapy, reported in 3039 patients with a 21-month follow-up, concluded that cultured stem cell applications in joints are safe, with no serious adverse effects reported.[29] However, further research is needed to evaluate long-term safety.

Our findings align with previous studies showing the safety and efficacy of MSCs in treating degenerative joint diseases. Sadri et al.[3] reported similar improvements in KOOS and WOMAC scores following a single dose of $100 \times 10^6$ allogeneic ADMSCs, with MRI assessments confirming cartilage regeneration. Both studies highlight the tolerability of ADMSC therapy, though our study extends the follow-up period to 60 months and utilizes a 2-dose regimen (mean total dose: $69.58 \times 10^6$ cells), providing stronger evidence for long-term efficacy.[3]

Huang et al.[30] conducted a meta-analysis to determine the optimal ADMSC dose for KOA treatment, categorizing doses as low ($0–25 \times 10^6$), moderate (25–50 × 106), and high ($>50 \times 10^6$). The high-dose group exhibited the most significant early improvements in pain and joint function, though higher doses were associated with increased adverse events. Kim et al.[31] utilized autologous ADMSCs in a 5-year study, reporting improvements in WOMAC scores and MRI-assessed cartilage volume. While their study focused on structural changes, our research emphasizes functional outcomes and safety over 60 months, with a larger sample size (29 patients vs. 11) and more frequent follow-up assessments.

Despite promising results, our study has limitations. The sample size of 29 patients, though informative, is relatively small, necessitating larger, more diverse cohorts to validate long-term safety and efficacy. An additional limitation relates to participant retention. Although some individuals did not return for scheduled in-person evaluations, all remained reachable by phone and were contacted repeatedly throughout the study. Their reasons for discontinuation included lack of interest in continued visits, perceived improvement, or reluctance to travel for further assessments. During these contacts, none of the discontinuing participants in either arm reported serious adverse effects, and all were reminded that any study-related care would be fully covered. Based on maintained communication and the absence of reported symptoms, we believe that these discontinuations were not related to safety concerns but rather reflect the challenges of long-term follow-up adherence in our setting.

Additionally, the optimal dosing regimen remains unclear. Comparative studies evaluating single versus multiple doses or varying intervals are needed to refine treatment protocols. Finally, while MRI assessments demonstrated cartilage improvement, advanced imaging techniques, and biomarker analyses could provide a more comprehensive evaluation of joint health over extended periods.[32]

**Table 4** Outcome measures of Knee Injury and Osteoarthritis Outcome Score (KOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 6 and 12 months.

| Outcome | | ADMSCs | | | Placebo | | |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Total | Male | Female | Total |
| KOOS | **Baseline (mean ± SD)** | 51.81 ± 11.51 | 49.53 ± 10.19 | 50.71 ± 11.9 | 54.50 ± 3.54 | 53.50 ± 8.33 | 51.25 ± 10.28 |
| | **6 months (mean ± SD)** | 87.86 ± 4.78 | 81.93 ± 12.54 | 83.90 ± 10.83 | 56.50 ± 4.95 | 52.33 ± 10.61 | 53.38 ± 9.36 |
| | **1 year (mean ± SD)** | 80.22 ± 12.95 | 78.31 ± 12.39 | 81.87 ± 11.3 | 54.50 ± 2.12 | 55.16 ± 8.07 | 45.63 ± 9.43 |
| | ***P*-value (Baseline vs. 1 year)** | **<0.0001** | **<0.0001** | **<0.0001** | **.29** | **.40** | **.27** |
| | **1 year responder rate (%)** | **50.00** | **73.33** | **66.67** | **0** | **0** | **0** |
| WOMAC | **Baseline (mean ± SD)** | 47.35 ± 10.53 | 51.65 ± 9.53 | 50.12 ± 11.94 | 46.85 ± 1.48 | 49.58 ± 1.05 | 47.95 ± 8.71 |
| | **6 months (mean ± SD)** | 17.99 ± 14.99 | 26.21 ± 11.67 | 23.47 ± 13.02 | 48.70 ± 5.23 | 47.50 ± 8.78 | 47.80 ± 7.70 |
| | **1 year (mean ± SD)** | 17.00 ± 11.66 | 21.16 ± 15.32 | 19.02 ± 11.42 | 47.35 ± 2.19 | 51.23 ± 1.55 | 52.00 ± 5.81 |
| | ***P*-value (Baseline vs. 1 year)** | **<0.0001** | **<0.0001** | **<0.0001** | **.42** | **.36** | **.29** |
| | **1 year responder rate (%)** | **83.33** | **71.43** | **71.43** | **0** | **0** | **0** |

| | KOOS for ADMSCs versus placebo | | | | WOMAC for ADMSCs versus placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | | 12 months | | Baseline | | 12 months | |
| **Intervention** | ADMSCs | Placebo | ADMSCs | Placebo | ADMSCs | Placebo | ADMSCs | Placebo |
| **Mean ± SD** | 50.71 ± 11.87 | 51.25 ± 10.28 | 81.87 ± 11.03 | 45.63 ± 9.43 | 50.12 ± 11.94 | 47.95 ± 8.71 | 19.02 ± 11.42 | 52.00 ± 0.00 |
| ***P*-value** | **.91** | | **.00** | | **.62** | | **.00** | |

**Table 5** MRI assessments at baseline, 6 and 12 months.

| Parameters[a] | | Cartilage | | | Osteophytes | | | BM lesion | | | Effusion | | | Synovitis | | | Subchondral sclerosis | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessment time** | | **B.L** | **6 m** | **12 m** | **B.L** | **6 m** | **12 m** | **B.L** | **6 m** | **12 m** | **B.L** | **6 m** | **12 m** | **B.L** | **6 m** | **12 m** | **B.L** | **6 m** | **12 m** |
| ADMSCs | **Average** | 2.43 | 1.86 | 1.50 | 2.50 | 1.93 | 1.57 | 2.36 | 1.50 | 1.36 | 1.57 | 0.64 | 0.29 | 1.14 | 0.21 | 0.07 | 2.21 | 1.64 | 1.36 |
| | **SD** | 0.65 | 0.66 | 0.76 | 0.65 | 0.73 | 0.51 | 0.50 | 0.52 | 0.50 | 0.51 | 0.50 | 0.47 | 0.66 | 0.58 | 0.27 | 0.43 | 0.63 | 0.50 |
| | ***P*-value (vs. baseline)** | | **.03** | **.00** | | **.04** | **.00** | | **.00** | **.00** | | **.00** | **.00** | | **.00** | **.00** | | **.01** | **.00** |
| | **Responder rate (%)** | | **7** | **36** | | **21** | **36** | | **50** | **64** | | **79** | **93** | | **79** | **93** | | **43** | **64** |
| Placebo | **Average** | 2.10 | 2.10 | 2.30 | 2.30 | 2.30 | 2.50 | 2.30 | 2.30 | 2.50 | 1.50 | 1.30 | 1.40 | 0.80 | 0.90 | 0.90 | 2.30 | 2.20 | 2.40 |
| | **SD** | 0.70 | 0.57 | 0.48 | 0.67 | 0.67 | 0.53 | 0.95 | 0.67 | 0.53 | 0.71 | 0.67 | 0.70 | 0.63 | 0.74 | 0.74 | 0.82 | 0.79 | 0.84 |
| | ***P*-value (vs. baseline)** | | **.31** | **.71** | | **1.00** | **.47** | | **1.00** | **.57** | | **.53** | **.75** | | **.75** | **.75** | | **.78** | **.79** |
| | **Responder rate (%)** | | **0** | **0** | | **10** | **0** | | **0** | **0** | | **20** | **20** | | **0** | **30** | | **0** | **0** |

Cartilage score was assessed on degree of cartilage damage.[18] All other parameters were assessed as described in Meredith et al.[17]
[a]Osteophytes were assessed based on the sum scores of all individual osteophytes to give compartmental score; effusion was assessed based on the greatest diameter of the effusion perpendicular to the long axis of the leg; and synovitis was assessed based in the number of thickened villi seen on T2-weighted sequences. Responder rate is calculated as the proportion of subjects who show at least a 50% improvement in the relevant category compared to their baseline measurement.

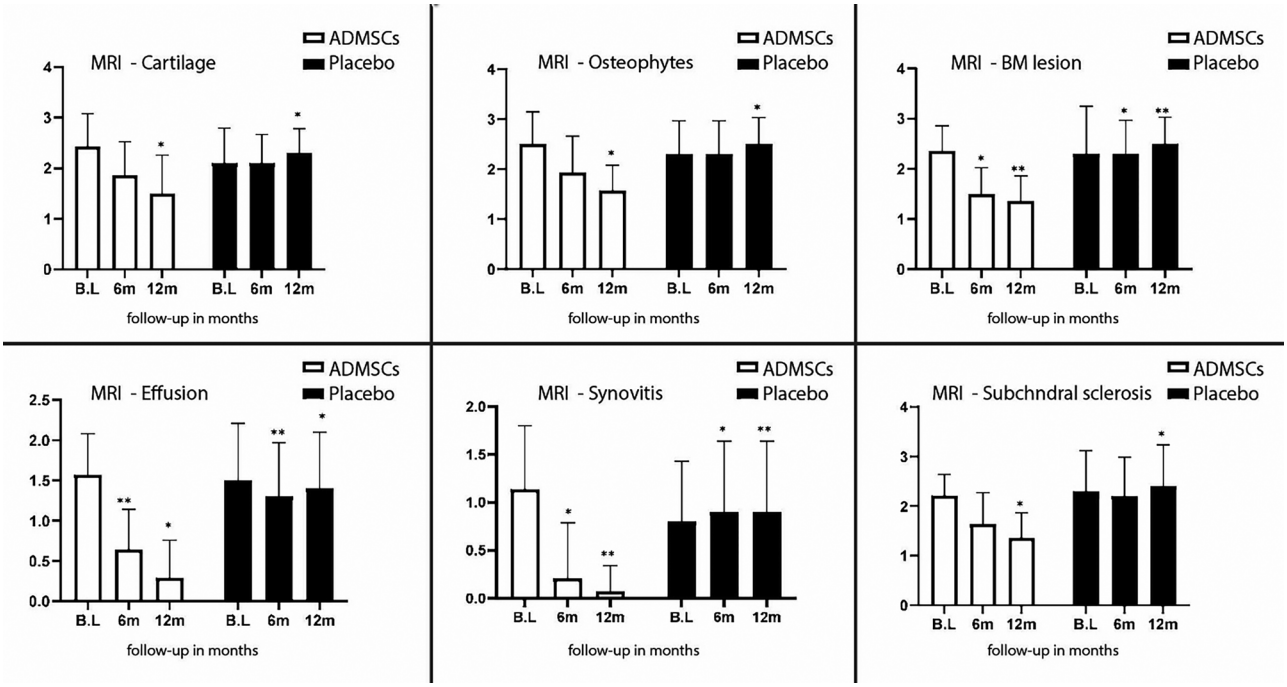



**Figure 4** Longitudinal magnetic resonance imaging (MRI) assessment of knee osteoarthritis following allogeneic adipose-derived mesenchymal stromal cells (ADMSCs) injection. MRI-based evaluation of cartilage integrity, osteophyte formation, bone marrow (BM) lesions, joint effusion, synovitis, and subchondral sclerosis in patients receiving either allogeneic ADMSCs (white bars) or placebo (black bars) at baseline (BL), 6 months, and 12 months post-injection against placebo control. *Y*-axis values represent the mean ordinal scores for each MRI parameter, graded on a 0-3 scale as described by Meredith et al.,[17] with higher values indicating more severe pathology. Data are presented as mean ± SD; **P* < .05, ***P* < .01.

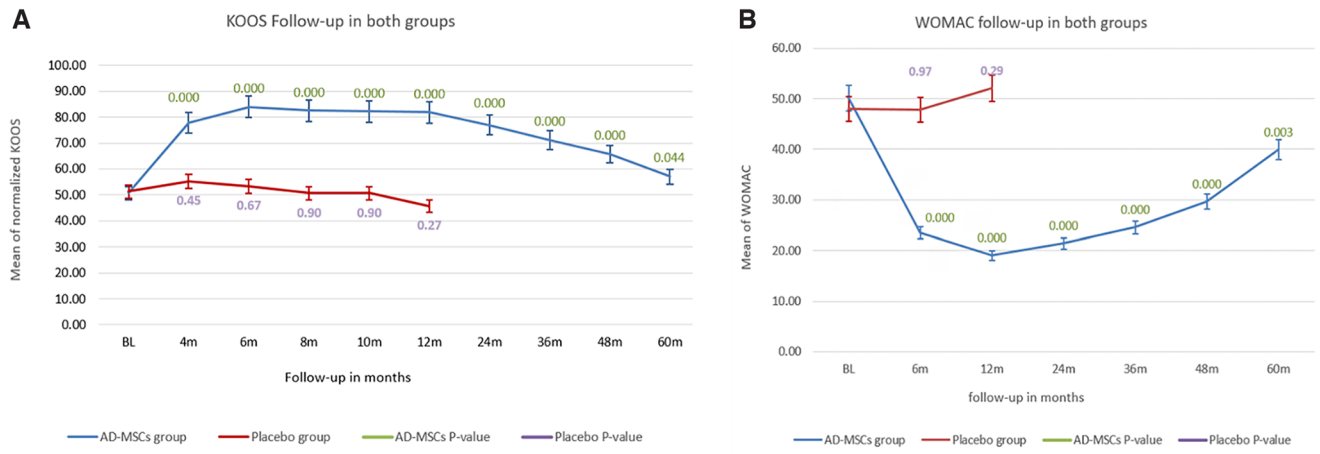



**Figure 5** Long-term functional outcomes following treatment with adipose-derived mesenchymal stromal cells (ADMSCs) or placebo, assessed over a 60-month follow-up period. (A) Knee Injury and Osteoarthritis Outcome Score (KOOS) and (B) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in both groups. The ADMSCs group (blue line) showed a significant improvement in KOOS and WOMAC scores compared to the placebo group (red line), with benefits lasting up to 60 months. However, a decline in functional scores was observed around month 36, though values remained significantly better than baseline. Statistical significance is indicated by green (ADMSCs group) and purple (placebo group) *P*-values.

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## Supplementary material

Supplementary material is available at *Stem Cells Translational Medicine* online.

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## Conflicts of interest

All authors declare no financial or non-financial competing interests.

## Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality rights. De-identified clinical data supporting the findings of this study can be shared by the corresponding author with qualified investigators upon approval by IRB of the Cell Therapy Center, University of Jordan.

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