

## Assessment of the Outcomes of the Intra-articular Abdominal Adipose-Derived Mesenchymal Stem Cell Therapy in Knee Osteoarthritis Patients

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**Objective:** The aim of this study was to evaluate the effectiveness of Intra-articular abdominal adipose-derived mesenchymal stem cell (AD-MSc) therapy in patients diagnosed with knee osteoarthritis and to compare its effectiveness in patients with grade 2 and grade 3 osteoarthritis.

**Material and Method:** The study group comprised 48 patients over the age of 18 that were diagnosed with Grade II or Grade III (Kellgren-Lawrence) primary knee osteoarthritis. Two-way comparative knee radiography was performed for all patients before the procedure. Intra-articular abdominal adipose-derived mesenchymal stem cell (AD-MSc) therapy was applied to all patients. The patients were evaluated with the VAS and WOMAC index before the treatment and 3 months and 6 months after the treatment.

**Results:** A statistically significant decrease was found in the six-month follow-up WOMAC and VAS scores compared to the pre-treatment scores regardless of the grade of their osteoarthritis ( $p < 0.001$ ).

**Conclusion:** In conclusion, it was observed that the intra-articular injection of the AD-MSCs provided satisfactory functional recovery and pain relief for patients with knee osteoarthritis at six-month follow-up. No procedure-related adverse events were observed during the follow-up period.

**Keywords:** Osteoarthritis, Stem cell, Abdominal fat, Intra-articular .

### INTRODUCTION

Osteoarthritis (OA) is a chronic disease that affects all structures of the joint and the periarticular tissues. Pathogenesis of OA involves joint cartilage degeneration, which develops as a result of the deterioration of the balance between cartilage production and cartilage destruction, new bone formation, sclerosis of subchondral bone, ligament and meniscus damage, periarticular muscle weakness, synovial inflammation and fibrosis. In the past, osteoarthritis (OA) was considered simply a degenerative joint disease. However, the pathogenesis of OA is much more complex than just wear and tear, and the term “osteoarthritis”, where the Latin suffix “-it is” is indicative of an inflammatory process, is indeed an accurate term<sup>1</sup>. Differential diagnosis should include inflammatory disorders such as psoriasis<sup>2</sup> that may present with knee joint involvement.

Treatment modalities for knee OA are very limited. The treatments for OA include physical therapy modalities, nonsteroidal anti-inflammatory drugs, analgesics, hyaluronic acid, platelet-rich plasma (PRP), stem cell therapy or corticosteroid-based intra-articular injections, and surgery. Among these treatments, stem cell therapy represents a milestone in regenerative medicine for the treatment of OA.

As multipotent cells widely distributed in bone marrow, periosteum, trabecular bone, fat pad tissue, synovial membrane, and many other tissues, mesenchymal stem cells (MSCs) have great potential to promote differentiation in to chondrocytes and regeneration of cartilage. Bone marrow and adipose tissue are the main sources for therapeutic MSCs<sup>3</sup>. Stem cells have the ability to multiply indefinitely, renew themselves, differentiate into other cells, and repair the damaged tissue which it is injected into<sup>4</sup>. This differentiation may exert effects on the regulation

of immunity<sup>5</sup>, provision of anti-inflammatory effect, achievement of pro-angiogenesis<sup>5</sup>, improvement of the microenvironment<sup>6</sup> and promotion of the regeneration<sup>7</sup>. Unlike synthetic substances, stem cells do not cause allergies or other problems; the fact that they are suitable for one's own nature makes their use even more attractive<sup>8</sup>. Adipose tissue consists of two main components, mainly mature adipocytes and the stromal vascular fraction (SVF) rich in blood vessels. Capillaries are the primary source for stem cells<sup>9</sup>. Extracting stem cells from adipose tissue is frequently preferred in recent years because it is an easier and less invasive technique with higher efficiency compared to extracting stem cells from bone marrow<sup>10</sup>. Apart from the difficulty in obtaining cells, which may be easier in fat, the other arguments are identical between adipose and bone marrow MSCs. There is no risk of rejection with MSCs, moreover when they are used autologously. Stem cell concentration extracted using the SVF method cannot be purified by 100%. It is possible to purify stem cells by 100% only in laboratory environment. With the last circular issued in our country in 2018, the use of any method other than minimal manipulation to extract stem cells is prohibited<sup>11</sup>. Cell content obtained by minimal manipulation (enzyme cannot be used and cultured) with the SVF method includes 64% regenerative (progenitor-type) cells, 22% mature endothelial cells and vascular smooth muscle cells, and 14% leukocytes<sup>12</sup>. There are approximately 2x10<sup>6</sup> stem cells in each ml of this heterogeneous cell population obtained by SVF. The current purification rate is sufficient to generate an effective number of stem cells to be applied intra-articularly<sup>12</sup>.

In this context, the objective of this study is to evaluate to evaluate the effectiveness of intra-articular abdominal fat-derived mesenchymal stem cell therapy in patients diagnosed with knee osteoarthritis and to compare its effectiveness in patients with grade 2 and grade 3 osteoarthritis.

## MATERIAL AND METHOD

### *Research Design*

This study was designed as a retrospective descriptive study. Written informed consent was obtained from each patient included in the study. Detailed written consent was obtained from all patients and their relatives for data analysis. The study protocol was approved by the Ethics Committee of University (04/01/2021/26). The study was conducted in accordance with the principles of the Declaration of Helsinki. After approval from the ethics committee, it was reviewed retrospectively.

### *Population and Sample*

The study population consisted of patients who were diagnosed with primary knee osteoarthritis according to the American College of Rheumatology (ACR) osteoarthritis diagnostic criteria and applied intra-articular abdominal fat-derived mesenchymal stem cell therapy between January 2021 and January 2023 in the Department of Algology, University Faculty of Medicine.

### *Data Collection*

2-way knee X-ray and magnetic resonance imaging of the knee, which were routinely requested before the procedure, and routinely requested MRI images of the knee at the 6th month after the procedure were examined by looking at the hospital registry system. All patients underwent physical examination, routine blood tests, serological tests, tumor screening and laboratory tests such as pregnancy test if indicated. Patients were evaluated with the Visual Analogue Scale (VAS) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) before the treatment and during the three-month and six-month follow-up visits after the treatment. The Kellgren-Lawrence OA grading system<sup>13</sup> was used to determine the radiographic severity of OA. Before the procedure, 2-way knee radiographs of the patients who underwent the procedure were examined, and the radiographic severity of OA was recorded. The medications used by the patients were recorded.

### *Quality of Life*

The evaluation of pain, stiffness and physical functions of the individuals included in the study was performed using the Turkish version of the WOMAC criterion<sup>14</sup>. WOMAC is a specific, valid and reliable criterion for OA and includes 24 questions under three sub-headings: pain, stiffness and physical function. Each question was scored according to the Likert scale as 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. The score of each section is calculated on its own and the total score ranges from 0 to 100. High scores indicate an increase in pain and stiffness and deterioration in physical function<sup>14</sup>. In the study, the WOMAC criterion was pre- and post-procedure under the supervision of algology doctor at 3. and 6 months completed by the patients. Values were recorded in the hospital system. Records were analyzed retrospectively.

### *Radiological Evaluation*

The right and left knee lateral and anterior-posterior graphics of the individuals included in the study were

classified and recorded by a specialist according to the radiological classification of C-L. OA stages according to this classification:

Stage 0: Normal

Stage 1: Suspected osteophytes, normal joint space

Stage 2: Significant osteophyte, suspicious narrowing of joint space

Stage 3: Moderate osteophytes, moderate joint space narrowing, mild sclerosis

Stage 4: Large osteophytes, severe narrowing of the joint space, significant subchondral bone sclerosis, were determined as cysts<sup>13</sup>.

### Pain

Pain was evaluated assessment of VAS pain scores. The VAS pain score was assessed as “without pain” (score =0) and “the worst pain” (score =10).

### Processing technique

The patients included in the study group underwent intra-articular abdominal adipose-derived mesenchymal stem cell (AD-MSC) therapy. The medications used by the patients were recorded. The OA medications of patients who have been using OA medication were discontinued for a washout period of two weeks. Patients were not allowed to use analgesics after the procedure, except for acetaminophen, which was allowed at a maximum dose of 4.000 mg per day in cases where necessary. Patients were evaluated with the Visual Analogue Scale (VAS) and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) before the treatment and during the three-month and six-month follow-up visits after the treatment. An efficacy and safety assessment was carried out at each follow up visit. Patients were recommended to avoid heavy exercises for 1 week from the day after the injection, and they were prescribed a knee exercise program to follow as of the start of the second week after the procedure.

Lipoaspiration and intra-articular injection procedures were performed under operating room conditions. The patient who was to undergo the procedure was placed in supine position, monitored, provided oxygen support, and his/her entire abdomen was sterilized with an antimicrobial solution. After the patient was sterilized and covered, 0.05 mg/kg midazolam was administered for sedation and 1-2 microgram/kg fentanyl was administered for analgesia. Subcutaneous adipose tissue anesthesia was achieved using a mixture, which was obtained by diluting 2% lidocaine in physiological saline using the tumescent technique<sup>15</sup>. After adequate anesthesia

was achieved, a 2 mm skin incision was made. Then, 40 cc of adipose tissue was collected with the help of a special aspiration needle and a 50cc injector attached to this needle. 40cc adipose tissue was then centrifuged at 3500 rpm for five minutes. Stem cell collection from adipose tissue was performed with a non-enzymatic method in a closed system within 20 minutes using a medical device kit (CTK-CELL™) that allows isolation of regenerative progenitor stem cells in adipose tissue.

Consequently, 4 cc concentrated AD-MSC liquid fraction was obtained from approximately 40 cc adipose tissue. Stem cell concentration obtained from adipose tissue was injected into the knee joint under C-arm fluoroscopy. The patients were kept under observation in the hospital for about 5 hours after the procedure and were discharged with recommendations.

### *Statistical analysis*

The research data were analyzed using the SPSS 21 (Statistical Package for Social Sciences for Windows, Version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package. Descriptive statistics were expressed using mean, standard deviation, median, minimum, maximum, frequency and percentage values. Shapiro-Wilk test was used to determine whether the variables conform to normal distribution. Subsequently, the student's t-test and Mann-Whitney U test and in the case of the categorical variables the Pearson's chi-squared test were used for statistical analyses. The variation of research data over time was analyzed with the Friedman Test. Wilcoxon Signed-Rank test with Bonferroni correction was used for paired comparisons ( $p=0.05/3=0.016$ ); on the other hand, in all other tests, the significance level was set at 0.05.

## **RESULTS**

The study group consisted of 48 patients. Of these patients, 23 (47.9%) had Grade II and 25 (52.1%) had Grade III primary OA as per the Kellgren-Lawrence OA grading system. There was no significant difference between the groups formed based on the primary OA grades in terms of age or Body Mass Index (BMI) ( $p=0.120$  and  $p=0.444$ , respectively). On the other hand, the rate of female patients in Grade III primary OA group was significantly higher than that of the Grade II primary OA group ( $p=0.039$ ) (Table I).

The analysis of the changes in the total WOMAC scores and the scores obtained from the WOMAC

**Table I.** — Distribution of demographic variables.

OA GRADE			
Variables	GRADE II	GRADE III	p value
Age	59.7 ± 13.7	64.7 ± 7.8	0.120
BMI	21.8 ± 1.6	22.1 ± 1.6	0.444
Gender	Female	21 (63.6)	0.039
	Male	11 (73.3)	
Categorical variables were expressed using frequency (percentage), whereas the continuous variables were expressed using mean ± standard deviation values. Yate's Continuity Correction, student's t-test and Mann-Whitney U test were used for statistical analyses. BMI: Body mass index, OA: osteoarthritis			

**Table II.** — Distribution of WOMAC Scores by osteoarthritis grades and follow-up periods.

OA GRADE								
Variables		Grade II			Grade III			p value
		Mean ± SD	Median	Min-Max	Mean ± SD	Median	Min-Max	
Total WOMAC score	BASELINE	43.2 ± 16.8	42	11 - 75	60,3 ± 19,7	63	9 - 91	0.002
	3 <sup>RD</sup> MONTH	25.2 ± 15.1	25	3 - 57	35,1 ± 17	31	0 - 71	0.042
	6 <sup>TH</sup> MONTH	25.1 ± 16.4	26	0 - 59	35,8 ± 15	36	0 - 59	0.016
	p value	<0.001			<0.001			
WOMAC Pain subscale score	BASELINE	8.7 ± 3.3	8.3	3,1 - 15,6	13,2 ± 4,3	13,5	4,2 - 20	<0.001
	3 <sup>RD</sup> MONTH	5.2 ± 2.9	5.2	1 - 13,5	7,9 ± 4,4	6,2	0 - 17,7	0.018
	6 <sup>TH</sup> MONTH	4.7 ± 3.1	4.2	0 - 13,5	8 ± 3,9	8,3	0 - 16	0.003
	p value	<0.001			<0.001			
WOMAC Stiffness subscale score	BASELINE	3.1 ± 1.2	3.1	1 - 6,2	4,9 ± 1,9	5,2	1 - 7,3	<0.001
	3 <sup>RD</sup> MONTH	1.8 ± 1.4	2.1	0 - 4,2	3,2 ± 1,7	3,1	0 - 6,2	0.005
	6 <sup>TH</sup> MONTH	1.8 ± 1.3	2.1	0 - 4,2	3,2 ± 1,6	3,1	0 - 6,2	0.002
	p value	<0.001			<0.001			
WOMAC Physical Function subscale score	BASELINE	33.1 ± 13.6	34.3	7,3 - 58,2	44,6 ± 15	48,9	4,2 - 68,6	0.007
	3 <sup>RD</sup> MONTH	19.7 ± 12.9	16.6	2,1 - 52	24,9 ± 12,3	22,9	0 - 52	0.17
	6 <sup>TH</sup> MONTH	19.5 ± 13.3	18.7	0 - 54,1	26 ± 10,8	27	0 - 41,6	0.036
	p value	<0.001			<0.001			
Mann-Whitney U and Friedman tests were used for statistical analyses. OA: osteoarthritis.								

pain, stiffness, and physical function subscales by the Kellgren-Lawrence OA grade over time following AD-MSK revealed that the initial scores have decreased statistically significantly over time in both Grade II and Grade III primary OA groups (Table II). The mean total WOMAC scores of the Grade II primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 43.2 ± 16.8, 25.2 ± 15.1, and 25.1 ± 16.4, respectively. The mean total WOMAC scores of the Grade III primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 60.3 ± 19.7, 35.1 ± 17, and 35.8 ± 15, respectively. The mean WOMAC pain subscale scores of the Grade II primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 8.7 ± 3.3, 5.2 ± 2.9, and 4.7 ± 3.1, respectively. The mean WOMAC pain subscale scores of the Grade III primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as

13.2 ± 4.3, 7.9 ± 4.4, and 8 ± 3.9, respectively. The mean WOMAC stiffness subscale scores of the Grade II primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 3.1 ± 1.2, 1.8 ± 1.4, and 1.8 ± 1.4, respectively. The mean WOMAC stiffness subscale scores of the Grade III primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 4.9 ± 1.9, 3.2 ± 1.7, and 3.2 ± 1.6, respectively. The mean WOMAC physical function subscale scores of the Grade II primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 33.1 ± 13.6, 19.7 ± 12.9, and 19.5 ± 13.3, respectively. The mean WOMAC physical function subscale scores of the Grade III primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as 44.6 ± 15, 24.9 ± 12.3, and 26 ± 10.8, respectively. A statistically significant decrease was observed in the total WOMAC scores and the scores obtained from the WOMAC pain,

stiffness and physical function subscales during the first three months of the treatment in both Grade II and Grade III primary OA groups ( $p < 0.001$ ). However, this decrease has not continued during the following 3 months (Figure 1,2). The total WOMAC scores and the WOMAC pain, stiffness and physical function scores were found to have differed by the Kellgren-Lawrence OA grades in almost all time periods.

However, the change observed in the total WOMAC and the WOMAC pain and stiffness scores according to the Kellgren-Lawrence OA grades decreased at the 3rd month of the treatment, and no significant change was observed in the case of WOMAC physical function scores ( $p=0.17$ ) (Table II). On the other hand, the analysis of the changes observed in the VAS scores by the Kellgren-Lawrence OA grade over

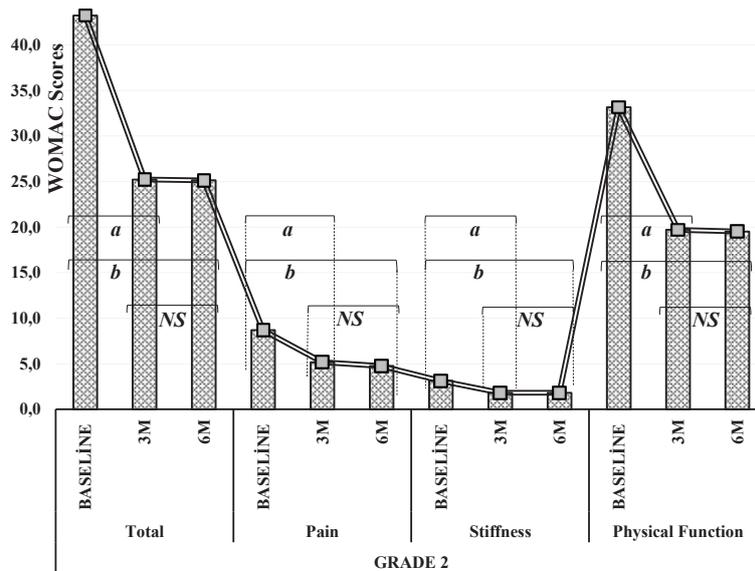


Fig. 1 — The change observed in the scores of Grade II OA patients according to the follow-up periods.

a: the difference between the baseline score and the score obtained at the 3rd month of the treatment, b: the difference between the baseline score and the score obtained at the 6th month of the treatment ( $p < 0.001$ ), NS: statistically insignificant.

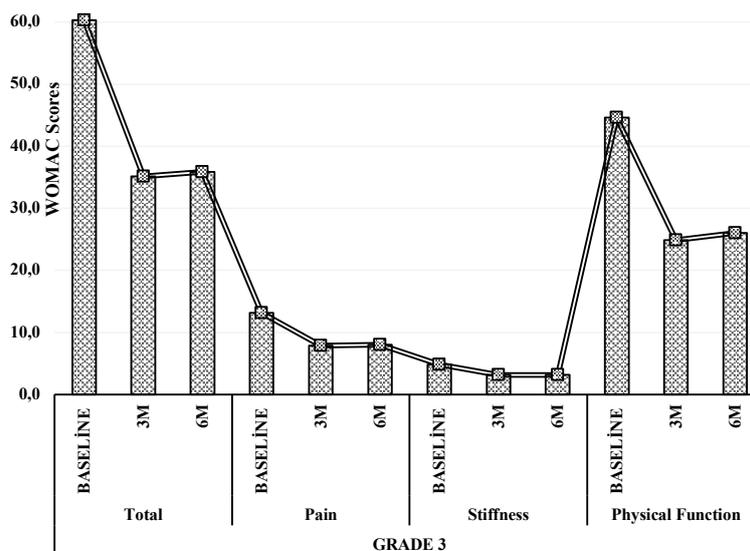


Fig. 2 — The change observed in the scores of Grade III OA patients according to the follow-up periods.

a: the difference between the baseline score and the score obtained at the 3rd month of the treatment, b: the difference between the baseline score and the score obtained at the 6th month of the treatment ( $p < 0.001$ ), NS: statistically insignificant.

time following the stem cell therapy revealed that the initial scores have decreased statistically significantly over time in both Grade II and Grade III primary OA groups (Table III). The mean VAS scores of the Grade II primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as  $4.4 \pm 1.4$ ,  $2.3 \pm 1.3$ , and  $2.3 \pm 1.5$ , respectively. The mean VAS scores of the Grade III primary OA group before the treatment and at the 3rd and 6th month of the treatment were calculated as  $6.0 \pm 1.6$ ,  $3.4 \pm 1.7$ , and  $3.4 \pm 1.7$ , respectively. A statistically significant decrease was observed in the VAS scores during the first three months of the treatment in both Grade II and Grade III primary OA groups ( $p < 0.001$ ), and also between the pre-treatment VAS scores and the VAS scores measured at the 6th month of the treatment ( $p < 0.001$ ). It is noteworthy that there were significant differences between the VAS scores categorized by the Kellgren-Lawrence OA grades in each time period and that these differences were the lowest at the 3rd month of the treatment ( $p = 0.001$ ,  $p = 0.031$  and  $p = 0.022$  for baseline, 3rd month and 6th month VAS scores, respectively).

## DISCUSSION

The findings of this study indicated that a satisfactory clinical and functional improvement was achieved in the patients by the 6-month of AD-MSC. Another important finding of this study was that no side effects were observed during the 6-month follow-up. During the 6-month follow-up period following the stem cell therapy, the WOMAC total scores decreased by 58% and 59.3% in the Grade II and Grade III primary OA groups, respectively. On the other hand, the VAS scores decreased by 52% and 56% in the Grade II and Grade III primary OA groups, respectively, during the same period. The decrease observed in the total WOMAC scores and in the scores obtained from the WOMAC subscales during the first three month-follow-up period was not observed in the following three month-period.

In a placebo-controlled study, Lee et al. determined that patients' scores obtained from the WOMAC pain and physical function subscales improved significantly in both Grade II and Grade III primary OA groups, compared to the control group, by the end of the 6-month follow-up period<sup>12</sup>. Similarly, in this study, a significant decrease was observed in the WOMAC and VAS scores by the end of the 6-month follow-up period. Difference between the findings of Lee et al.'s study and the findings of this study is that

the WOMAC and VAS scores continued to decrease during the three-month follow-up period following the first three-month follow-up period albeit at a lower pace in Lee et al.'s study, whereas that the decrease observed in the total WOMAC scores, the scores obtained from the WOMAC subscales and the VAS scores in both Grade II and Grade III primary OA groups during the first three-month follow-up period plateaued during the next three-month follow-up period in this study. In a meta-analysis including five randomized controlled studies on intra-articular MSC treatment, a significant improvement was observed in the VAS scores, but not in the WOMAC scores. In addition, the MR images did not indicate any significant difference in cartilage regeneration. It has been concluded as a result of the said meta-analysis that the evidence for the intra-articular MSC's role in pain relief and functional improvement in knee osteoarthritis is limited<sup>6</sup>.

In a study conducted on the efficacy of AD-MSC treatment on pain, function, and disease modification in knee OA, Freitag et al. detected a clinically significant improvement in knee OA in terms of pain and function by the end of a 12-month follow-up period<sup>17</sup>. The changes observed in the WOMAC and VAS scores during the first and second three-month follow-up periods in the single-injection AD-MSC treatment group in the said study are comparable to the changes observed in the WOMAC and VAS scores of both groups investigated within the scope of this study during the same periods. However, in the said study, the decreases observed in the WOMAC and VAS scores in the double-injection AD-MSC treatment group, continued until the 12th month after the administration of the second injection at the 6th-month<sup>17</sup>. This finding brings to mind that additional AD-MSC injections may be needed during the follow-up periods.

As a result of their study, Chris et al. recommended putting on partial weight with finger touch only for 8 weeks, a period comparable to the period used in cartilage regeneration treatments. While this prolonged period of putting on partial weight may allow some natural repair, it has also been demonstrated that it reduces and delays the recovery of knee function after injection<sup>8</sup>. In contrast, in this study, patients were recommended to return to normal daily activities after they had the injection and prescribed an exercise program to be started 1 week after the injection.

Orozco et al administered intra-articular bone-derived stem cell injection to 12 patients with knee osteoarthritis. Consequentially, they detected a rapid

and progressive decrease in pain, thereby an increase in the quality of life and a decrease in disability. They also demonstrated that sustained improvement was achieved in cartilage quality during a 2-year follow-up after stem cell transplantation according to the MR images<sup>19</sup>. To the contrary, in this study, no improvement was observed in the MR images of the patients during the 6-month follow-up period. Then again, it is highly likely that cartilage recovery could have also been achieved in this study, were the follow-up periods longer than six months have been implemented.

The chondrogenic potential of bone marrow and adipose tissue-derived stem cells decreases with age<sup>20</sup>. Nevertheless, synovium-derived MSC was found to be superior to the AD-MSC in terms of differentiation and proliferation, independently of age<sup>19</sup>. In a study with 10 patients with a mean age of 34.1 years, Sekiya et al. reported that intra-articular transplantation of synovium-derived MSC was found to be more effective radiologically, histologically, and clinically as a result of an observation and quantitative evaluation that lasted longer than three years<sup>21</sup>. Given that the mean age of the patients included in this study was 62.2 years, better results might have also been obtained in this study in terms of WOMAC and VAS scores, if synovium-derived AD-MSC was used instead of AD-MSC. In a study conducted to investigate the efficacy of a combined therapy, a mixture of adipose tissue-derived stem cells and platelet-rich plasma was administered to 21 patients with grade II to III knee OA. Consequentially, joint functions had improved and pain had decreased significantly by the end of the third month of the procedure. In addition, the MR images indicated an increase in the thickness of the cartilage layer as of the sixth month following the procedure. Combined injection of PRP and AD-MSC has been reported to be a safe and effective method for use in the treatment of grade II and III OA<sup>22</sup>. In this context, administration of a regenerative treatment in addition to the treatment administered could have provided better results also in this study in terms of clinical and functional improvement.

In a recent meta-analysis of 43 studies, the clinical efficacies and the treatment-related adverse events of intra-articular hyaluronic acid, leukocyte-poor platelet-rich plasma, leukocyte-rich platelet-rich plasma, bone marrow mesenchymal stem cells (BM-MSCs), adipose mesenchymal stem cells (AD-MSC), and saline (placebo) were comparatively analyzed in terms of the VAS and WOMAC scores measured at the 6th-month and 12th-month of the treatment.

The VAS scores and the scores obtained from the WOMAC pain subscale at the 6th-month of the treatment indicated that AD-MSC treatment was the best treatment option in terms of efficacy, whereas that leukocyte-poor platelet-rich plasma was the best treatment option in terms of treatment-related adverse events<sup>23</sup>. In comparison, in this study, in addition to the efficacy of AD-MSC treatment as demonstrated by the statistically significant decrease observed in the WOMAC and VAS scores at the 6th-month of the treatment, the fact that no adverse events related to the procedure were observed in patients, who were administered AD-MSC treatment, during the first six-months following the procedure indicated that intra-articular AD-MSC treatment is both a safe and effective option.

Apart from its strengths mentioned throughout the text, there were also some limitations to this study. First, the sample size was relatively small. Secondly, the follow-up period was 6 months, which might be considered insufficient by some. As a reason, longer follow-up periods may produce more results on the clinical efficacy, side effects, and structural outcomes of the treatment. Thus, further studies with larger sample sizes and longer follow-up periods will be pertinent. Lastly, the effect of interventions on cartilage regeneration could not be evaluated histopathologically.

In conclusion, intra-articular injection of AD-MSCs provided satisfactory functional recovery and pain relief for patients with knee OA without any adverse events during a 6-month follow-up period. Although intra-articular injections of stem cells derived from the adipose tissue using minimal manipulation are currently used in clinical routine, further studies involving larger sample sizes and long-term follow-up periods are needed to develop a standardized approach with regards to the use of intra-articular abdominal adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis.

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