Acta Orthop. Belg., 2022, **88**, 811-819

ORIGINAL STUDY

doi.org/ 10.52628/88.4.10243

Evaluation of the effect of intra-articular platelet-rich plasma and hyaluronic acid injections on femoral cartilage thickness in chronic knee osteoarthritis

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Femoral cartilage thickness may be an important objective parameter in detecting the progression of knee osteoarthritis(KOA). In this study, we aimed to examine the possible effects of intra-articular Hyaluronic Acid(HA) and platelet-rich plasma(PRP) injections on femoral cartilage thickness and to investigate their possible superiority over each other in KOA. A total of 40 KOA patients were included in the study and randomized to the HA and PRP groups. Pain complaints, stiffness, and functional status were evaluated with the Visual Analog Scale(VAS) and Western Ontario and Mc Master Universities Osteoarthritis(WOMAC) indices. Ultrasonography was used for measuring the femoral cartilage thickness. At the 6th month measurements, significant improvements were observed in VAS-rest, VAS-movement, and WOMAC scores in both HA and PRP groups compared to the measurements performed before the treatment. No significant difference was observed between the effects of the two treatment methods. There were significant changes in the medial, lateral and mean cartilage thicknesses on the symptomatic knee side in the HA group.

The most important finding of this prospective randomized study, in which we compared the effects of PRP and HA injections on KOA, was the increase in knee femoral cartilage thickness in the HA injection group. This effect started in the 1st month and continued until the 6th month. No similar effect was detected with PRP injection. In addition to this basic result, both treatment approaches had significant positive effects on pain, stiffness, and function and no superiority was observed over each other.

No benefits or funds were received in support of this study.
None of the authors have a conflict of interest.

Keywords: Knee; osteoarthritis; platelet rich plasma; hyaluronic acid; cartilage thickness.

INTRODUCTION

Knee osteoarthritis (KOA) is one of the most common articular cartilage diseases and is among the leading causes of chronic disability worldwide *(1)*. It is estimated that 16.7% of individuals over the age of 45 have symptomatic KOA, and 27.8% show radiological signs of cartilage degeneration *(2)*. The incidence of KOA has increased because of the aging population and the increasing prevalence of obesity *(3)*. Patients often progress through more than one treatment to prevent progression; however, there is no definitive treatment with proven disease-modifying effect in KOA *(4)*.

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For the treatment of KOA, minimally invasive approaches have been highlighted in current guidelines. In particular, Hyaluronic acid (HA) injection is recommended as a second-line treatment, due to its potency similar to oral non-steroidal anti-inflammatory drugs (NSAIDs), long duration of action, and good safety profile *(5,6)*. HA injection can physically lubricate the joint surface, reduce damage, increase the nutrition of the articular cartilage and delay progressive joint damage *(7,8)*. Even though there are still no clear recommendations in the guidelines, the use of autologous blood products has increased in the treatment of KOA in recent years, as in many fields of medicine. Platelet-rich plasma (PRP) is extracted from the blood by centrifugation, and the platelet concentration can be increased approximately by 10 folds. PRP can release macrophages and growth factors, which are useful for the repair and regeneration of articular cartilage as well as destroying necrotic tissue and reducing the inflammatory response *(8,9)*.

Femoral cartilage thickness is an important measure in detecting the onset and progression of KOA *(10,11)*. Although the earliest stages of KOA may increase cartilage thickness, it appears that the structural changes in the development and progression of clinical KOA are characterized mostly by erosion and loss of articular cartilage *(11)*. Accurate measurements of cartilage thickness can be clinically useful in detecting and monitoring the effects of treatments. Due to its ease of use and relatively low cost of clinical evaluation, ultrasound has recently gained popularity in pathological KOA populations for its ability to assess the condition of the femoral cartilage *(12)*.

The efficacy of both HA and PRP in clinical parameters in KOA such as pain and stiffness has been demonstrated by many studies. However, studies on its effects on objective parameters such as femoral cartilage thickness are quite rare. In this study, our main aim was to examine the possible effects of HA and PRP injection on femoral cartilage thickness in KOA and to investigate their possible superiority over each other.

MATERIAL AND METHODS

This study was designed as a prospective and randomized study with 2 groups and 2 treatment methods (PRP group receiving 1 PRP injection; HA group receiving 1 HA injection) with level of evidence 2. The flow chart of the study is shown in Figure 1. The study was approved by the Ethics Committee of our institution, and it was registered in Clinical Trials (NCT03761472). The research was carried out with the support of the Bezmialem Vakıf University Department of Scientific Research Projects (project number: 9.2017/14).

Written informed consent was obtained from all patients before participating in the study. Inclusion criteria for the study were determined as being between the ages of 18-80, meeting the criteria for KOA of American College of Rheumatology (ACR) *(13)*, and having the Kellgren-Lawrence stage 2/3 osteoarthritis evidences *(14)* on knee radiographs. Patients, who had previous/active knee infection, history of knee trauma, fracture or surgery, collagen tissue disease, inflammatory joint disease or systemic diseases, history of knee injections in the last 6 months, active malignancies and pregnancy were excluded from the study.

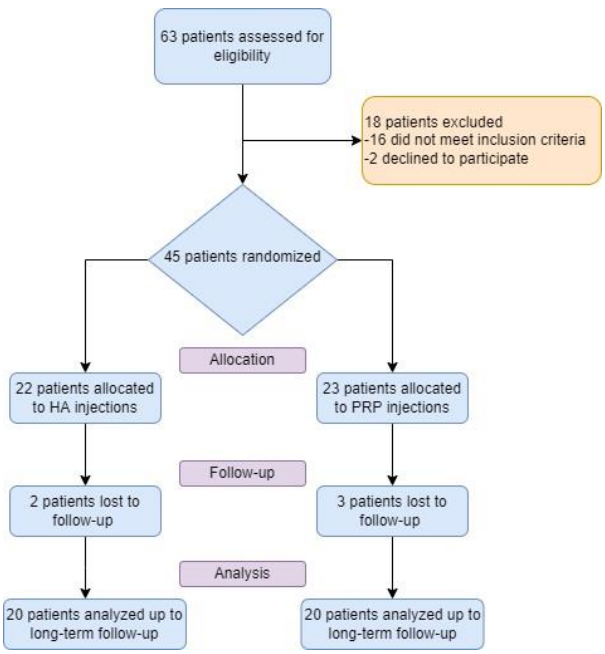

Figure 1. — The flow chart of the study.

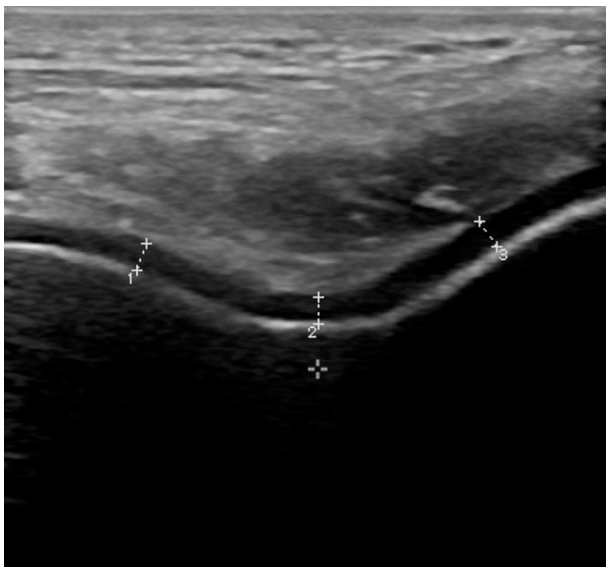

Figure 2. — Cartilage thickness measurement zones on ultrasound.

A total of 45 patients who were eligible to be included in the study were randomized to HA (n:22) and PRP (n:23) injection groups. First of all, an information form was filled in for all participants recording age, gender, body mass index (BMI), occupation, duration of symptoms, habits (smoking, etc.), and symptomatic knees.

The level of knee pain of the patients was evaluated with Visual Analogue Scale (VAS) *(15)* at rest and during exercise. The stiffness and functional conditions of the patients were evaluated along with pain using the Western Ontario and Mc Master Universities Osteoarthritis (WOMAC) Index *(16)*. Femoral cartilage thickness measurements were performed in both knees of the patients by a researcher (O.V.Y.) with at least five years of experience in musculoskeletal ultrasonography, with single-blind technique, and in accordance with the protocols used in previous similar studies *(17-19)*. Asymptomatic knee measurements were used as a control group to compare the effects of treatments on cartilage thickness. The cartilage thickness was measured in millimeters from the middle, medial and lateral points of the hyperflexed knees, in the transverse plane, superior to the patella, from the region where the patella ended and the femoral cartilage was visible, using ultrasonography (GE Logiq P5; GE Healthcare, Chicago, IL) (Figure 2). Medial and lateral measurements were taken from the corners of the femoral condyles, from the midpoint of the line drawn to the middle of the femoral groove. The mean of the femoral cartilage thickness was calculated by taking the mean of the medial, lateral, and middle points. The participants were evaluated 3 times; before the treatment, at the 1st month, and the 6th month of the treatment. The VAS and WOMAC scores and femoral cartilage thickness measurements were repeated in each evaluation.

To obtain PRP, 150 ml of peripheral venous blood was taken from the patients into the PRP-BAG blood bag (Sakura Medikal, Istanbul, Turkey). The collected blood was centrifuged at 1800 rpm for 10 minutes after resting for 15 minutes. At this stage, erythrocytes were separated from whole blood with the help of a manual extractor. The remainder was centrifuged again at 3500 rpm for 15 minutes. Platelets and some plasma were separated also with the help of a manual extractor. As a result, about 15 ml of PRP liquid was obtained. 5 ml of this PRP was injected into the knee with the complaint. It has been shown that in PRP obtained with this system, the amount of platelets increased approximately 7.66 ± 3.49 times, there was no significant change in white blood cells level compared to whole blood, and the remaining erythrocyte amount was at negligible levels *(20)*. Patients in the HA group were injected with a high molecular weight (48 milligrams, 3 Mda molecular weight = Reviscon Mono, VSY Biotechnology, Amsterdam, Netherlands) preparation. Before injection, meticulous aseptic technique is performed. The point of entry was cleansed with povidone solution.The standard supero-lateral technique was used. The patient is positioned supine on the examination table, with the legs extended. The landmark was the intersection of 2 imaginary lines; horizontal line from the superior border of the patella, and another line intersecting the lateral border of the patella. The needle was inserted 1 cm above and 1 cm lateral to the superolateral margin of patella at a 45° angle in the cephalolateral to caudomedial direction. The injection was performed by a single physician (O.K)

who has more than 10 years' experience in the intra-articular injections.

Data Analysis

Data were evaluated using the IBM SPSS version 21.0 for Windows (IBM Corp., Armonk, NY, USA) statistical package software. Explanatory statistics of the study were presented as mean ± standard deviation for continuous data, and as frequency and percentage for categorical variables. Demographic data and baseline measurements were compared between groups using the Mann-Whitney U test or Student's T-test according to the normal distribution. The nominal demographic data of the patients were compared between the groups using the Chi-square test. Wilcoxon Signed Ranks Test was used for intra-group comparisons of the measurements performed before and after the treatment, and Mann-Whitney U test was used for comparisons between groups. Subgroup analyses of within-group comparisons were performed using the Friedman Test with Bonferroni correction. The value of 0.05 was considered statistically significant. The sample size was calculated with GPower 3.1. packed programme. It was calculated that at least 19 cases were required for each group for 80% power with 0.05 margin of error.

RESULTS

Five patients were excluded from the study because they did not come for follow-up. The study was completed with 20 patients in both groups. The mean age, BMI, and symptom duration of the patients included in the study were 57.2 ± 10.2, 29.3 ± 5.4, and 25.8 ± 32.7, respectively. In terms of demographic data, a significant difference was observed between the groups only in terms of symptom duration. Patients in the HA group had a longer symptom duration. Demographic data and comparisons between groups are presented in Table I in detail.

There was no significant difference between the two groups in terms of the VAS and WOMAC scores before the treatment. Statistically significant improvements were observed in VAS-rest, VAS-movement, and WOMAC scores in both HA and PRP groups in intra-group analyses performed to evaluate the level of response to treatments. Therefore, sub-group analyses were performed for both groups separately. The VAS-rest scores decreased

Table I. — Baseline characteristics

	PRP (n:20)	**HA** (n:20)	**All participants** (n:40)	**p value**
Age (year)	57.5 (10.6)	57.0 (10.1)	57.2 (10.2)	0.807*
Gender				
Male	4 (%10.0)	6 (%15.0)	10 (%25.0)	
Female	16 (%40.0)	14 (%35.0)	30 (%75.0)	0.465[k]
BMI	29.8 (6.8)	28.9 (3.6)	29.3 (5.4)	0.787*
Symptom duration (month)	20.4 (38.9)	31.2 (24.8)	25.8 (32.7)	**0.016***
Occupation				
Not working	11 (%27.5)	18 (%45.0)	29 (%72.5)	
Office job	4 (%10.0)	0 (%0.0)	4 (%10.0)	
Standing job	5 (%12.5)	2 (%5.0)	7 (%17.5)	0.310[f]
Smoking				
Yes	5 (%12.5)	6 (%15.0)	11 (%27.5)	
No	15 (%37.5)	14 (%35.0)	29 (%72.5)	0.723[c]
Symptomatic Knee				
Right	14 (%35.0)	11 (%27.5)	25 (%62.5)	
Left	6 (%15.0%)	9 (%22.5)	15 (%37.5)	0.327[c]

PRP: Platelet Rich Plasma; HA:Hyaluronic Acid; BMI: Body Mass Index. *:Mann Whitney U Test; f: Fischer's Exact Test; c: Chi Square Test.

Table II. — The changes in VAS and WOMAC scores with treatment

	PRP	HA
VAS- Rest		
BT:	4.15 (2.4)	2.90 (2.1)
1st month:	2.65 (2.3)	1.75 (1.9)
6th month:	2.35 (2.3)	1.45 (1.8)
p value:	**0.008**[f]	**0.002**[f]
VAS- Movement		
BT:	6.75 (2.1)	7.40 (1.5)
1st month:	4.42 (2.0)	5.05 (1.7)
6th month:	4.75 (2.9)	4.90 (2.1)
p value:	**0.001**[f]	**0.000**[f]
WOMAC		
BT:	50.8 (20.4)	53.4 (13.1)
1st month:	33.5 (19.8)	40.8 (14.7)
6th month:	35.0 (27.4)	41.1 (14.7)
p value:	**0.000**[f]	**0.002**[f]

Subgroup analyzes (Wilcoxon test, with Bonferroni correction <0.016 p value considered significant)
VAS-Rest: PRP group; BT-1st month p=0.063, **BT-6th month p=0.003**, 1st -6th month p=0.621
HA group; **BT-1st month p=0.004**, **BT-6th month p=0.011**, 1st -6th month p=0.351
VAS-Movement: PRP group**; BT-**1st month **p=0.001**, **BT -6**th month **p=0.009**, 1st -6th month p=0.491
HA group; **BT -1**st month **p=0.000**, **BT -6**th month **p=0.001**, 1st -6th month p=0.479
WOMAC: PRP group; **BT -**1st month **p=0.001**, **BT -6**th month **p=0.001**, 1st -6th month p=0.432
HA group; **BT -1**st month **p=0.001**, **BT -6**th month **p=0.006**, 1st -6th month p=1.000
VAS: Visual Analog Scale; WOMAC: Western Ontario and Mc Master Universities Arthritis Osteoarthritis Index; PRP: Platelet Rich Plasma; HA: Hyaluronic Acid; BT: Before Treatment; f: Friedman Test

significantly between BT (Before Treatment) and the 6th month (p=0.003) in the PRP group, and between BT and 1st month (p=0.004), and BT and 6th month (p=0.011) in the HA group. VAS-movement scores decreased significantly between BT and 1st month (p=0.001) and BT and 6th month (p=0.009) in the PRP group, and between BT and 1st month (p=0.000) and BT and 6th month (p=0.001) in the HA group, similarly. WOMAC scores decreased significantly between BT and the 1st month (p=0.001) and BT and the 6th month (p=0.001) in the PRP group, and between BT and 1st month (p=0.001), and BT and 6th month (p=0.006) in the HA group. No significant difference was observed between the 1st and 6th months in any score in any of the groups. The changes in VAS and WOMAC scores in the groups after the treatment are presented in Table II in detail.

It was investigated whether the two treatments had any superiority over each other in terms of effectiveness by comparing the level of change in VAS-rest, VAS-movement, and WOMAC scores of the patients in both groups compared to the scores before the treatment. As a result of the analysis, no significant difference was found between the two groups (Table III).

When the change of knee cartilage thickness with treatment was examined, there were statistically significant changes in the medial, lateral, and mean cartilage thicknesses on the symptomatic knee side only in the HA group. When subgroup analysis was performed for the detailed analysis of this change, a statistically significant increase was found in the HA group, in terms of medial cartilage thickness between BT and 6th month (p=0.002), in terms of lateral cartilage thickness between BT and 1st month (p=0.004), BT and 6th month (p=0.000), and 1st month and 6th month (p=0.004), and in terms of mean cartilage thickness between BT and 6th month (p=0.001) and 1st month and 6th month (p=0.003). No significant change was observed in control knee measurements in both treatment groups. A detailed analysis of the change in femoral cartilage thickness according to treatments is presented in Table IV.

DISCUSSION

This prospective and randomized study reported the effect of intra-articular PRP and HA injections on KOA. The most important finding of the study was the increase in knee femoral cartilage thickness in the HA injection group. This effect started in the 1st month and continued until the 6th month. In addition to this basic result, both treatment approaches had significant positive effects on pain, stiffness, and function.

HA is the most important component of joint fluid and is responsible for the viscoelastic and lubricating properties in the joints. In addition to providing chondroprotection by increasing the synthesis of proteoglycans and glycosaminoglycans, it has anti-inflammatory effects. There is good evidence for the efficacy of HA according to RCTs, multiple meta-

Table III. — Comparison of PRP and HA treatments in terms of effect on VAS and WOMAC scores

	PRP	HA	p
VAS-Rest			
BT-1st month difference	1.5 (2.9)	1.2 (1.4)	0.527*
BT -6th month difference	1.8 (2.2)	1.5 (2.0)	0.923*
1st -6th month difference	0.3 (2.8)	0.3 (1.4)	0.779*
VAS-Movement			
BT -1st month difference	2.4 (2.4)	2.4 (1.6)	0.934*
BT -6th month difference	2 (3.1)	2.5 (2.2)	0.230*
1st -6th month difference	-0.4 (2.7)	0.2 (1.3)	0.258*
WOMAC			
BT -1st month difference	17.3 (18.0)	11.1 (11.9)	0.223*
BT -6th month difference	15.8 (16.8)	10.9 (15.8)	0.735*
1st -6th month difference	-1.5 (17.5)	-0.2 (9.3)	0.441*

VAS: Visual Analog Scale; WOMAC: Western Ontario and Mc Master Universities Arthritis Osteoarthritis Index; PRP: Platelet Rich Plasma; HA: Hyaluronic Acid; BT: Before Treatment; *: Mann-Whitney U.

Table IV. — Comparison of femoral cartilage thickness with baseline after HA and PRP treatment

	PRP			p	HA			p
	BT	**1st month**	**6th month**		**BT**	**1st month**	**6th Month**	
Symptomatic knee								
Medial	19.70 (5.3)	21.7 (4.9)	21.1 (4.7)	0.344[f]	19.05 (3.5)	19.90 (3.1)	20.65 (3.1)	**0.003**[f]
Middle	20.30 (5.7)	22.75 (7.5)	21.55 (7.4)	0.511[f]	19.85 (4.0)	20.05 (3.3)	20.05 (2.9)	0.270[f]
Lateral	18.75 (5.7)	19.35 (5.2)	19.40 (4.6)	0.843[f]	19.15 (3.0)	20.45 (3.2)	21.45 (3.4)	**0.000**[f]
Mean	19.57 (4.7)	21.27 (5.1)	20.68 (4.9)	0.287[f]	19.38 (2.9)	20.13 (2.7)	20.93 (2.5)	**0.000**[f]
Control knee								
Medial	20.35 (3.6)	19.40 (5.4)	19.00 (5.2)	0.669[f]	20.40 (4.2)	20.70 (3.6)	20.65 (3.2)	0.275[f]
Middle	19.80 (4.7)	20.70 (5.6)	20.25 (5.0)	0.368[f]	20.95 (4.5)	20.65 (4.4)	20.65 (4.0)	0.632[f]
Lateral	16.90 (4.1)	17.70 (5.4)	17.30 (3.4)	0.139[f]	20.95 (3.5)	20.55 (3.6)	21.10 (3.5)	0.262[f]
Mean	19.03 (3.6)	19.28 (4.6)	18.85 (3.9)	0.786[f]	20.78 (3.4)	20.67 (3.5)	20.80 (3.2)	0.824[f]

Subgroup analyzes for significant changes in the HA group
Medial cartilage thickness: BT -1st month p=0.062, BT -6th month **p=0.002**, 1st -6th month p=0.030
Lateral cartilage thickness: BT -1st month **p=0.004,** BT -6th month **p=0.000**, 1st -6th month **p=0.004**
Mean cartilage thickness: BT -1st month p=0.038, BT -6th month **p=0.001**, 1st -6th month **p=0.003**
PRP: Platelet Rich Plasma; HA: Hyaluronic Acid; BT: Before Treatment; f: Friedman Test

analyses, and real-life experience *(21-23)*. HA has a slow onset of action, its effectiveness on pain is usually evident at 4 weeks, it peaks at 8 weeks, and its effect is observed for up to 6 months *(24,25)*. After 8 weeks of injection, its effect is superior to intra-articular corticosteroids, and it has longer efficacy *(26)*.

Based on preclinical research, PRP is known to ameliorate cartilage degeneration by stimulating mesenchymal stem cell migration, proliferation, and differentiation into joint chondrocytes. PRP influences the progression of KOA by inhibiting inflammatory cytokines and changing the level of enzymatic expression, thereby promoting cartilage repair *(27)*. In addition, several clinical studies and systematic reviews have demonstrated that PRP can relieve symptoms such as pain and stiffness, including pain, stiffness, and dysfunction for up to 12 months after injection *(28)*.

Many studies and reviews focused on the clinical results of HA and PRP injections in KOA. In a recent study with a high number of patients (189

symptomatic knee OA), both HA and PRP were found to be effective in improving knee symptoms and functional status of patients, and the effect remained stable for up to 18 months. PRP was found to be more effective in terms of needing re-injection until the 36th month *(29)*. Similarly, some meta-analyses observed no significant difference between the two treatments *(30,31)* and some demonstrated that PRP was a more effective treatment *(32,33)*. On the other hand, the common feature of all these studies is that they provide an evaluation of clinical outcomes such as pain and stiffness based on only patient reports. Our results indicated that there was no difference in efficacy between the two treatments from this point of view.

Looking at the effect of intra-articular treatments on femoral cartilage thickness, which was the most unique aspect of our study, there a very limited number of studies was found in the literature. In a study comparing the effects of PRP, HA and oral NSAID treatment on femoral cartilage thickness, no significant difference was found with magnetic resonance imaging (MRI) after 52 weeks of follow-up *(34)*. In a study with a 6-month follow-up period, no significant difference was observed between the PRP and saline groups in terms of cartilage thickness change *(35)*. In another PRP study, femoral cartilage thickness was measured by ultrasonography at the 3rd month and the 6th month follow-ups; however, no significant change was observed *(36)*. In the only study in which a significant increase in cartilage thickness was observed with PRP (p=0.041), the groups receiving PRP and NSAID+chondroprotective oral agents were compared, and femoral cartilage thickness was evaluated by ultrasonography at 6 months *(37)*.

There are also a very limited number of studies on the effect of HA injection on the thickness of the femoral cartilage. In 49 patients with stage II-III arthrosis, who underwent a single intra-articular HA injection, femoral intercondylar cartilage thickness increased significantly in the measurements performed after 3rd and 6th months *(38)*. In another study, patients received HA injections and evaluated at baseline and 1st, 3rd, and 6th months. Femoral intercondylar cartilage thickness improved significantly at both 3rd and 6th months *(39)*. A larger placebo-controlled, open-label, prospective, multicenter clinical trial examining the disease-modifying activity of treatment with HA evaluated femoral cartilage thickness. According to MRI results, cartilage volume and thickness increased in the lateral femoral and lateral trochlear compartments, albeit not in the medial compartment *(40)*.

CONCLUSION

Our study was one of the few studies examining the effect of PRP and HA treatments on the femoral cartilage thickness in KOA measured by ultrasound. Our results suggested that HA injection had more positive effects on cartilage thickness in the knee joint. In addition, both treatments had similar positive effects on pain, stiffness, and function. We may have some limitations due to the use of ultrasound as an imaging method. Ultrasound has limitations such as the lack of a standardised measuring method and validated scoring system, operator-dependent imaging and reliability and establishment of adequate acquisition parameters. The accuracy of the femoral cartilage measurements may have been affected by discrepancies in patellar positioning, structural differences between each patient and minor probe placement errors. The absence of a separate control group can also be considered as a limitation of our study. However, this situation was partially compensated by using asymptomatic knee measurements. Another limitation was that our follow-up period was limited to 6 months, and this may have prevented us from observing longer-term effects. Studies with a larger number of patients and a longer follow-up period are required to reveal this issue more clearly.

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