# Comparison of Clinical and Imaging Outcomes of Different Doses of Adipose-Derived Stromal Vascular Fraction Cell Treatment for Knee Osteoarthritis

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# Abstract

**Background:** Favorable clinical outcomes of the intra-articular injection of adipose-derived stromal vascular fraction (SVF) cells for knee osteoarthritis (OA) have been reported. This study aimed to compare the short-term clinical and imaging outcomes of different doses of SVF cells for knee OA treatment.

**Methods:** This study included 60 patients with knee OA who underwent intra-articular injection of SVF cells. The follow-up period was at least 12 months. The envelope method was used to prospectively quasi-randomized the patients to undergo treatment with different doses of SVF cells. Thirty patients received an intra-articular injection of $2.5\times10^7$ SVF cells (low-dose group), and the remaining 30 patients received an intra-articular injection of $5.0\times10^7$ SVF cells (high-dose group). Clinical evaluations were performed for range of motion, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS) for pain, and the Knee injury and Osteoarthritis Outcome Score (KOOS). Imaging evaluations, which included the hip-knee-ankle angle and magnetic resonance imaging Osteoarthritis Knee Score (MOAKS) features (bone marrow lesions, cartilage defects, osteophytes, Hoffa's synovitis, and effusion synovitis), were also performed. All clinical and imaging evaluations were performed preoperatively and 12 months postoperatively and compared between the groups.

**Results:** No significant differences in demographic data were found between the two groups. The knee extension angle at 12 months postoperatively was significantly higher than the preoperative angle in both groups. The total WOMAC and VAS scores at 12 months postoperatively were significantly more favorable than preoperative scores in both groups. The bone marrow lesions and Hoffa's synovitis and effusion synovitis improved approximately 30-40% from baseline to 12 months postoperatively in both groups. However, there were no significant differences in the preoperative and postoperative results of any clinical or imaging evaluation between the two groups.

**Conclusions:** The short-term clinical and imaging outcomes of intra-articular injection of SVF cells for knee OA were excellent, regardless of whether a low- or high-dose was administered. Intra-articular injection of SVF cells for knee OA is an innovative approach.


# Background

Osteoarthritis (OA) is a chronic progressive disease characterized by cartilage degeneration, osteophyte formation, bone reorganization, and loss of joint function [1]. The knee is the most frequently involved weight-bearing joint, and OA is associated with significant morbidity and healthcare expenditures [2]. Knee OA leads to changes in the cartilage, tendons, ligaments, and muscles of the joint, resulting in poor psychosocial outcomes, imbalance, increased risk of falls, and limited physical activities [3–5]. Treatment for knee OA includes conservative methods and surgical therapies and depends on patients' age, the severity of symptoms, and the type of lesion. Conservative treatments range from nonpharmacological (e.g., weight loss, physical therapy, and exercise) to pharmacological (e.g.,

nonsteroidal anti-inflammatory drugs or glucocorticoid injections) to surgical treatments (e.g., arthroscopic debridement with bone marrow stimulation, osteochondral grafts, or microfracture), with total knee arthroplasty as the last option for most patients [6–8].

In recent years, cell therapy using adipose tissue-derived mesenchymal stem cells (ADSCs) has attracted attention as a new potential treatment for knee OA [9, 10]. ADSCs, which share similar properties with bone marrow-derived mesenchymal stem cells (BMSCs), have the potential to differentiate into adipogenic, osteogenic, chondrogenic, and other mesenchymal lineages and have been widely applied in knee OA studies [11, 12]. However, ADSCs require culturing, which requires a few weeks between isolation and application, and cell culturing is expensive.

Adipose-derived stromal vascular fraction (SVF) cells are a heterogeneous cell population that contains regenerative cells such as ADSCs, macrophages, pericytes, fibroblasts, blood cells, vessel-forming cells including endothelial and smooth muscle cells, and their progenitors [13, 14]. These heterogeneous cell populations include cells with stem cell elements in addition to ADSCs and are thought to have a synergistic effect with ADSCs [15–17]. Unlike ADSCs, SVF cells can be readily obtained from liposuction samples without the need for cell separation or culturing conditions, which render them more cost-efficient and convenient [18, 19]. Furthermore, SVF cells are considered as effective as or more effective than ADSCs. Their use provides additional functional advantages over the use of ADSCs, such as structural support [20, 21]. It was also reported that no significant difference in pain, activity of life, sports and quality of life subscales of Knee injury and Osteoarthritis Outcome Score (KOOS) was observed between SVF cells and ADSCs treatments for knee OA [22]. Although we previously reported excellent short-term clinical effects of the intra-articular injection of $2.5\times10^7$ SVF cells on knee OA, the effect of the dose of SVF cells was not examined [23]. Jo et al. reported that a high-dose intra-articular injection of ADSCs improved knee function and pain and reduced cartilage defects more effectively than a low-dose injection [9]. However, the effect of different doses of SVF cells alone for knee OA treatment has not been reported.

The purpose of this study was to compare the short-term clinical and radiographic outcomes of different doses of intra-articular injections of SVF cells used to treat knee OA. It was hypothesized that the clinical and radiographic results would be significantly different depending on the dose of SVF cells administered.

# Methods

### Patient selection

This study included 60 patients with knee OA who received unilateral treatment with intra-articular injection of SVF cells between February 2017 and January 2018. The minimum clinical and radiographic follow-up was 12 months (mean, 17.2 months; range, 12–21 months). The knee OA grade was evaluated using the Kellgren-Lawrence classification, and patients with grade I to IV OA participated in this study.

The inclusion criteria were (a) patients diagnosed with knee OA at any age; (b) complaints of substantial pain and loss of function; (c) ineffectiveness of conservative treatment including rehabilitation, medication, and intra-articular injection of hyaluronic acid or steroids; and (d) written informed consent. The exclusion criteria were (a) severe bony defects on preoperative radiographs; (b) previous knee injury requiring operation; (c) active or previous knee joint infection; and (d) past history of serious, related conditions, including systemic inflammatory diseases and vascular changes. The envelope method was used to prospectively quasi-randomized the patients to undergo treatment with different doses of intra-articular injection of SVF cells. Thirty patients (19 women and 11 men) received an intra-articular injection of $2.5\times10^7$ SVF cells (low-dose group) and 30 patients (24 women and 6 men) received an intra-articular injection of $5.0\times10^7$ SVF cells (high-dose group). Patients were asked to perform daily home exercises by themselves after treatment according to a standardized rehabilitation protocol, in addition to rehabilitation with a physical therapist.

## Treatment procedures (Fig. 1)

Treatment procedures were performed in the same way as in the previous study [23]. SVF cells were extracted from the patient's abdominal or breech subcutaneous fat using the Celution® 800/CRS system (Cytori Therapeutics Inc., San Diego, CA). This system consists of two parts: one for tissue washing and digestion and one for cell concentration. All patients underwent a liposuction procedure under general anesthesia to obtain 290-440 mL of adipose tissue. The extracted tissue was processed using the Celution® 800/CRS System according to the manufacturer's instructions. Briefly, the tissue was washed to remove blood and debris, and then Celase® GMP, a mixture of highly purified collagenase and neutral protease enzyme, was added. The tissue was incubated at 37°C for 20 minutes with continuous mixing to assist indigestion. After digestion of the tissue, the SVF cells were concentrated by centrifugation and washed to remove the Celase® reagent. The SVF cells were then extracted and counted to prepare the specified dose in 5 mL of lactated Ringer's solution. The entire procedure was performed aseptically using clinical-grade solutions such as saline and lactated Ringer's and the single-use Celution™ consumable sets. The SVF cell count and viability calculation were performed at each investigational site using the NC-100™ NucleoCounter® Automated Cell Counting System (Chemometec, Allerod, Denmark).

The mean volume of liposuction, number of purified SVF cells, and viability of SVF cells are listed in Table 1. The intra-articular injection of $2.5\times10^7$ or $5.0\times10^7$ SVF cells to each patient was administered depending on the number of purified SVF cells. If the joint fluid level was excessive, aspiration was performed prior to cell transplantation. Cell transplantation into the knee joint was performed without anesthetic and under echo guidance.

## Clinical evaluations and scores

Clinical evaluations and scores were assessed at 1, 3, 6, and 12 months after treatment with SVF cells. Clinical evaluations included knee range of motion and muscle force of knee extension and flexion using a hand-held dynamometer. Clinical scores included the Western Ontario and McMaster Universities

Osteoarthritis Index (WOMAC), visual analog scale (VAS) for pain (0-100), Japanese Knee Osteoarthritis Measure (JKOM), and KOOS. To measure the muscle force of knee extension and flexion, patients were in a prone position with their knees at 45° flexion. The hand-held dynamometer was placed at the center of the lower leg, and the patients were instructed to bend the knee and hold for 3 seconds to measure hamstring strength and to straighten the knee and hold for 3 seconds to measure quadriceps strength. The examiner added resistance to maintain the knee at 45° and measured the displayed value as muscle strength. These tests were performed three times, and the average value was recorded. Clinical evaluations were performed by an independent experienced physiotherapist.

### Imaging evaluations

Imaging evaluations included the hip-knee-ankle (HKA) angle assessed via radiography [24] and the magnetic resonance imaging (MRI) Osteoarthritis Knee Score (MOAKS) using a 1.5-T MRI unit (Sigma Exite HDx; GE Healthcare, Waukesha, WI, USA). MOAKS is a semi-quantitative tool [25]; therefore, changes in the MRI features are an important tool for monitoring knee OA [26]. The HKA angle was assessed at 1, 3, 6, and 12 months after treatment with SVF cells. The main MOAKS features (bone marrow lesions (BMLs), cartilage defects, osteophytes, Hoffa's synovitis, and effusion synovitis) were assessed at 12 months after treatment with SVF cells. Scores of each evaluation item at 12 months postoperatively were compared with those at baseline and classified into three categories: improvement, no change, and progression. BMLs, cartilage defects, and osteophytes were evaluated in each of three anatomical areas: the medial tibiofemoral (TF) joint, lateral TF joint, and patellofemoral (PF) joint. Radiographic evaluations were performed twice by an independent orthopedic surgeon with 15 years of experience in analyzing the MRI features of knee OA. The average kappa value of intra-observer reliability for the first main MOAKS features assessment was.

### Statistical Analysis

All values are expressed as mean ± standard deviation. Data analyses were performed using IBM SPSS statistical software (version 21; IBM Corp., Armonk, NY USA). The Shapiro-Wilk test was also used to analyze normally distributed data. Clinical evaluations and the HKA angle were compared among the five-time periods using repeated measures analysis of variance in each low-dose and high-dose group and between the two groups using an unpaired t-test. Furthermore, we evaluated the main MOAKS features (BMLs, cartilage defects, osteophytes, Hoffa's synovitis, and effusion synovitis) preoperatively and at 12 months postoperatively and investigated the number of patients who showed improvement, no change, and progression in each group using Pearson's chi-square test. $P<0.05$ was considered statistically significant. A statistical power analysis was performed prior to the study using G*Power 3, which indicated that a sample size of 30 was needed for a power of 0.8, based on a prespecified significance level of <0.05, and assumed effect size of 0.65 [27].

## Results

### Demographic data and adverse events

No significant differences were found in the demographic data between the two groups (Table 2). Neither death nor life-threatening adverse events were observed during the 12-month follow-up after cell therapy in either group. There were also no moderate adverse events such as infections during follow-up. However, mild adverse events such as swelling and pain of the knee were observed in 10.0% and 6.7% of the low-dose and high-dose groups, respectively. Symptoms disappeared within 3 days in all cases.

### Clinical evaluations

The improvement in the mean extension angle from baseline to 6 and 12 months in the low-dose group and 12 months in the high-dose group was statistically significant. However, there was no significant difference between the two groups at any time point. The mean flexion angle did not significantly improve from baseline in either group, and there was no significant difference between the two groups at any time point (Table 3a). Although the mean muscle force of knee extension was significantly higher at 12 months postoperatively than preoperatively in the low-dose group, there was no significant difference between the two groups at any time point. The improvement in the mean muscle force of knee flexion from baseline to 6 months in the low-dose group and 12 months in the high-dose group was statistically significant. However, there was no significant difference between the two groups at any time point (Table 3a).

The mean total WOMAC scores from baseline to 12 months postoperatively were significantly improved in both groups. However, there was no significant difference between the two groups (Table 3b). The mean VAS scores from baseline to 12 months postoperatively were significantly improved in both groups, without a significant difference between the groups (Table 3b). The mean total JKOM scores from baseline to 12 months postoperatively showed no significant difference in either group, and there was no significant difference in the scores preoperatively and 12 months postoperatively between the two groups (Table 3b). The improvement in the average 5-subscale KOOS scores from baseline to 12 months postoperatively was significantly different in the high-dose group; however, there was no significant difference in the scores preoperatively and 12 months postoperatively between the two groups (Table 3b). The detailed scores for each subscale of WOMAC, VAS, JKOM, and KOOS are shown in Additional file 1.

### Imaging evaluation

There was no significant improvement in the HKA angle from baseline to any time point in either group, and there was no significant difference in the HKA angle between the two groups at any time point (Table 4a). The improvement rate of BMLs in the medial TF joint from baseline to 12 months postoperatively was 30.0% in the low-dose group and 33.3% in the high-dose group; however, there was no significant difference between the groups (Table 4b, Table 5a, Fig. 2 a). Although the improvement rate of cartilage defects in both the medial and lateral TF joints from baseline to 12 months postoperatively was 13.3% in the low-dose group and 16.7% in the high-dose group, there was no significant difference between the groups (Table 4c, Table 5b, Fig. 2 b). No patients showed improvement in the osteophytes subscale from baseline to 12 months (Table 4d, Table 5c). The improvement rate of Hoffa's synovitis from baseline to 12 months postoperatively was 36.7% in the low-dose group and 43.3% in the high-dose group; however,

there was no significant difference between the groups (Table 4e, Table 5d, Fig. 2 c). Furthermore, the improvement rate of effusion synovitis from baseline to 12 months postoperatively was 30.0% in the low-dose group and 36.7% in the high-dose group, which was also not significantly different between the groups (Table 4e, Table 5d, Fig. 2 c).

# Discussion

The clinical and radiographic results of the patients in this study improved in both the low-dose and high-dose groups from baseline to 12 months postoperatively. However, there was no significant difference in the clinical or imaging results between the groups, which does not support our hypothesis.

Favorable clinical outcomes of ADSC cell therapy for knee OA have been reported [10, 28, 29]. ADSCs have properties similar to those of BMSCs but require several weeks to isolate, culture, and amplify in specialized laboratories. In contrast, SVF cells are not cultured and can be harvested, prepared, and re-injected in a single procedure. Similar to BMSCs, SVF cells include cells with multilineage potential, can be easily isolated in large quantities from autologous adipose tissues, and can be used without culturing [18, 19]. Several studies have reported the use of autologous SVF cells alone for the treatment of knee OA [23, 30, 31]. Michialek et al. have reported that the intra-articular injection of SVF cells is a safe and clinically effective strategy for improving the quality of life; however, detailed clinical evaluations were not conducted in their clinical trial [30]. Fodor et al. reported that autologous SVF cells are safe and present a new potential treatment to reduce pain in patients with knee OA; however, their sample size was small [31]. In our previous report, we found that the short-term clinical effects of intra-articular injection of $2.5\times10^7$ SVF cells for knee OA were excellent, and our study included an effective sample size [23]. The effects of intra-articular injection treatment with different doses of ADSCs have been investigated [9, 10]. Pers et al. reported significant improvements in terms of pain, function, and mobility only in patients treated with the even lowest dose of ADSCs at the 6-month follow-up [10]. Jo et al. also reported that a high-dose, intra-articular injection of ADSCs improves knee function and pain and reduces cartilage defects in patients with knee OA more effectively than a low-dose injection [9]. However, to the best of our knowledge, the present study is the first study to evaluate the effect of different doses of SVF cells for the treatment of knee OA.

While no significant difference in clinical evaluations was observed between the high- and low-dose groups in this study, the high-dose group tended to have better clinical evaluation scores than the low-dose group. The mean extension angle from baseline to 12 months in both groups was significantly improved as the muscle force of knee extension gradually improved postoperatively. However, the mean flexion angle did not significantly improve from baseline in either group. The mean total VAS scores at 1, 3, 6, and 12 months postoperatively were significantly better than the preoperative VAS score. Although Luc-Harkey et al. reported that greater quadriceps and hamstring muscle strength was associated with less pain [32], the improvement in knee pain may influence extension muscle strength more than flexion muscle strength.

In this study, the mean total WOMAC scores in both groups at 6 and 12 months postoperatively were significantly better than the preoperative scores. The mean 5-subscale KOOS scores from baseline to 6 months postoperatively were also significantly improved in both groups. There was no significant difference between the groups in the mean total WOMAC and average 5-subscale KOOS scores at 12 months postoperatively, indicating no significant difference in postoperative functional activity between the groups. Furthermore, no significant improvement in clinical scores was observed from 6 months to 12 months in either group, suggesting that there is an option to re-inject SVF cells into the knee joint about 12 months around the first intra-articular injection. Minonzio et al. reported that freeze adipose-derived SVF cells maintained their growth and differential potential [33]. Kaita et al. also reported that frozen SVF cells comprised a heterogeneous cell population, including stem cells and leukocytes, and expressed high levels of mesenchymal stem cell markers, similar to fresh SFV cells [34]. These results indicate that treatment options for knee OA can include initial doses of $2.5\times10^7$ SVF cells, with cryopreservation of the remaining cells for subsequent re-injection.

A larger baseline BML size is associated with greater baseline knee pain and structural damage as well as disease progression, and baseline BML size may be particularly important when assessing the associations between changes in BML size and disease progression [35, 36]. In the present study, approximately 30% of BMLs located in the medial TF joint improved at 12 months postoperatively compared to baseline in both the low-dose and high-dose groups. Wojdasiewicz et al. reported that mediating cytokines and their signaling pathways are upregulated in OA joints and most often have catabolic effects; these cytokines include interleukin-1 beta and tumor necrosis factor-alpha, and their levels are elevated in the synovial fluid, synovium, cartilage, and subchondral bone of OA patients. The synergistic effects of these cytokines on signaling pathways result in an increase in inflammation and cartilage degradation during the OA process [37]. Approximately 30-40% of Hoffa's synovitis and effusion synovitis improved at 12 months postoperatively compared to baseline in both the low-dose and high-dose groups in this study. SVF cells obtained from adipose tissue also contain a significant proportion of cells that are involved in the immunoregulatory function and cells of hematopoietic origin that are involved in vascular remodeling [38]. Macrophages present in rodent adipose tissue constitute 20% of the cells in SVF cells, 70% of which are positive for the anti-inflammatory M2 macrophage marker CD301 [39, 40]. The anti-inflammatory effect of M2 macrophages is thought to contribute to the improvement of BMLs, Hoffa's synovitis, and effusion synovitis in knee OA, thereby resulting in postoperative functional and pain improvements.

The patients followed a standardized rehabilitation protocol after the procedure which required them to perform daily exercises at home by themselves in addition to being treated by a physical therapist. Sun et al. reported that moderate physical exercise is effective for a decreased risk of severe osteoarthritis of the knee and suggested that exercise has a protective effect against cartilage degradation [41]. Hawker et al. also reported that an exercise program that combined endurance and strength training in patients with osteoarthritis increased functional capacity and reduced pain [42]. Rehabilitation is recommended in addition to regenerative medicine [43], and it is considered that

rehabilitation contributed to the improvement in the clinical score in addition to the effect of SVF cell treatment in the current study.

The present study has some limitations. First, the study compared only two groups and did not include a control group that underwent other intra-articular interventions. The association between SVF cells and other intra-articular interventions should be investigated in the future. Second, the clinical and imaging evaluations were only performed preoperatively and at 1, 3, 6, and 12 months after the intra-articular injection of SVF cells. A long-term investigation of the clinical and structural changes is warranted. Third, we did not evaluate the relationship between the clinical and imaging results. Fourth, although the high-dose group tended to have better clinical evaluation scores than the low-dose group, there was no significant difference between the two groups. This may be due to an insufficient number of cases. However, it is the preoperative clinical score of the high-dose group was better than that of the low-dose group and this could have contributed to the bias in the results. Finally, this study focused on patients who underwent a single injection of SVF cells. In order to determine the optimal treatment for OA, multiple injections should be evaluated in these patients.

# Conclusions

The short-term clinical and radiographic outcomes of different doses of SVF cell injections for knee OA were well improved in both the low-dose and high-dose groups, with no significant difference in clinical and radiographic results between the groups. Intra-articular injection of SVF cells into the knee joint can be considered an innovative approach to treat patients with knee OA.

# Abbreviations

Osteoarthritis (OA)

adipose tissue-derived mesenchymal stem cells (ADSCs)

bone marrow-derived mesenchymal stem cells (BMSCs)

stromal vascular fraction (SVF)

Knee injury and Osteoarthritis Outcome Score (KOOS)

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

visual analog scale (VAS)

Japanese Knee Osteoarthritis Measure (JKOM)

hip-knee-ankle (HKA)

magnetic resonance imaging (MRI)

magnetic resonance imaging Osteoarthritis Knee Score (MOAKS)

bone marrow lesions (BMLs)

tibiofemoral (TF)

patellofemoral (PF)

# Declarations

### Ethics approval, guidelines and consent to participate

This study was approved by the Ethics Committee of Sobajima Clinic (identification number: 170181) and conducted according to the guidelines. Written, informed consent was obtained from each participant.

### Consent for publication

Informed consent was obtained from all individual participants included in this study.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.


### Funding

Not applicable.


### Authors' contributions

All authors have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted.

The specific contributions of the authors are as follows:

(1) Conception and design of the study: [TM]1, SS, RK.

(2) Analysis and interpretation of the data: all authors, Drafting of the article: [TM]2, HI, MT.

(3) Final approval: all authors

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# Tables

**Table 1.** Stromal vascular fraction cell characteristics; number of purified SVF cells and SVF cell viability.

| Characteristics | Low-dose group | High-dose group | P value |
|---|---|---|---|
| **Volume of liposuction; ml** | 327.3 ± 51.2 | 352.8 ± 29.3 | 0.02※ |
| **Number of purified SVF cells** | $4.2 \pm 1.8 \times 10^7$ | $8.5 \pm 3.1 \times 10^7$ | <0.01※ |
| **SVF cell viability; %** | 90.0 ± 2.5 | 91.3 ± 3.1 | 0.08 |
| **Stromal vascular fraction (SVF)**<br>**Mean value ± Standard deviation**<br>**※ Statistically significant** | | | |

**Table 2.** Patient characteristics.

| Characteristics | | Low-dose group | High-dose group | P value |
|---|---|---|---|---|
| **Sex (M/F); n (%)** | | 19/11 (72%/28%) | 24/6 (72%/28%) | 0.15 |
| **Age; yrs** | | 69.0 ± 8.3 | 70.7 ± 5.3 | 0.14 |
| **Body mass index; kg/m$^2$** | | 24.9 ± 3.2 | 25.8 ± 2.6 | 0.24 |
| **Duration of follow-up; months** | | 16.4 ± 3.8 | 15.3 ± 2.3 | 0.18 |
| **Hip-knee-ankle angle at baseline; degree** | | 6.5 ± 7.4 | 9.1 ± 5.9 | 0.14 |
| **Knee extension angle; degree** | | -8.2 ± 7.1 | -6.5 ± 6.0 | 0.33 |
| **Knee flexion angle; degree** | | 127.7 ± 16.0 | 134.3 ± 11.7 | 0.07 |
| **Kellgren-Lawrence classification; n (%)** | I | 0 (0%) | 0 (0%) | 0.70 |
| | II | 4 (13.3%) | 5 (16.7%) | |
| | III | 15 (50.0%) | 17 (56.6%) | |
| | IV | 11 (36.7%) | 8 (26.7%) | |
| **Mean value ± Standard deviation** | | | | |

**Table 3a.** Clinical evaluation results of range of motion and muscle force.

| Range of motion of the knee | | | | | |
|---|---|---|---|---|---|
| **Extension** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | -8.2 ± 7.1 | | -6.5 ± 6.0 | | 0.33 |
| **1 month** | -6.3 ± 5.2 | 0.20 | -5.8 ± 5.6 | 0.63 | 0.72 |
| **3 months** | -5.8 ± 5.3 | 0.11 | -5.3 ± 5.2 | 0.39 | 0.71 |
| **6 months** | -5.2 ± 4.6 | 0.04※ | -5.0 ± 5.4 | 0.27 | 0.90 |
| **12 months** | -5.0 ± 5.3 | 0.03※ | -3.7 ± 3.9 | 0.04※ | 0.27 |
| **Flexion** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 127.7 ± 16.0 | | 134.3 ± 11.7 | | 0.07 |
| **1 month** | 130.5 ± 14.9 | 0.46 | 134.3 ± 13.2 | - | 0.30 |
| **3 months** | 132.7 ± 13.0 | 0.19 | 136.3 ± 11.2 | 0.54 | 0.25 |
| **6 months** | 131.8 ± 13.5 | 0.27 | 135.3 ± 13.3 | 0.76 | 0.32 |
| **12 months** | 129.3 ± 15.7 | 0.66 | 133.7 ± 13.1 | 0.84 | 0.25 |
| **Muscle force** | | | | | |
| **Extension (Quadriceps)** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 199.2 ± 79.0 | | 200.6 ± 80.1 | | 0.95 |
| **1 month** | 182.1 ± 88.2 | 0.47 | 197.8 ± 65.0 | 0.88 | 0.44 |
| **3 months** | 207.7 ± 89.1 | 0.72 | 213.3 ± 62.9 | 0.50 | 0.78 |
| **6 months** | 214.3 ± 88.2 | 0.52 | 233.3 ± 78.2 | 0.08 | 0.38 |
| **12 months** | 248.7 ± 109.0 | 0.04※ | 237.5 ± 75.1 | 0.051 | 0.64 |
| **Flexion (Hamstrings)** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 90.4 ± 35.8 | | 102.8 ± 35.6 | | 0.18 |
| **1 month** | 95.0 ± 36.2 | 0.35 | 111.4 ± 35.4 | 0.69 | 0.08 |
| **3 months** | 109.4 ± 68.2 | 0.36 | 111.2 ± 31.8 | 0.10 | 0.90 |
| **6 months** | 112.0 ± 40.4 | 0.02※ | 124.3 ± 36.3 | 0.07 | 0.22 |

| | | | | | |
|---|---|---|---|---|---|
| **12 months** | 117.2 ± 36.0 | 0.10 | 117.9 ± 37.2 | 0.02※ | 0.94 |

**※ Statistically significant**

**Table 3b.** Clinical evaluation results of each clinical score.

| Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) | | | | | |
|---|---|---|---|---|---|
| **Total Score** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 36.8 ± 21.2 | | 32.0 ± 14.3 | | 0.31 |
| **1 month** | 29.7 ± 16.4 | 0.13 | 25.0 ± 13.2 | 0.045※ | 0.23 |
| **3 months** | 27.5 ± 17.9 | 0.051 | 20.2 ± 10.8 | <0.01※ | 0.06 |
| **6 months** | 25.2 ± 17.2 | 0.02※ | 22.2 ± 13.4 | <0.01※ | 0.46 |
| **12 months** | 26.3 ± 18.1 | 0.03※ | 21.8 ± 14.5 | <0.01※ | 0.30 |
| **Visual analog scale (VAS)** | | | | | |
| | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 53.2 ± 21.9 | | 44.3 ± 24.3 | | 0.14 |
| **1 month** | 33.4 ± 20.4 | <0.01※ | 29.5 ± 19.8 | 0.03※ | 0.46 |
| **3 months** | 31.4 ± 19.8 | <0.01※ | 27.5 ± 20.9 | 0.02※ | 0.46 |
| **6 months** | 30.8 ± 19.9 | <0.01※ | 30.7 ± 19.7 | 0.01※ | 0.99 |
| **12 months** | 39.9 ± 24.8 | 0.02※ | 31.1 ± 21.7 | 0.02※ | 0.15 |
| **Japanese Knee Osteoarthritis Measure (JKOM)** | | | | | |
| **Total score** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 38.3 ± 18.9 | | 32.8 ± 17.5 | | 0.24 |
| **1 month** | 35.5 ± 18.7 | 0.58 | 28.6 ± 14.6 | 0.29 | 0.11 |
| **3 months** | 33.5 ± 20.8 | 0.35 | 23.2 ± 13.8 | 0.02※ | 0.03※ |
| **6 months** | 28.0 ± 18.8 | 0.046※ | 24.5 ± 15.7 | 0.04※ | 0.44 |
| **12 months** | 33.2 ± 22.1 | 0.32 | 25.7 ± 15.3 | 0.08 | 0.13 |
| **Knee injury and Osteoarthritis Outcome Score (KOOS)** | | | | | |
| **Average score of 5 subscales** | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 90.3 ± 27.2 | | 98.7 ± 21.9 | | 0.19 |

| | | | | | |
|---|---|---|---|---|---|
| **1 month** | 100.8 ± 27.0 | 0.14 | 111.0 ± 22.0 | 0.03※ | 0.12 |
| **3 months** | 102.3 ± 27.2 | 0.09 | 115.3 ± 21.0 | <0.01※ | 0.04※ |
| **6 months** | 108.6 ± 26.5 | 0.01※ | 111.9 ± 21.8 | 0.02※ | 0.60 |
| **12 months** | 103.0 ± 28.9 | 0.07 | 114.0 ± 23.3 | <0.01※ | 0.11 |
| **※ Statistically significant** | | | | | |

**Table 4a.** Imaging evaluation results of Hip-knee-ankle angle.

| **Range of motion of the knee** | | | | | |
|---|---|---|---|---|---|
| | **Low-dose group** | **P value** | **High-dose group** | **P value** | **P value between two groups** |
| **Preoperative** | 6.5 ± 7.4 | | 9.1 ± 5.9 | | 0.14 |
| **1 month** | 6.8 ± 6.8 | 0.86 | 8.6 ± 5.7 | 0.71 | 0.28 |
| **3 months** | 6.7 ± 7.0 | 0.89 | 9.0 ± 5.6 | 0.97 | 0.16 |
| **6 months** | 6.6 ± 7.1 | 0.95 | 8.8 ± 5.3 | 0.86 | 0.17 |
| **12 months** | 6.8 ± 7.2 | 0.86 | 9.5 ± 5.5 | 0.77 | 0.10 |

**Table 4b.** Imaging evaluation results of bone marrow lesions by magnetic resonance imaging Osteoarthritis Knee Score system.

| Bone marrow lesions | | | |
|---|---|---|---|
| **Medial TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 17/30 (56.7%) | 17/30 (56.7%) | 1.00 |
| **Progression** | 4/30 (13.3%) | 3/30 (10.0%) | 0.69 |
| **No change** | 17/30 (56.7%) | 17/30 (56.7%) | 1.00 |
| **Improvement** | 9/30 (30.0%) | 10/30 (33.3%) | 0.78 |
| **Lateral TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 6/30 (20.0%) | 5/30 (16.7%) | 0.74 |
| **Progression** | 1/30 (3.3%) | 1/30 (3.3%) | 1.00 |
| **No change** | 27/30 (90.0%) | 25/30 (83.3%) | 0.45 |
| **Improvement** | 2/30 (6.7%) | 4/30 (13.3%) | 0.39 |
| **Patellofemoral joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 1/30 (3.3%) | 0/30 (0.0%) | 0.31 |
| **Progression** | 1/30 (3.3%) | 0/30 (0.0%) | 0.31 |
| **No change** | 29/30 (96.7%) | 30/30 (100.0%) | 0.31 |
| **Improvement** | 0/30 (0.0%) | 0/30 (0.0%) | 1.00 |
| **Tibiofemoral (TF)** | | | |

**Table 4c.** Imaging evaluation results of cartilage defects by magnetic resonance imaging Osteoarthritis Knee Score system.

| Cartilage defects | | | |
|---|---|---|---|
| **Medial TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 18/30 (60.0%) | 20/30 (66.7%) | 0.59 |
| **Progression** | 3/30 (10.0%) | 3/30 (10.0%) | 1.00 |
| **No change** | 23/30 (76.7%) | 22/30 (73.3%) | 0.77 |
| **Improvement** | 4/30 (13.3%) | 5/30 (16.7%) | 0.72 |
| **Lateral TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 19/30 (63.3%) | 21/30 (70.0%) | 0.58 |
| **Progression** | 3/30 (10.0%) | 3/30 (10.0%) | 1.00 |
| **No change** | 23/30 (76.7%) | 22/30 (73.3%) | 0.78 |
| **Improvement** | 4/30 (13.3%) | 5/30 (16.7%) | 0.72 |
| **Patellofemoral joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 14/30 (46.7%) | 14/30 (46.7%) | 1.00 |
| **Progression** | 5/30 (16.7%) | 1/30 (3.3%) | 0.09 |
| **No change** | 25/30 (83.3%) | 28/30 (93.3%) | 0.23 |
| **Improvement** | 0/30 (0.0%) | 1/30 (3.3%) | 0.33 |
| **Tibiofemoral (TF)** | | | |

**Table 4d.** Imaging evaluation results of osteophytes by magnetic resonance imaging Osteoarthritis Knee Score system.

| Osteophytes | | | |
|---|---|---|---|
| **Medial TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 27/30 (90.0%) | 29/30 (%) | 0.30 |
| **Progression** | 2/30 (6.7%) | 1/30 3.3(%) | 0.55 |
| **No change** | 28/30 (93.3%) | 29/30 (96.7%) | 0.55 |
| **Improvement** | 0/30 (0.0%) | 0/30 (0.0%) | 1.00 |
| **Lateral TF joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 27/30 (90.0%) | 28/30 (93.3%) | 0.64 |
| **Progression** | 1/30 (3.3%) | 0/30 (0.0%) | 0.31 |
| **No change** | 29/30 (96.7%) | 30/30 (100.0%) | 0.31 |
| **Improvement** | 0/30 (0.0%) | 0/30 (0.0%) | 1.00 |
| **Patellofemoral joint** | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 27/30 (90.0%) | 27/30 (90.0%) | 1.00 |
| **Progression** | 1/30 (3.3%) | 1/30 (3.3%) | 1.00 |
| **No change** | 29/30 (96.7%) | 29/30 (96.7%) | 1.00 |
| **Improvement** | 0/30 (%) | 0/30 (0.0%) | 1.00 |
| **Tibiofemoral (TF)** | | | |

**Table 4e.** Imaging evaluation results of Hoffa's synovitis and effusion synovitis by magnetic resonance imaging Osteoarthritis Knee Score system.

| Hoffa's synovitis | | | |
|---|---|---|---|
| | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 27/30 (90.0%) | 27/30 (90.0%) | 1.00 |
| **Progression** | 1/30 (3.3%) | 1/30 (3.3%) | 1.00 |
| **No change** | 18/30 (60.0%) | 16/30 (53.3%) | 0.60 |
| **Improvement** | 11/30 (36.7%) | 13/30 (43.3%) | 0.60 |
| **Effusion synovitis** | | | |
| | **Low-dose group** | **High-dose group** | **P value between two groups** |
| **Baseline prevalence** | 28/30 (93.3%) | 27/30 (%) | 0.64 |
| **Progression** | 0/30 (0.0%) | 1/30 (3.3%) | 0.31 |
| **No change** | 21/30 (70.0%) | 17/30 (56.7%) | 0.28 |
| **Improvement** | 9/30 (30.0%) | 11/30 (36.7%) | 0.58 |

**Table 5a.** Number of Grading in evaluation of bone marrow lesions.

| Bone marrow lesions | | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| **Medial TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 13/30 | 17/30 | 13/30 | 18/30 |
| **Grade I** | 11/30 | 8/30 | 11/30 | 8/30 |
| **Grade II** | 3/30 | 5/30 | 2/30 | 3/30 |
| **Grade III** | 3/30 | 0/30 | 4/30 | 1/30 |
| **Lateral TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 24/30 | 24/30 | 25/30 | 26/30 |
| **Grade I** | 2/30 | 3/30 | 2/30 | 2/30 |
| **Grade II** | 2/30 | 2/30 | 2/30 | 2/30 |
| **Grade III** | 2/30 | 1/30 | 1/30 | 0/30 |
| **Patellofemoral joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 29/30 | 28/30 | 30/30 | 30/30 |
| **Grade I** | 1/30 | 2/30 | 0/30 | 0/30 |
| **Grade II** | 0/30 | 0/30 | 0/30 | 0/30 |
| **Grade III** | 0/30 | 0/30 | 0/30 | 0/30 |
| **Tibiofemoral (TF)** | | | | |

**Table 5b.** Number of Grading in evaluation of cartilage defects.

| Cartilage defects | | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| **Medial TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 12/30 | 13/30 | 10/30 | 11/30 |
| **Grade I** | 1/30 | 1/30 | 2/30 | 2/30 |
| **Grade II** | 3/30 | 2/30 | 2/30 | 2/30 |
| **Grade III** | 14/30 | 14/30 | 16/30 | 15/30 |
| **Lateral TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 11/30 | 11/30 | 11/30 | 11/30 |
| **Grade I** | 3/30 | 3/30 | 3/30 | 4/30 |
| **Grade II** | 8/30 | 9/30 | 6/30 | 6/30 |
| **Grade III** | 8/30 | 7/30 | 10/30 | 9/30 |
| **Patellofemoral joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 16/30 | 13/30 | 15/30 | 14/30 |
| **Grade I** | 3/30 | 4/30 | 6/30 | 7/30 |
| **Grade II** | 4/30 | 5/30 | 3/30 | 3/30 |
| **Grade III** | 7/30 | 8/30 | 6/30 | 6/30 |
| **Tibiofemoral (TF)** | | | | |

**Table 5c.** Number of Grading in evaluation of osteophytes.

| Osteophytes | | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| **Medial TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 1/30 | 1/30 | 1/30 | 1/30 |
| **Grade I** | 8/30 | 7/30 | 4/30 | 3/30 |
| **Grade II** | 7/30 | 7/30 | 5/30 | 6/30 |
| **Grade III** | 14/30 | 15/30 | 20/30 | 20/30 |
| **Lateral TF joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 1/30 | 1/30 | 1/30 | 1/30 |
| **Grade I** | 15/30 | 14/30 | 9/30 | 9/30 |
| **Grade II** | 7/30 | 8/30 | 12/30 | 12/30 |
| **Grade III** | 7/30 | 7/30 | 8/30 | 8/30 |
| **Patellofemoral joint** | **Low-dose group** | | **High-dose group** | |
| **Grade 0** | 2/30 | 2/30 | 1/30 | 1/30 |
| **Grade I** | 15/30 | 14/30 | 9/30 | 8/30 |
| **Grade II** | 6/30 | 7/30 | 12/30 | 13/30 |
| **Grade III** | 7/30 | 7/30 | 8/30 | 8/30 |
| **Tibiofemoral (TF)** | | | | |

**Table 5d.** Number of Grading in evaluation of Hoffa's synovitis and effusion synovitis.

| Hoffa's synovitis | | | | |
|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| | Low-dose group | | High-dose group | |
| Grade 0 | 3/30 | 9/30 | 3/30 | 11/30 |
| Grade I | 12/30 | 12/30 | 11/30 | 12/30 |
| Grade II | 11/30 | 9/30 | 12/30 | 7/30 |
| Grade III | 4/30 | 0/30 | 4/30 | 0/30 |
| Effusion synovitis | | | | |
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| | Low-dose group | | High-dose group | |
| Grade 0 | 2/30 | 3/30 | 3/30 | 4/30 |
| Grade I | 13/30 | 19/30 | 10/30 | 17/30 |
| Grade II | 13/30 | 8/30 | 13/30 | 9/30 |
| Grade III | 2/30 | 0/30 | 4/30 | 0/30 |

# Figures

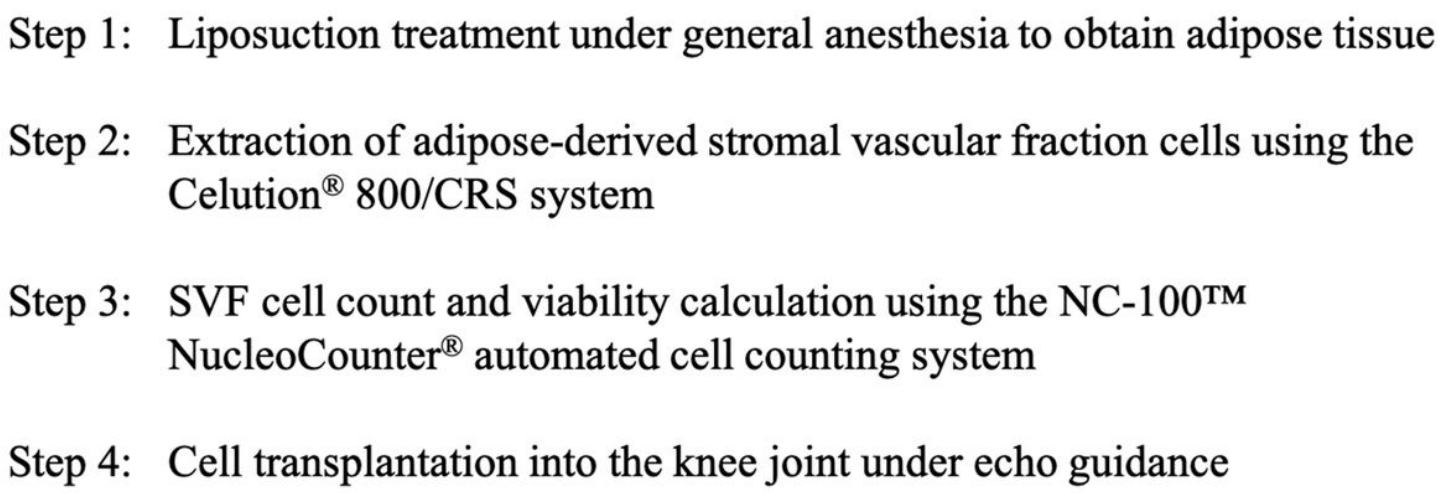


**Figure 1**

Schema of treatment procedures.

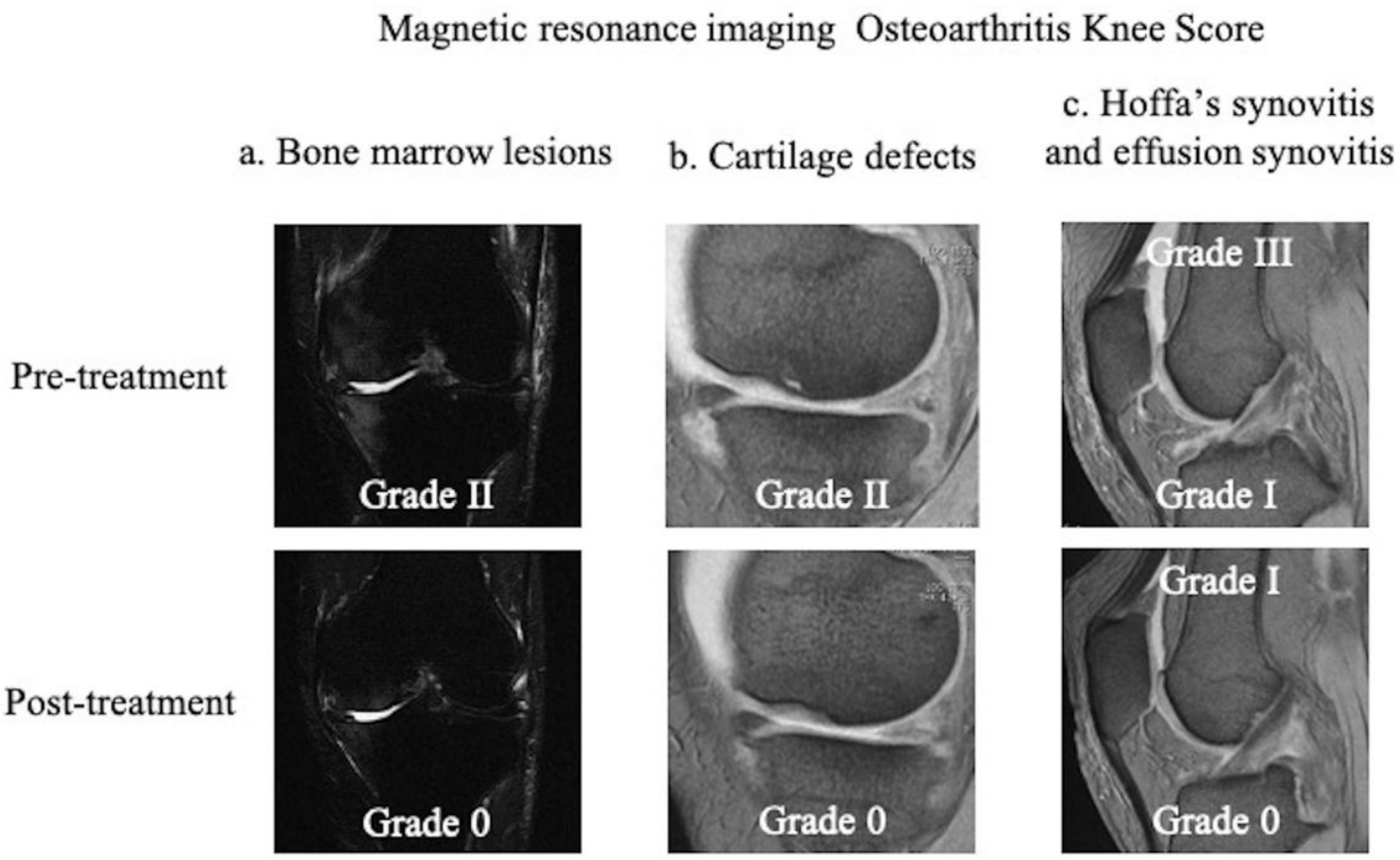


**Figure 2**

Representative cases of imaging evaluations. a) Bone marrow lesion improved from Grade II to 0 before and after treatment. b) Cartilage defects improved from Grade II to Grade 0 before and after treatment. c) Hoffa's synovitis improved from Grade I to 0 before and after treatment, and effusion synovitis also improved from Grade III to I before and after treatment.

## Supplementary Files

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