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The role of adipose-derived stem cells in knee osteoarthritis treatment: insights from a triple-blind clinical study

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Abstract

Background Osteoarthritis (OA) is a degenerative joint disease that primarily affects older adults, characterized by cartilage degradation, synovitis, and osteophyte formation. Despite its prevalence, no medical treatment can reverse the joint cartilage degradation, leading many patients to undergo invasive procedures such as arthroplasty. Mesenchymal stem cells (MSCs), particularly those derived from adipose tissue, have emerged as a promising therapeutic approach due to their ability to differentiate into chondrocytes and potentially regenerate cartilage. While MSCs from bone marrow and umbilical cord have shown efficacy in treating OA, adipose-derived MSCs (ADMSC) are more accessible and cost-effective. This study aims to evaluate the safety and efficacy of allogeneic ADMSC in treating knee OA.

Methods This triple-blind, interventional clinical trial included 20 patients with idiopathic knee OA, meeting the American College of Rheumatology (ACR) criteria. Patients were randomly assigned to receive an intra-articular injection of either 0.5×10^8 allogeneic ADMSC or saline (control group). Participants were evaluated for clinical signs of inflammation at baseline, and then at 2 weeks, 2 months, and 6 months post-injection using clinical assessments, the Visual Analogue Scale (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), range of motion (ROM), and Magnetic Resonance Arthrography (MRA).

Results The ADMSC group exhibited significant improvement in pain reduction as measured by VAS scores compared to the control group ($P < 0.05$). However, no significant differences were observed between the groups in ROM, and based on KOOS; quality of life, activity of daily living (ADL), recreation and sports activities, symptom and pain. Although there were no significant changes in ADL, recreation, and sports activities between groups, the ADMSC group showed significant improvements between several follow-up periods. Similar improvements were reported in the ADMSC group between several follow-ups' periods on other scales. Radiological outcomes showed a significant increase in cartilage thickness at specific locations (e.g., middle-lateral patella ($P = 0.017$), Tibial compartment lateral ($P < 0.000$)) in the ADMSC group after 6 months, demonstrating the regenerative potential of ADMSC in certain MRA sites. Multivariable analysis underlines the complexity of the interactions among treatment, time, and baseline level of variables. Although ADMSC treatment shows potential for some measures, its effects are not consistently significant for all measures.

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Conclusion Allogeneic ADMSC are safe and effective in reducing pain (based on VAS scale) and increasing cartilage thickness in knee OA patients. However, they do not significantly enhance quality of life or daily activity compared to placebo. Further research with larger sample sizes and longer follow-up periods is needed to confirm these findings and determine optimal dosing strategies.

Trial registration: Trial Registry Code: IRCT20160211232 98N3, 20 February 2016. https://irct.behdasht.gov.ir/trial/19909

Keywords Osteoarthritis, Clinical trial, Triple-blind, Adipose-derived stem cells, Stem cell

Background

With the aging population and increased life expectancy [1], age-related diseases are expected to become a major public health concern [2]. Osteoarthritis (OA) is a degenerative joint disease characterized by the degradation of cartilage, changes in subchondral bone and synovium, and consequent damage to the underlying bone tissue [3, 4]. It leads to morphological changes such as subchondral sclerosis, subchondral bone cysts, osteophyte formation, and synovitis [3, 5]. OA is a disease affecting the entire joint; each joint might have distinct alterations, such as meniscal degeneration, inflammation, and fibrosis of the infrapatellar fat pad in the knee joint.[6] OA predominantly affects older individuals [4]. This disease progresses slowly, resulting in the degradation of hyaline cartilage in the joint, pain, and reduced activity [7].

OA can affect all joints in the body, with weight-bearing joints that are frequently subjected to mechanical stress being the most commonly involved [8, 9]. Neuropathic pain, depression, and sleep disorders are also associated with OA, contributing to the increased disease burden on society [10–12].

Despite the prevalence of OA, there is no established medical treatment that can reverse the degradation of joint cartilage [13]. Cellular therapies have been under investigation for treating early to advanced stages of OA for approximately two decades [14]. Autologous chondrocyte transplantation has the potential to repair and regenerate cartilage, but it is a slow process with limited self-renewal and regeneration capacity [15–17]. Furthermore, it is an invasive procedure that requires surgical extraction of cartilage tissue from non-weight-bearing joints and transplantation to affected joints [15].

The shortcomings of conventional medical treatments often lead to arthroplasty in patients with end-stage OA, where the damaged joint surfaces are replaced with prosthetics [18]. In recent years, researchers have focused on less invasive therapeutic methods to regenerate the full thickness of damaged joint cartilage, such as the use of stem cells [19]. Over the past decade, a new approach in OA treatment has emerged through tissue engineering and the application of mesenchymal stem cells (MSCs) [19]. MSCs are multipotent progenitor cells commonly found in various tissues, especially bone marrow and adipose tissue. They have the ability to differentiate into osteocytes, adipocytes, and chondrocytes, and can be easily harvested from tissues and used in patient treatments [20, 21].

Our team did a previous study on the efficacy of placental mesenchymal stem cells in treating knee OA, [22] and there have been other studies on the subject [23, 24]. To date, numerous studies have been published examining the efficacy of autologous or allogeneic stem cells in the treatment of knee OA which indicate that mild to moderate OA can be effectively improved using autologous or allogeneic stem cells derived from adipose tissue or bone marrow [25–30].

Given the accessibility of adipose-derived mesenchymal stem cell (ADMSC) through less invasive methods compared to bone marrow-derived stem cells, along with their lower cost and insufficient evidence regarding the clinical application of ADMSC in treating OA [31], we decided to conduct a study to determine the efficacy and safety of allogeneic ADMSC in treating knee OA among patients visiting the physical medicine and rehabilitation clinic in the year 2015.

Methods

Overview

The study was conducted as an interventional triple-blind clinical trial according to the CONSORT guidelines [32] after the institutional board review by Iran University of medical sciences (ethic code number: IR.IUMS.REC.1394.26914, 24 January 2016 and Trial Registry Code: IRCT20160211232 98N3, 20 February 2016). Twenty patients with idiopathic knee OA were selected and enrolled in the study with informed consent. The ethics of this study are in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards [33].

Initially, we administered 10^8 abdominal ADMSC to two patients. Both experienced mild adverse effects, including transient inflammation in both cases and a single instance of skin rash. As a result, the cell count of injection was reduced to 0.5×10^8 cells, with no observed adverse effects at this lower dose, as was observed in pervious study [34]. We subsequently adopted this cell count for all further treatments. Both patients who received the

higher cell count were excluded from the study. A total of 0.5×10^8 abdominal ADMSC were injected intra-articularly under sterile conditions into 10 patients in the intervention group, who were randomly assigned.

Patients were evaluated for clinical signs of inflammatory reactions 30 min after the injection, and then at intervals of two weeks, two months, and six months post-injection. They underwent clinical assessments (inflammatory reaction symptoms, VAS, KOOS, ROM, etc.) and paraclinical evaluations –magnetic resonance arthrography (MRA)- at baseline and six months after the injection (Fig. 1).

Participants

Twenty patients with knee OA were enrolled and randomly assigned to two groups: control (n = 10) and ADMSC (n = 10). We enrolled the patients into this study based on the following criteria: 1. Patients with diagnosis of knee osteoarthritis based on the American College of Rheumatology (ACR) criteria, [35] graded as 2, 3, or 4 according to the Kellgren-Lawrence criteria. [36] 2. Patients with the ability to follow up with the study.

Also, patients with following conditions were excluded from the study. 1. Age below 18 or above 75 years. 2. Presence of any acute or chronic infection. 3.Significant knee deformity (varus > 10° or valgus > 20°). 4. Pregnant or breastfeeding women. 5. Presence of any neoplasia. 6. BMI > 35. 7. Conditions associated with immune system weakness. 8. Presence of inflammatory joint diseases or secondary osteoarthritis. 9. Intra-articular injections within the past three months. 10. History of knee surgery. 11. Renal dysfunction (Creatinine > 2.0 mg/dL). 12. Liver dysfunction (Bilirubin > 2.0 mg/dL, AST/ALT > 100 IU/L). 13. Uncontrolled diabetes.

Donor eligibility and suitability was assessed referring to the national guidelines for cell manufacturing [37].

Cell production from adipose tissue

For the isolation of MSCs from adipose tissue, necessary arrangements were made with the surgical departments of medical centers, and informed consent was obtained from donors. All procedures were carried out in a Good Manufacturing Practice (GMP) facility (A class clean room) following current GMP guidelines [38]. The adipose tissue was collected and washed three times with physiological serum (0.9% sodium chloride solution) to remove any remaining blood. The washed tissue was then exposed to 15 mL of an enzymatic solution (0.1% Collagenase IV (gibco—ThermoFisher) in DMEM f12 medium (gibco—ThermoFisher)). The tissue was incubated at 37°C for 0.5 to 1 h and shaken every 10 min. After enzymatic digestion by collagenase, 15 mL of physiological

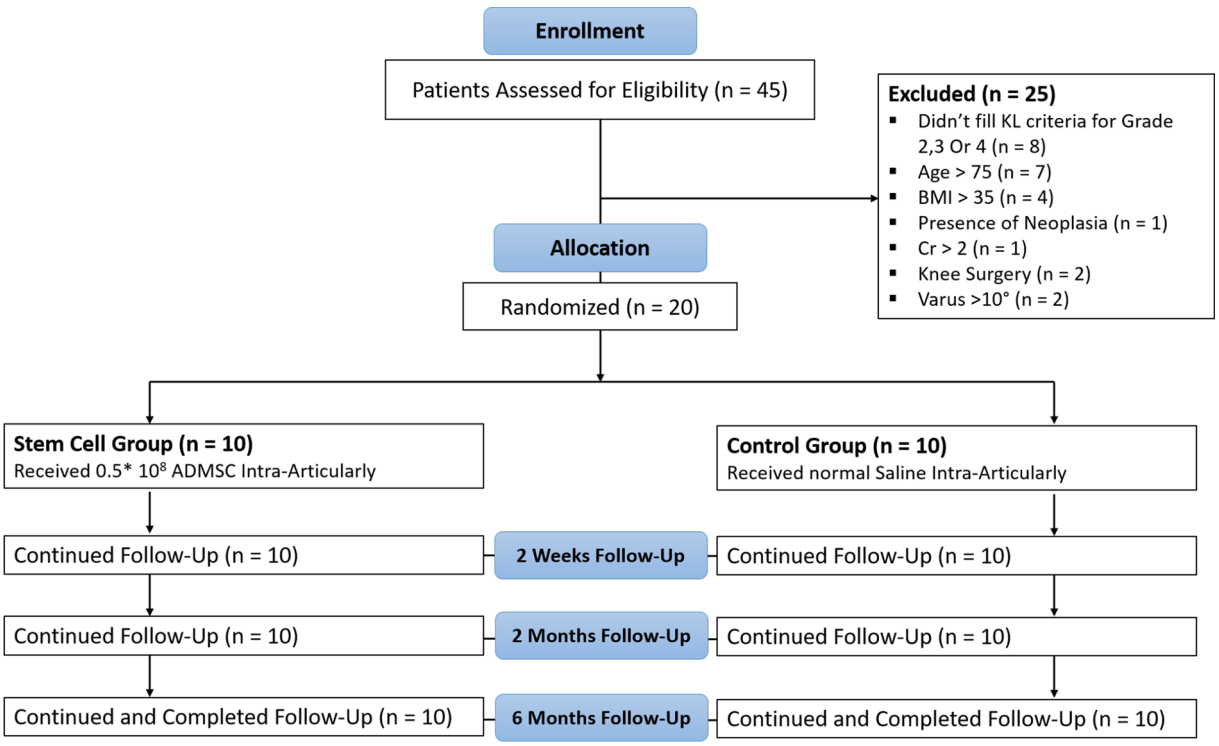

Fig. 1 Consort diagram. Subjects were randomized to a 1:1 ratio. No patients withdrew from the study after randomization till the end of follow up duration. Cr; Creatinine, KL; kellgren-lawrence, BMI; Body Mass Index

serum was added, and the mixture was centrifuged in 1200 rpm for 5 min. The supernatant was discarded, and the sedimented cells were cultured in a specific medium (DMEM f12 (gibco—ThermoFisher) + 10% human serum (gibco—ThermoFisher) + 50 u/mL penicillin + 50µg/mL streptomycin (gibco – ThermoFisher) + 1 mM L-glutamine (gibco – ThermoFisher)). Subsequently, the cells were characterized by assessing surface markers and differentiation potential. These cells must have the potential to differentiate into three lineages: adipocytes, osteoblasts, and chondrocytes, and be positive for markers CD73, CD90, CD105, and negative for markers CD34, CD31, CD45. It is important to note that since the cells in this study were used allogeneically, necessary tests to prevent contamination transfer to the host and cytology were conducted in accordance with the national guidelines for the use of stem cells (approved by the Ministry of Health). The cells were injected into the patient's knee by a specialist physician at passage 4 in 2 cc of normal saline. In the control group, normal saline was injected.

Randomization and blinding

This study was designed as a triple-blind clinical trial to eliminate bias in the treatment and outcome assessments. Twenty patients with knee OA were enrolled and randomly assigned to two groups: the control group (n = 10) and the ADMSC group (n = 10).

A random number sequence generated by a computer was used for randomization. Allocation concealment was accomplished by placing group assignments in sequentially numbered, opaque, sealed envelopes that were only opened at the time of the intervention.

Blinding was maintained at three levels. 1. Patients were not informed about their group or type of injection. 2. Healthcare practitioners giving interventions were blinded to group allocations using identical syringes for both groups. A third party not participating in the study labeled the syringes with simply the participant's number. 3. Outcome assessors were unaware of group allocations to ensure unbiased evaluation of results.

In the control group, patients got an intra-articular injection of normal saline, whereas the case group received 0.5×10^8 ADMSC. Both interventions were designed to appear equal in volume and color, ensuring that the blinding remained consistent throughout the research.

Measures

Questionnaire 1 contains the demographic questionnaire for patients before ADMSC injection, which includes age, gender, weight, height, BMI, education level, medical history, medication history, and history of major knee trauma. *Questionnaire 2* (KOOS) presents the KOOS (Knee injury and OA Outcome Score) questionnaire, consisting of 42 questions covering five domains: symptoms, pain, Activities of daily living (ADL), recreational/sport activities, and quality of life (QOL) [39].

Questionnaire 3 comprises the follow-up form for knee OA patients after ADMSC injection, which includes Visual Analogue Scale (VAS) results, scores from the five domains of the KOOS questionnaire, knee functional metrics (Range of Motion (ROM) and flexion contracture) via examination, radiological parameters of the knee, and the level of patient compliance. *Questionnaire 4* is a form providing information on MSC injection and reminders for patient follow-up at 2 weeks, 2 months, and 6 months post-injection, which is given to the patient before the injection. The results of the knee functional metrics (ROM and flexion contracture) are assessed through examination, while the VAS is used to measure the patient's pain intensity. Radiological parameters of the knee are reported based on MRA films taken before and 6 months after the ADMSC injection which are listed in Table 1.

Radiological imaging measures

We conducted Magnetic Resonance Angiography (MRA) utilizing a Siemens Avanto Fit 1.5T equipment. A 20 mL solution of gadolinium (0.6% concentration, DOTAREM) was administered under sterile circumstances using a lateral parapatellar route. The images were examined in coronal, sagittal, and axial perspectives using Marco-Pacs software. Subsequently, an experienced radiologist, who was unaware of the treatment groups, assessed the images. The thickness of the cartilage was measured in millimeters at 14 specific locations (as shown in Table 1). The minimum and maximum thickness were recorded, resulting in a total of 28 measurements per patient.

Statistical analysis

The primary outcome of this study was the change in KOOS score from baseline to six months. The sample size was determined based on data from a previous study [40]. Using a significance level (α) of 0.05, an effect size (Cohen's d) of 1.96, a statistical power of 80% ($1-\beta$), a mean KOOS score difference of 33.3, and an estimated standard deviation of 17.0, the initial calculation yielded a required sample size of 5 participants per group. However, a moderate effect size (Cohen's $d \approx 0.5$) was applied to ensure a more conservative and robust estimation, resulting in an adjusted sample size of 12 participants per group. To further enhance our study's reliability and statistical power, we increased the final sample size to 20 patients per group.

Table 1 There was a total of 28 places where the thickness of the cartilage was measured, with a minimum and maximum value recorded at each of the 14 separate sites. Max refers to the highest possible value, whereas min refers to the lowest possible value

No	Site abbreviation	Site description	Value
1	SLP	Superior lateral patella	Max–Min
2	MLP	Middle lateral patella	Max–Min
3	ILP	Inferior lateral patella	Max–Min
4	SMP	Superior medial patella	Max–Min
5	MMP	Middle medial patella	Max–Min
6	IMP	Inferior medial patella	Max–Min
7	MFF	Medial femoral facet	Max–Min
8	LFF	Lateral femoral facet	Max–Min
9	LCN	Lateral compartment, non-weight-bearing	Max–Min
10	LCW	Lateral compartment, weight-bearing	Max– Min
11	MCN	Medial compartment, non-weight-bearing	Max– Min
12	MCW	Medial compartment, weight-bearing	Max– Min
13	TCM	Tibial compartment, medial	Max– Min
14	TCL	Tibial compartment, lateral	Max– Min

The collected data were entered into a computer after being cleaned and were analyzed using SPSS software version 24 [41]. Fisher's exact and chi-square tests were used for categorical variables, and t-test and one-way ANOVA were used for continuous variables. $P < 0.05$ was regarded as statistical significance. The sample size for this pilot trial was determined using the precedent set by previous safety and pharmacokinetic investigations [42–44]. Then, no explicit a priori power calculation was performed for secondary exploratory endpoints.

Additionally, a repeated-measures multivariate analysis of variance (MANOVA) was conducted to examine how stem cell treatment influences multiple outcome measures over three-time points: 2 weeks, 2 months, and 6 months. The study included time as a within-subjects factor and group assignment (ADMSC vs. Control) as a between-subjects factor. To account for potential confounding effects, the analysis controlled for several covariates, including age, sex, baseline scores (such as ADL Baseline, Sport and Recreational Baseline, QOL Baseline, and VAS Baseline), BMI, and KLS. Multiple multivariate significance tests were applied to assess the interaction effects of time and other covariates, including Pillai's trace, Wilks' lambda, Hotelling's trace, and Roy's largest root. Additionally, Mauchly's test of sphericity was used to check whether the assumption of sphericity was met. If violations were detected, Greenhouse–Geisser corrections were applied. As a follow-up, univariate tests were performed to analyze within-subject and between-subject effects, helping to identify which specific variables contributed to significant interactions. A significance threshold of $p < 0.05$ was set for all statistical analyses.

Results

Demographic

A total of 20 patients were enrolled in the study and completed it in its entirety. Due to the small sample size, Fisher's Exact Test was used to compare gender distribution between the two groups, which showed no significant difference between them (p-value = 0.585). Additionally, the participants in the two groups were also similar in terms of age and body mass index (BMI) (p-value > 0.05–p-values respectively 0.52, and 0.71). The information regarding the comparison of other variables between the two groups is presented in the Table 2.

Non-radiologic outcomes

Visual analogue scale (VAS) and range of motion (ROM)

Since there was a significant difference in VAS for pain between the two groups at the baseline of this variable, the baseline value was included as a covariate in further analyses. The interaction effect of group and time on this outcome was significant (p-value = 0.011). In the stem cell group, there was a significant difference between certain time intervals, such as between the first follow-up and the third and fourth follow-ups (p-values respectively = 0.001, and 0.007). In the placebo group, all follow-ups showed a significant difference compared to the initial visit, but there was no significant difference between the follow-up intervals themselves.

In ROM evaluation, the interaction effect of group and time on this outcome was not significant

Table 2 Variables in each group at baseline

Variables		Mean in ADMSC group	Mean in control group	*P*-value
Age		54.5	55.8	0.522
Sex		F(9) M(1)	F(9) M(1)	0.585
ROM		121.0	111.8	0.208
BMI		31	28.9	0.716
Knee injury and osteoarthritis outcome score (KOOS)	QOL	58.5	41.3	0.424
	Sport and reactions	21.3	3.00	0.477
	ADL	51.3	45.7	**0.006**
	Symptom	42.4	38.8	**0.042**
	Pain	45.7	40.1	**0.009**

BMI body mass index, *ADL* activity of daily living, *QOL* quality of life, *ROM* range of motion, *ADMSC* adipose-derived mesenchymal stem cell. The bold *P*-values represent the significant differences

(*P*-Value = 0.165), indicating that the changes observed over the specified time intervals did not differ between the two groups. In the stem cell group, the differences in ROM were not significant at any time point before the injection or between follow-ups (*P*-Value > 0.05).

Knee injury and osteoarthritis outcome score (KOOS)

Regarding the KOOS questionnaire, the interaction effect of group and time on *QOL* was not significant (*P*-Value = 0.736), meaning that the behavior of the two groups did not differ significantly. This difference was not observed in any of the time intervals. Within the stem cell group. However, there was a significant difference between the baseline and the 6 months follow-up (p-value = 0.032) and 2 weeks and 6 months follow-up (p-value = 0.019).

In *ADL*, given that there was a significant difference between the two groups at the baseline of this variable, the baseline value was included as a covariate in further analyses. The interaction effect of groups and time on ADL was not significant (*P*-Value = 0.758) meaning that the daily activity of the two groups did not differ significantly. Also the *symptom*, given the significant difference between the two groups at the baseline of this variable, the baseline value was included as a covariate in further analyses. The interaction effect of group and time on symptoms was not significant (*P*-Value = 0.267), indicating that the behavior of the two groups was statistically similar. In the ADMSC group, there were no notable changes were observed during follow-up stages for both ADL and symptom except between 2 weeks and 2 months' follow-ups for both ADL and symptoms (p values respectively = 0.011, and 0.012) and baseline and 2 months' follow-up for symptom (p-value = 0.030).

The interaction effect between group and time on *recreational/sport activities* was not significant (p-value = 0.477), meaning that the behavior of the two groups was not significantly different from each other. However, within the stem cell group, the improvement in recreational and sports activities was significant between the baseline and 2-month follow-up, as well as between the two-week follow-up and the 2-month follow-up (p-values respectively = 0.040, and 0.003).

The interaction effect of group and time on *pain* was not significant (*P*-Value = 0.141), indicating that the pain in groups was not statistically different. Within the ADMSC group, pain improvement was only significant between the baseline and the 8-week follow-up, as well as between the 2-week and 6 months follow-ups (*P*-Values respectively = 0.001, and 0.015).

For detailed information, See Tables 3, 4, and 5.

Radiologic outcomes

The interaction effect of group and time on the thickness of the cartilage in MRA evaluation was significant in SLP (max) (p-value = 0.031) and LFF(max) (p-value = 0.041), and LCN (max) (p-value = 0.043) showing the significant improvement of some sites after 6 months of follow-up by injecting ADMSC. However, no significant differences were shown in the other MRA sites.

Among the 28 locations where cartilage thickness was measured in each patient, there was a notable and statistically significant increase in cartilage thickness in the following areas after 24 weeks of treatment in the ADMSC group: MLP (Max), TCL (Max), MCN (Max), LCW (Max), MFF (Max), LCN (Max), LFF (Max), LFF(min), MMP(max), and SLP (Max) (Table 6).

Adverse effects

No serious adverse effects were observed following stem cell injection or during the follow-up period in any of the study participants. However, in the initial phase of the study, two patients who received a higher cell dose (10^8 cells) experienced mild and transient

Table 3 Trajectory of variables mean during follow ups

	Variables	Groups	Baseline	2 weeks follow up	2 Months follow up	6 Months follow up	Time*group interaction significance
Visual analogue scale		ADMSC	7.50	6.60	4.20	3.40	**0.01**
		CG	6.90	4.40	4.20	3.30	
Range of motion		ADMSC	121.00	121.00	126.50	126.50	0.16
		CG	111.80	117.30	121.60	127.10	
Knee injury and osteo-arthritis outcome score (KOOS)	Quality of Life	ADMSC	58.50	57.00	68.40	68.80	0.73
		CG	41.30	41.80	47.40	51.90	
	Activity of daily living	ADMSC	51.30	52.20	68.00	68.50	0.75
		CG	45.70	51.50	60.00	66.50	
	Symptom	ADMSC	42.40	43.30	51.60	52.60	0.26
		CG	38.80	45.80	46.20	51.90	
	sports and recreation score	ADMSC	21.30	22.20	38.00	36.90	0.47
		CG	3.00	7.50	10.50	29.50	
	Pain	ADMSC	45.70	44.60	60.10	61.50	0.14
		CG	40.10	51.00	54.20	62.50	

ADMSC adipose-derived stem cell group, *CG* control group. The bold *P*-values represent the significant differences

Table 4 Between-Group time significances of each variable

	Between-group time significances (*P*-values)						
	Visual analogue scale	Range of motion	Knee injury and osteoarthritis outcome score (KOOS)				
			Quality of life	Activity of daily living	Symptom	sports and recreation score	Pain
Baseline—2 Week	**0.020**	0.076	0.688	0.319	**0.032**	0.513	0.034
Baseline—2 Months	–	–	–	–	**0.025**	**0.027**	**0.013**
Baseline—6 Month	0.658	0.147	0.949	0.747	0.607	0.272	0.443
2 Weeks—2 Months	**0.002**	0.706	0.190	0.247	0.234	0.090	**0.045**
2 Weeks—6 Months	0.060	0.304	0.733	0.872	0.535	0.420	0.437
2 Months—6 months	0.909	**0.017**	0.461	0.106	0.234	0.090	**0.045**

The bold *P*-values represent the significant differences

Table 5 Inter group-time significances of each variable

	Within group-time significances (*p*-values)													
	Visual analogue scale		Range of motion		Knee injury and osteoarthritis outcome score (KOOS)									
					Quality of life		Activity of daily living		Symptom		sports and recreation score		Pain	
	ADMSC	CG	ADMSC	CG	ADMSC	CG	ADMSC	CG	ADMSC	CG	ADMSC	CG	ADMSC	CG
Baseline—2 Week	0.345	0.000	1.000	0.095	1.00	1.00	1.00	0.620	1.000	0.008	1.000	1.000	1.000	0.052
Baseline—2 Months	**0.000**	0.001	1.000	0.119	0.410	1.00	0.110	0.236	**0.030**	0.115	**0.040**	1.000	**0.042**	0.048
Baseline—6 Month	**0.000**	0.001	1.000	0.022	**0.032**	.026	0.239	0.092	0.107	0.021	0.205	0.006	0.097	0.009
2 Weeks—2 Months	**0.000**	1.000	0.139	0.410	**0.008**	.477	**0.011**	0.385	**0.012**	1.000	**0.003**	1.000	**0.001**	1.000
2 Weeks—6 Months	**0.002**	0.926	0.429	0.019	**0.019**	.056	0.059	0.096	0.109	0.632	0.183	0.015	**0.015**	0.167
2 Months—6 months	1.000	0.936	1.000	0.009	1.000	1.000	1.000	0.107	1.000	0.293	1.000	0.007	1.000	0.011

ADMSC Adipose-derived mesenchymal stem cell group, *CG* control group. The bold *P*-values represent the significant differences

Table 6 Thickness of the cartilage in 28 MRA sites at baseline and after 6 months follow-up

Sites	Mean cartilage thickness at baseline (mm)		Mean cartilage thickness after 6 months follow-up (mm)		*P*-value (between time and groups)	*P*-value (inter group—ADMSC)
	ADMSC	CG	ADMSC	CG		
SLP (max)	1.98	2.50	2.34	2.48	**0.031**	**0.006**
SLP (min)	1.36	1.64	1.55	1.69	0.362	0.905
MLP (max)	2.26	2.42	2.50	2.52	0.290	**0.017**
MLP (min)	0.92	1.51	1.00	1.74	0.278	0.354
ILP (max)	2.04	2.16	2.17	1.97	0.368	0.602
ILP (min)	0.87	1.06	1.03	0.88	0.079	0.231
SMP (max)	2.03	1.77	2.02	1.85	0.287	0.865
SMP (min)	0.79	0.62	0.97	0.98	0.081	0.163
MMP (max)	2.24	1.93	2.46	1.90	0.075	**0.030**
MMP (min)	1.03	0.81	1.04	0.98	0.075	0.925
IMP (max)	1.86	2.05	1.87	2.23	0.072	0.913
IMP (min)	0.74	1.28	0.95	1.48	0.951	0.083
MFF (max)	2.59	2.58	2.83	2.70	0.374	**0.019**
MFF (min)	1.21	1.51	1.46	1.74	0.928	0.124
LFF (max)	2.50	2.13	2.89	2.12	**0.041**	**0.007**
LFF (min)	1.32	1.72	1.52	1.71	0.127	**0.045**
LCN (max)	1.66	1.96	1.91	1.93	**0.043**	**0.013**
LCN (min)	0.51	0.83	0.63	0.92	0.850	0.293
LCW (max)	1.27	1.68	1.56	1.85	0.403	**0.009**
LCW (min)	0.55	0.89	0.66	0.92	0.588	0.297
MCN (max)	2.19	2.33	2.35	2.43	0.466	**0.012**
MCN (min)	0.83	0.89	0.91	1.00	0.688	0.141
MCW (max)	1.39	1.29	1.36	1.37	0.454	0.771
MCW (min)	0.30	0.42	0.40	0.18	0.086	0.459
TCM (max)	2.17	1.64	2.30	1.81	0.782	0.213
TCM (min)	0.80	0.53	0.81	0.58	0.276	0.696
TCL (max)	2.11	2.29	2.52	2.43	0.058	**0.000**
TCL (min)	0.69	0.88	0.78	0.95	0.765	0.069

ADMSC adipose-derived stem cell group, *CG* control group, *mm* millimeter, *MRA* magnetic resonance arthrography. For more detailed regarding sites, see Table 1. The bold *P*-values represent the significant differences

adverse effects, including fever in both cases and one instance of a skin rash. To ensure the consistency of the study, these two patients were excluded from further analysis.

Multivariate analysis

The multivariate test ($p=0.049$) showed a notable Time × Group interaction for pain outcomes (VAS); this effect was not significant after sphericity was corrected ($p=0.112$). This implies weak evidence of variations in the trajectory of pain reduction between ADMSC and placebo groups. A notable quadratic effect of time ($p=0.023$) suggested a non-linear trend in pain scores; BMI was then found to interact with this trend ($p=0.024$) strongly, implying BMI modulates pain changes across time. However, no significant overall treatment effect of ADMSC on pain was observed ($p=0.364$).

Time × Group interaction ($p=0.032$) for ROM revealed that ADMSC therapy affected ROM changes differently than placebo. Over time, notable linear ($p=0.011$) and quadratic trends ($p=0.009$) were seen; baseline ROM notably predicted changes ($p<0.001$). No significant overall group variance in ROM was noted ($p=0.395$).

With indications of a curvilinear pattern, quality of life (QOL) showed a trend toward significant changes with time ($p=0.094$). With a $p=0.031$, group differences were significant, and the ADMSC group had better QOL scores than the placebo. However, no significant

interactions between time and other factors such as age, BMI, or baseline QOL were observed.

There was no notable overall shift across time regarding sport and recreational activity. However, the study found a strong quadratic interaction between time and group ($p=0.014$), implying a more complex pattern of change in the stem cell and placebo groups than a straightforward rise or reduction. This indicates that the two groups followed different trajectories over time. Furthermore, a major predictor of outcomes ($p=0.032$) was baseline sport and recreational activity levels; therefore, people with higher or lower baseline activity levels followed different change patterns.

The analysis indicates that baseline ADL performance and time were key change factors, with some evidence of differential trajectories between treatment groups. However, the influence of ADMSC therapy on ADL improvements remains inconclusive based on our findings.

These findings underline the complexity of the interactions among treatment, time, and baseline level of variables, highlighting the use of baseline predictors such as BMI, ROM, and baseline activity levels in shaping outcomes. Although stem cell treatment shows potential for some measures, its effects are not consistently significant across all measures.

Discussion

The results of the present study indicated that based on the VAS, the therapeutic intervention had a significant impact on reducing pain in patients compared to the control group. The VAS scores for patients in the ADMSC group decreased after six months. In the assessment of ROM, the changes observed over the specified time intervals between the two groups did not differ significantly. This suggests that stem cells did not have a greater effect than placebo in improving patients' ROM. Moreover, the results from QOL, ADL, Symptom scores, and the mean scores for sports and recreational activities indicated no significant difference between the two groups.

Although there were no significant changes in KOOS criterions (ADL, symptom, pain, QOL and sprots and recreational activities) between groups, within ADMSC group significant improvements were observed between several follow-up periods. Almost all studies that used MSCs to treat knee OA demonstrated varying clinical benefits in MSC-applied group [22, 29, 45, 46]. Notably, within the control group, we observed clinical improvement in several KOOS subscales during follow-up periods. Some studies found that injecting normal saline had a considerable placebo effect in improving patient-reported outcomes for knee OA [47, 48]. There is no clear scientific explanation for this finding.

A similar study by Soltani et.al was conducted on 20 patients with knee OA, where 10 patients received stem cells from the placenta and were compared to 10 patients in the placebo group. In this study, only the improvement in ROM and one criterion of the KOOS questionnaire, Symptoms, showed a significant difference between the placenta-derived stem cells and placebo groups. Other variables, such as VAS and radiological changes, did not show significant differences compared to the placebo group [22].

A study assessed the safety and efficacy of allogeneic adipose-derived mesenchymal progenitor cells in 22 patients with bilateral knee OA. Patients received either low (1×10^7), medium (2×10^7), or high (5×10^7) dosages by two intra-articular injections. Outcomes included pain and functional improvements and a slight increase in cartilage volume in the low-dose group based on MRI. The findings indicated the safety and potential benefits of these cells for OA [42]. In a study conducted by Murphy et.al., the role of autologous bone marrow-derived MSCs injected into the knee joints for the repair and regeneration of damaged joint tissue following OA induction showed that intra-articular injection of 10×10^6 cells, the cell treatment resulted in a decrease in the degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis in the joints [49]. Another study evaluated the effect of autologous ADMSC on dogs with chronic OA, showing beneficial effects on disease improvement [50]. For another experiment, a total of 55 patients who received various doses of allogeneic bone marrow MSCs. Following a 2-year observation period, no negative effects were seen, and the group of individuals who received the cells experienced an increase in meniscal volume and a notable decrease in pain as assessed by the VAS [51]. A clinical trial involving four patients with moderate to severe OA was conducted where MSCs were administered intra-articularly. The results indicated that this method is safe and without complications; however, the effect of these stem cells on disease and pain severity was not notable [52]. Other studies also showed the similar results [53–57].

We employed MRA assessment to enhance the accuracy and precision of measuring chondral thickness [58, 59]. It was noted that the therapeutic intervention did not significantly affect changes in MMP, ILP, MFF, LCW, MCN, MCW, TCM, and IMP in patients over the course of treatment. Out of the 28 locations used to test cartilage thickness in each patient, there was a significant increase in cartilage thickness in the following areas between the initial treatment and the 6 months follow-up in the ADMSC group: MLP (Max), TCL (Max), MCN (Max), LCW (Max), MFF (Max), LCN (Max), LFF (Max), LFF(min), MMP(max), and SLP (Max). Although, Soltani

and colleagues' investigation did not find any significant alterations in MRA characteristics; chondral thickness experienced a notable increase in around 10% of the assessed regions of cartilage in the knee joints of patients who were administered MSCs [22]. Also the Lu et.al study showed increase in cartilage thickness [42]. Other studies also showed similar results [60, 61].

MSCs are versatile cells found in various tissues such as bone marrow, periosteum, trabecular bone, fat pad tissue, synovial membrane, and others. They can significantly stimulate the growth of chondrocytes and transform them into cartilage, making them extremely valuable for tissue regeneration [62, 63]. The main sources of therapeutic MSCs are bone marrow and adipose tissue. It is worth noting that MSCs derived from different tissues can differentiate into cartilage [63]. Also it is noteworthy that, the downregulation of major histocompatibility complex (MHC) proteins and T-cell co-stimulatory molecules in MSCs enables the safe and effective use of these cells both systemically and locally, without the risk of severe immune reactions [64].

The primary influence of MSCs on the restoration of OA joints is the stimulation of the local microenvironment through paracrine signaling. MSCs have demonstrated the ability to promote tissue regeneration through paracrine signals originating from MSCs [65]. Nevertheless, the precise mechanics of these processes are currently under investigation. Also Efficiently determining the optimal dosage of MSCs for effective treatment of knee OA is currently a subject of ongoing research. debates persist regarding the optimum number of stem cells required to enhance the symptoms of OA [66].

Strengths and limitations

This study is one of few clinical trial that specifically investigates the utilization of allogeneic ADMSC cells from fat tissue for the treatment of knee OA. An extensive evaluation methodology was utilized, incorporating clinical assessments, patient-reported outcomes (such as the KOOS questionnaire and VAS scores), and MRA to determine the effectiveness and safety of the treatment. Also the selection of participants was based on particular criteria, such as age, BMI, and the severity of OA. This ensured that the sample of individuals with knee OA was diverse and representative.

The investigation was conducted with a limited sample size of only 20 patients, which restricts the statistical power and the capacity to extrapolate findings to the wider community. A six-month follow-up period may not provide enough time to assess the long-term effectiveness and safety of ADMSC therapy in knee OA. The precise dosage of ADMSC for the treatment of knee OA remains unknown. Also, the study employed a precise cell dosage, nevertheless, ongoing discussions continue to exist over the optimal therapeutic dosage that would maximize advantages while minimizing potential hazards. Further investigation is warranted to examine the correlation between dosage and response in order to ascertain the optimal treatment protocols. Additionally, the effects of stem cell therapy on other knee joint tissues, such as the infrapatellar fat pad and synovial membrane, were not evaluated. Future research should explore these aspects to provide a more comprehensive understanding of the therapeutic potential of stem cells in knee OA.

Conclusion

Allogeneic ADMSC are safe for treating patients with knee OA, providing improvements in pain (based on VAS score) and radiological aspects related to the disease. However, they do not offer additional benefits over placebo in improving quality of life, daily activities, and sports activities. Further studies are needed to include this treatment in the therapeutic algorithm for patients with knee OA.

Abbreviations

OA	Osteoarthritis
MSCs	Mesenchymal stem cells
KOOS	Knee injury and osteoarthritis outcome score
VAS	Visual analogue scale
ROM	Range of motion
MRA	Magnetic resonance arthrography
ADL	Activities of daily living
QoL	Quality of life
MLP	Middle-lateral patella
ILP	Inferior-lateral patella
SMP	Superior-medial patella
MMP	Middle medial patella
IMP	Inferior-medial patella
MFF	Medial femoral facet
LFF	Lateral femoral facet
LCN	Lateral compartment non-weight bearing
LCW	Lateral compartment weight bearing
MCN	Medial compartment non-weight bearing
MCW	Medial compartment weight bearing
TCM	Tibial compartment medial
TCL	Tibial compartment lateral

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Author contributions

Conceptualization: B.F., G,R.; Data collection, analysis, and visualization: S.P, M.A.K, M.M.K.; Writing—Original Draft: S.P.M., M.T.J, S.P., M.A.K, M.M.K; Writing–Review & Editing: S.S., K.M., B.F.; Resources: B.F., G.R.; Supervision: S.S., All authors have read and approved the manuscript prior to submission.

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Availability of data and material
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
We conducted this interventional triple-blind clinical trial entitled "The Effect And Safety Of Allogenic Adipose-Derived Mesenchymal Stem Cells In Treatment Of Knee Osteoarthritis, Pilot Study" after the institutional board review by Iran University of medical sciences (Ethics code number: IR.IUMS.REC.1394.26914, 24 January 2016). The ethics of this study are in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. Trial Registry Code: IRCT2016021123298N3, 20 February 2016.

Informed consent
Written informed consent was obtained from the patient for publication and any accompanying images.

Competing interests
The authors declare no conflict of interest.

AI declaration
The authors declare that they have not use AI-generated work in this manuscript.

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