Journal of Back and Musculoskeletal Rehabilitation 25 (2012) 275–284
DOI 10.3233/BMR-2012-0336
IOS Press

Assessment of the effect of glucosamine sulfate and exercise on knee cartilage using magnetic resonance imaging in patients with knee osteoarthritis: A randomized controlled clinical trial

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Abstract. *Introduction*: Osteoarthritis (OA) is a chronic disease characterized by the focal deterioration and abrasion of articular cartilage. The goals of therapy are preserving normal joint function, relieving pain and improving quality of life (QOL). This study is performed to investigate whether glocosamine sulfate and exercise could both delay joint structure degradation evaluated with magnetic resonance imaging (MRI) and improve symptoms in a short time period.
Materials and methods: Thirty-nine women with the diagnosis of knee OA were enrolled in the study. Patients were randomized into two groups. Group I ($n = 20$) received an exercise program, while group II ($n = 19$) received glucosamin sulphate (1500 mg/day) in addition to the exercise therapy. Both groups were treated for 12 weeks. The patients were evaluated before and after the treatment regarding pain, disability, functional performance, muscle strength, QOL, depression and MRI findings (cartilage volume, medial and lateral cartilage thickness).
Results: Both groups showed significant improvements in pain, disability, functional performance, QOL and depression with no statistically significant difference between the groups after the therapy. While there were significant improvements for all MRI parameters expect right knee cartilage volume and lateral cartilage thickness in two groups, statistically significant differences could not be demonstrated between the groups after the therapy.
Conclusion: We found no additional effect of glucosamine in delaying the radiological progression and relieving the symptoms of OA. We also demonstrated that exercise alone was adequate to prevent structural changes and cartilage loss of the knee joint as assessed by MRI.
Level of evidence: Diagnostic study (prospective study).

Keywords: Exercise, glucosamine sulfate, osteoarthritis, knee cartilage, magnetic resonance imaging

1. Introduction

Osteoarthritis (OA) is a slow chronic disease characterized by focal deterioration and abrasion of articular cartilage. OA is also major cause of pain and physical disability in the elderly [1]. Guidelines for the management of patients with knee OA recommend a combination of pharmacologic agents [such as, simple analgesic or anti-inflammatory drugs] and non-pharmacologic modalities [such as, patient education and exercise therapy] with the goals of to relieve pain, to improve functional limitation, and to increase quality of life (QOL). Interfering with the anatomical progression of OA ap-

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ISSN 1053-8127/12/$27.50

pears to be a method to preserve normal joint function. Substances that protect articular cartilage during the course of OA have been termed as chondroprotective agents. When they appear to alter the course of the disease these agents may be termed as disease-modifying OA drugs (DMOADs) [2].

Glucosamine occurs naturally in all human tissues. It is an aminosaccharide acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and subsequently for the production of aggrecan and other proteoglycans of cartilage, although the precise mechanism of action remains to be established [3]. For a few years, glucosamine sulfate has been considered a potential DMOAD for OA however there are conflicting results regarding the effectiveness of glucosamine as a DMOAD [4].

Several studies have demonstrated beneficial effects of exercise therapy on pain, physical functioning and patients' self perceived effect [5–7]. Due to the avascular nature of articular cartilage, cartilage development, maintenance and aging is dependent upon the type and magnitude of mechanical loading [8]. Immobilization or load deprivation alters the morphological, biochemical and biomechanical properties of articular cartilage [8], and ultimately results in decrease of cartilage thickness [9]. Exercise has been thought to reduce OA progression through 2 pathways. In the first pathway, an improvement in the knee joint stability may help to protect and prevent further cartilage degeneration [10,11]. In the second pathway, the moderate controlled loading of exercise may stimulate cartilage synthesis [12]. Although the effects of exercise on clinical parameters have been studied, studies investigating the effectiveness of exercise on cartilage structure are very limited.

Loss of knee cartilage is a hallmark of the early development of knee OA. Radiographic joint space width, the most widely used method to assess damage in OA, provides only an approximation of cartilage volume because it is an indirect and two-dimensional measurement. Magnetic resonance imaging (MRI), which can directly visualize joint structure three dimensionally and with its superior soft tissue contrast, provides a valid and accurate measure of articular cartilage volume [13,14].

The primary focus of the present study was to investigate whether glocosamine sulfate and exercise could delay joint structure degradation evaluated with MRI in a short time period in patients with knee OA. Secondly we aimed to examine the effects of glocosamine sulfate and exercise on pain, disability, muscle strength, walking performance, QOL, and depression.

2. Material and methods

Thirty-nine women aged between 42 and 74 years, who had been diagnosed as knee OA according to American College of Rheumatology (ACR) [15] criteria were enrolled in the study. Anteroposterior and lateral radiographs of both knees of each patient were obtained, and the severity of OA in the tibiofemoral compartment was graded according to the criteria of Kellgren-Lawrence by a radiologist (IKB) who was blind to patients' clinical data. A demographic data including age, body mass index (BMI) (kg/m2), educational level, duration of symptoms and job were recorded. The subjects were housewives, or they were retired (they had been living a sedentary life and had no regular or irregular sports habits). A complete examination was performed by the same physician. Exclusion criteria were:

(1) Those who had radiographic evidence of inflammatory disease
(2) Serious medical conditions for which exercise would be contraindicated
(3) Had exercise program that may cause increase of muscle strength within the previous 6 months
(4) Contracture, grade 4 OA
(5) Previous trauma
(6) The pregnancy
(7) The presence of severe structural deformity
(8) Indication for hip or knee replacement within 1 year
(9) Inability to understand the Turkish language
(10) Systemic diseases such as Diabetes Mellitus or neurological disorders.

The patients were informed about the purpose of the study and gave their consent. The study was approved by the ethical committee of Ondokuz Mayis University.

2.1. Exercise program

Patients were randomized (using concealed envelopes) into two groups. Group I ($n = 20$) received an exercise program, while group II ($n = 19$) received glucosamine sulphate (1500 mg/day) in addition to the exercise therapy. All patients came to the outpatient department for exercise treatments. For both groups, 45-min duration therapy was applied 3 days a week. Exercises were taught by a physiatrist who was blind to patients' clinical and radiographic data. The subjects in both groups were treated with a group-exercise program composed of 45 min isometric and isotonic exer-

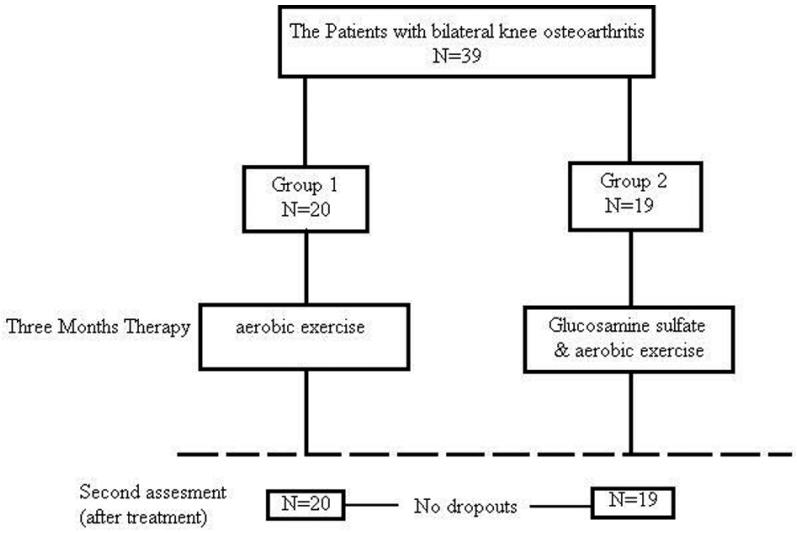

Fig. 1. The overall plan of the study.

cises with a warm-up and cool-down period of 5 min stretching exercises 3 times a week under the supervision of the same physiatrist [16,17]. Both groups were given an exercise program consisted of 4 exercises:

(1) Active range-of-motion exercises
(2) Muscle strengthening (isometric and isotonic)
(3) Muscle stretching
(4) Flexibility.

Both groups were treated for 12 weeks. Patients were evaluated before and after the therapy. No dropouts occurred during the trial and all subjects in both groups completed the treatment.

The overall plan of the study is shown in Fig. 1.

2.2. Clinical assessments

The patients were evaluated before and after the treatment, in accordance with pain, disability, walking performance, muscle strength, QOL, and depression.

2.3. Pain and disability

Outcome measure for pain was Western Ontario McMaster osteoarthritis index (WOMAC) pain score. The WOMAC is a self-reporting instrument used to assess lower extremity pain, stiffness and physical function. Disability and stiffness were assessed with WOMAC physical function and stiffness score [18,19].

2.4. Walking performance

The 6-min walk distance (6MWD) test was used as a test of objective assessment of functional performance and endurance. Subjects completed this test on a 42.6-m walkway. Subjects were given the same standard verbal instructions before each test and instructed to walk their maximum distance in a 6-min period. The total distance covered in meters during the 6 min of walking was used as the score for each session.

2.5. Muscle strength

Quadriceps muscle strength (QMS) (isometric muscle force of knee extension) was measured with a hand-held dynamometer (Baseline Push-Pull Dynamometer, Digital (LCD) Hydraulic New York, NY) by the same tester. The patients sat with the hip and knee at an angle of 90° and with against fixed back support. The end piece of the dynamometer was applied to the anterior surface of the distal tibia. Subjects were asked to take 1 or 2 s to come to maximum effort and, then, to straighten their knees as forcefully as possible. The maximum force realized during a 3- to 5-s effort was recorded in kilograms [20]. The test was performed three times with a 30-s interval between tests, and the average was recorded.

2.6. Quality of life

Quality of life was assessed with short form 36 (SF-36). The SF-36 is a widely applied generic instrument for measuring health status and consists of eight dimensions: physical functioning, social functioning, physical role, emotional role, mental health, vitality, bodily pain and general health perceptions. Scores range from

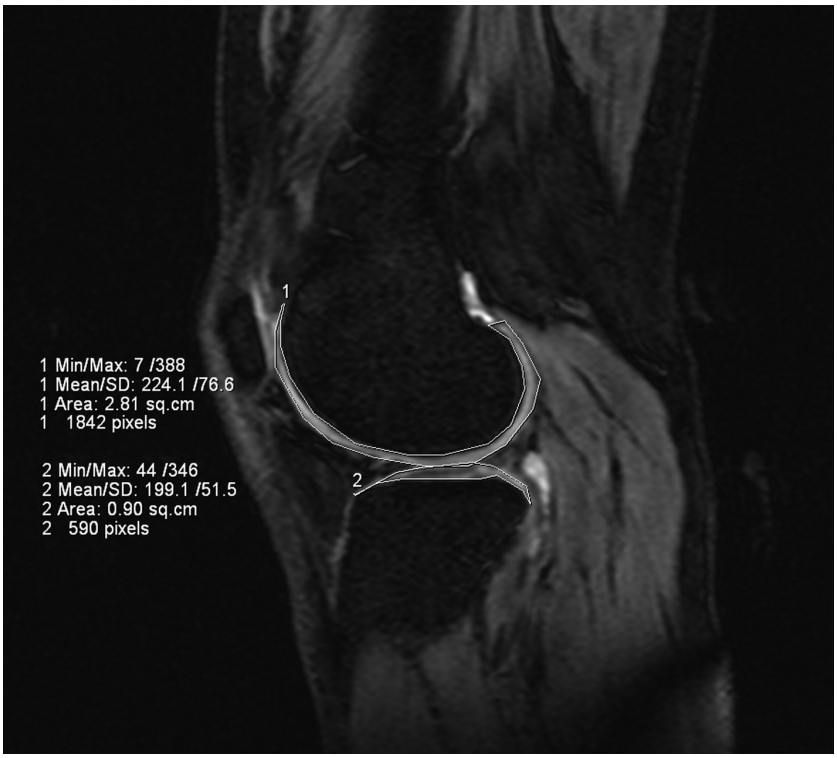

Fig. 2. Region of interest placed to encompass the entire cartilage of femur and tibia.

0 (worst) to 100 (best) with higher scores indicating better health stratus [21]. The validity and reliability study of the Turkish version of SF-36 was completed on patients with a chronic disease and the test-retest reliability and internal consistency were 0.94 and 0.92, respectively [22].

2.7. Depression

Depression was assessed with Beck depression inventory (BDI). BDI is a 21-item test presented in multiple-choice format which purports to measure presence and degree of depression. Responses are made on a four-point, minimally anchored scale, ranging from 0 to 3, with 3 representing the most severe symptoms [23, 24].

2.8. MRI acquisitions

Magnetic resonance imaging of cartilage of knee performed with a 1.5-T Siemens Symphony system (Siemens Medical Solutions, Erlangen, Germany) using a circumferential knee coil. Sagittal fat-suppressed T2-weighted three dimensional (3D) spoiled gradient echo [FS-3DSPGR: 22/10, 40° flip angle, 14 cm FOV, 256 × 128 matrix, contiguous 1.5-mm slices covering all articular cartilage plates in right and left knee, superior–inferior, one excitation, frequency-selective fat saturation, superior–inferior saturation bands to minimize pulsation artifacts]. The total time required for MRI, including patient setup, was 20 min (Fig. 2) [25,26].

2.9. Image analysis

Images were transferred to a dedicated offline computer workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany). ROI was placed over the entire cartilage of femur and tibia in all slices. Sum of total volume in every slice was accepted total cartilage volume for the knee. The patellar cartilage was not calculated and added in the total cartilage volume because to determine it exactly in sagittal views was not easy. No automated software was used to calculate the cartilage volume so the total time required for image evaluation of both knees of a patient was 60 min. Cartilage thickness was also recorded. The thickness was measured at the deepest location of concave lateral and medial tibia plateau. The thickness of cartilage in epicondyle of femora was measured just above the lo-

cations where tibial cartilage measurements were done. Sum of tibial and femoral cartilage thickness was obtained both lateral and medially. All image analysis and calculations were done by the same radiologist who was blind to patients' clinical data (IKB) [25,26].

2.10. Statistical analyses

Statistical analyses were performed with SPSS 13.0 for windows. Descriptive data were presented as mean ± standard deviation (SD) or minimum–maximum (median) when needed according to the normal distribution of the parameters. The Shapiro–Wilk test was used to analyze normal distribution assumption of the quantitative outcomes. To compare two groups Mann–Whitney U test (Womac pain, Womac disability, Womac morning stiffness, depression, physical role limitation, emotional role limitation) and Independent Samples t test were used when needed according to the normal distribution of the parameters. Wilcoxon's signed rank test (Womac pain, Womac disability, Womac morning stiffness, depression, physical role limitation, emotional role limitation) or paired t test was used for within-group change used when needed according to the normal distribution of the parameters. The sociodemographical characteristics of the groups were evaluated by Chi-square test. P values less than 0.05 were considered statistically significant.

3. Results

Clinical and demographic features of group 1 and group 2 are described in Table 1. There was no statistically significant difference for age, BMI, educational level, duration of symptoms (years) and job between the groups before the therapy ($p > 0.05$).

3.1. Pain, physical function and walking performance

Both groups showed significant improvements in WOMAC pain score, WOMAC physical function scores and walking distance. There was no statistically significant difference between the groups regarding post-treatment scores ($p > 0.05$) (Table 2).

3.2. Quality of life and depression

Both groups showed significant improvements in QOL and depression. Statistically significant differences could not be demonstrated between the groups regarding post-treatment scores ($p > 0.05$) (Table 3).

3.3. MRI assessments

While there were significant improvements for all MRI parameters expect right knee cartilage volume and lateral cartilage thickness in two groups, statistically significant differences could not be demonstrated between the groups regarding post-treatment scores ($p > 0.05$) (Table 4).

At basal time, no significant correlation was found between WOMAC pain score and medial and lateral cartilage thickness ($p > 0.05$).

4. Discussion

This randomised study was performed to evaluate the short term effects of glucosamıne sulfate combined with exercise on joint space narrowing along with pain, disability, muscle strength, walking performance, QOL, and depression in the patients with knee OA. In the present study, both groups showed significant improvements in clinical parameters, QOL, depression and in most MRI parameters with no difference after the therapy.

Osteoarthritis is also major cause of pain and physical disability which often leads to moderate to severe limitations and a decreased QOL in the elderly. The changes in the osteoarthritic cartilage include superficial fibrillation, disorganization of the collagen and proteoglycans network, joint capsule thickening, and osteophyte formation [27]. An additional goal of therapy is limiting the progression of joint damage, often referred to as structure modification. The rate of joint space narrowing, a variable derived from serial measurements of joint space width, is currently the accepted biomarker for structural progression [2].

Glucosamine is an aminosaccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans of cartilage [28]. The ability of glucosamine-containing nutraceuticals to reduce proteoglycan loss, impede cartilage degeneration, delay joint-space narrowing, and improve pain has been extensively reported [29,30]. The exact mechanism of action for the possible effect of glucosamine is unknown [31]. Possible mechanisms of action for the chondroprotective effect of glucosamine include direct stimulation of chondrocytes, incorporation of sulfur into cartilage, and protection against degradative processes within the body through altered gene expression [32,33]. Therefore, glucosamine has a role

Table 1
Clinical and demographic features of the patients

	Group 1 ($n = 20$) Mean ± SD	Group 2 ($n = 19$) Mean ± SD	p
Age (year)	57.05 ± 1.30	57.68 ± 1.44	0.536
BMI (kg/m^2)	28.58 ± 0.79	27.74 ± 1.03	0.523
Duration of symptoms (year)	4.90 ± 3.09	4.42 ± 3.64	0.660
Job			
n (%)			
Housewife	10 (50.0)	7 (36.9)	0.307
Retired	10 (50.0)	12 (63.1)	
Education			
n (%)			
Primary education	5 (25.0)	2 (11.4)	0.497
Secondary education	10 (50.0)	11 (57.0)	
College	5 (25.0)	6 (31.6)	
Knee grade			
n (%)			
I	5 (25.0)	4 (21.6)	0.873
II	11 (55.0)	12 (63.2)	
III	4 (20.0)	3 (15.2)	

$p < 0.05$ significant.

Table 2
Baseline and the final results of clinical parameters of the patients

		Group I			Group II		
		BT	AT	p	BT	AT	p
WOMAC Pain	Med (Min-max)	7.5 (1–15)	1.0 (0–10)	**0.001**	5.0 (1–19)	0 (0–2)	**0.001**
WOMAC Disability	Med (Min-max)	27.0 (5–45)	7.5 (0–42)	**0.001**	25.0 (3–39)	2.0 (0–10)	**0.001**
WOMAC Morning Stiffness	Med (Min-max)	3.0 (0–7)	0.5 (0–3)	**0.001**	2.0 (0–4)	0 (0–2)	**0.001**
Muscle strength right (kg)	Mean ± SD	17.70 ± 2.59	21.70 ± 2.08	**0.001**	16.47 ± 2.65	20.94 ± 2.69	**0.001**
Muscle strength left (kg)	Mean ± SD	17.45 ± 3.12	21.25 ± 2.29	**0.001**	16.42 ± 2.93	20.84 ± 3.35	**0.001**
6 MWD (m)	Mean ± SD	467.0 ± 52.17	548.9 ± 73.68	**0.001**	456.5 ± 61.88	560.5 ± 54.00	**0.001**

*$p < 0.05$ significant. 6 MWD: 6 minute walk distance. VAS: visual analogue scale. WOMAC: Western Ontario McMaster osteoarthritis index. $p > 0.05$: after treatment comparisons for all parameters. BT: before treatment. AT: after treatment.

in the protection of the cartilage matrix and chondrocyte metabolism, suggesting a possible mechanism by which glucosamine may help to alleviate clinical signs and retard progression of OA [2]. However, conflicting results have been reported regarding the effects of glucosamine on clinical parameters [28,29,31,36]. Reginster et al. [28] showed that patients taking glucosamine sulfate had modest pain reduction in the WOMAC index compared with baseline. In a similar study, 202 patients with knee OA were given placebo or 1,500 mg of glucosamine and were followed for three years and those receiving glucosamine showed statistically significant improvement in symptoms of pain and stiffness compared with placebo [31]. Contrary to these findings, there are also high-quality design studies showing no overall improvement in pain or function [34–39]. There are also conflicting results regarding the ability of glucosamine to protect the cartilage from further loss [29, 38–40]. Although Pavelka [29] and Reginster [40] detected beneficial effect of glucosamine on radiological progression, Rozendaal et al. [38] did not. Studies usually describe the effects of glucosamine on symptoms and to a lesser extent on structural modification. In the present study we investigated the effects of glucosamine on clinical parameters in addition to cartilage volume and thickness. We found no additional effect of glucosamine as a DMOAD in a short period.

Exercise therapy is widely used for lower-limb OA to improve joint range of motion, muscle strength, tendon lengthening, aerobic performance and proprioception. The modalities of exercise are numerous and should be adapted to the joint affected and the health of the patient [41]. Several studies have demonstrated beneficial short-term effect of exercise therapy on pain, disability, muscle strength, physical functioning, QOL and patients' self perceived effect [5–7,42]. In our study, both groups showed significant improvements in all clinical parameters. The beneficial role of moderate exercise in OA is not known; whether it is effective via the stabilization of the joints through muscle strength and

Table 3
Baseline and the final results of quality of life, depression of the patients

		Group 1			Group 2		
		BT	AT	p	BT	AT	p
Depression	Med (Min-max)	10.0 (1–23)	2.0 (0–11)	**0.001**	12.0 (3–23)	1.0 (0–12)	**0.001**
SF-36							
Physical function	(Mean ± SD)	54.50 ± 18.20	85.30 ± 16.91	0.001	61.57 ± 17.56	86.84 ± 14.26	**0.001**
Mental health	(Mean ± SD)	69.60 ± 13.94	84.55 ± 13.38	0.001	62.21 ± 17.18	82.78 ± 13.14	**0.001**
Pain	(Mean ± SD)	51.70 ± 13.86	78.90 ± 18.22	0.001	55.00 ± 14.20	86.84 ± 10.30	**0.001**
General health	(Mean ± SD)	56.00 ± 18.60	73.25 ± 18.37	0.001	52.89 ± 20.77	71.57 ± 13.23	**0.001**
Social function	(Mean ± SD)	66.55 ± 19.37	77.20 ± 17.73	0.001	76.42 ± 12.42	85.10 ± 8.06	**0.001**
Energy	(Mean ± SD)	61.75 ± 21.10	79.75 ± 17.35	0.001	55.78 ± 17.58	79.47 ± 16.74	**0.001**
Physical role limitation	Med (Min-max)	32 (0–100)	100 (50–100)	0.001	25 (0–100)	100 (50–100)	**0.01**
Emotional role limitation	Med (Min-max)	25 (0–100)	100 (33–100)	0.001	33 (0–100)	100 (33–100)	**0.01**

$p < 0.05$ significant. BT Before treatment. AT After treatment. SF-36 Short Form 36. Med (Min-max) Median (Minimum-maximum). Mean ± SD Mean ± Standart Deviation. $p > 0.05$, after treatment comparisons for all parameters.

Table 4
Baseline and the final results of MRI parameters of the patients

	Group 1			Group 2		
	BT Mean ± SD	AT Mean ± SD	p	BT Mean ± SD	AT Mean ± SD	p
Total cartilage volume (cm^3)	322.08 ± 68.11	327.26 ± 66.44	**0.027**	292.34 ± 62.90	302.07 ± 63.72	**0.015**
Cartilage volume (right) (cm^3)	159.92 ± 42.20	162.56 ± 40.82	0.209	149.15 ± 32.88	152.27 ± 32.29	0.102
Cartilage volume (left) (cm^3)	162.34 ± 34.38	165.60 ± 32.41	**0.036**	143.17 ± 37.50	152.76 ± 38.39	**0.027**
Lateral cartilage thickness (right) (mm)	46.75 ± 11.54	47.40 ± 11.44	0.050	49.26 ± 8.08	50.31 ± 7.87	0.066
Lateral cartilage thickness (left) (mm)	45.45 ± 10.82	48.10 ± 12.77	**0.022**	41.42 ± 12.71	44.52 ± 12.35	**0.001**
Medial cartilage thickness (right) (mm)	44.05 ± 11.43	45.65 ± 11.93	**0.025**	48.73 ± 9.35	50.26 ± 9.04	**0.014**
Medial cartilage thickness (left) (mm)	41.15 ± 10.24	43.40 ± 9.53	**0.004**	38.68 ± 11.01	42.05 ± 11.09	**0.001**

$p < 0.05$ significant. $p > 0.05$, after treatment comparisons for all parameters. **BT** before treatment. **AT** after treatment.

control, or whether exercise has a direct effect on the joint cartilage and the synovium. Exercise has been suggested to positively modulate low-grade inflammation in elderly patients [43]. It is therefore possible that regular moderate exercise may induce changes in the intraarticular and perisynovial tissue that encourages anti-inflammatory activity as well as releases potential chondroprotective substances [44]. The hallmark of structural changes occurring in the OA joint is cartilage loss. Although, in animal studies, it has been shown that exercise may protect against cartilage degeneration [45, 46], there is limited clinical trial showing the effects of exercise on the structure of cartilage. In humans, Roos et al. [47] found that moderate supervised exercise improved knee-cartilage GAG content in patients at risk of OA and they also found that improvements in pain and function were observed in parallel with the structural improvement. Manninen et al. [48] investigated the association between physical exercise and the risk of severe knee osteoarthritis requiring arthroplasty, they found that moderate recreational physical exercise is associated with a decrease in the risk of knee OA. Conflicting results have been reported regarding the effect of quadriceps strength on structural progression of knee OA [6,49–51]. While Foley et al. [49] demonstrated that lower-limb muscle strength was positively associated with both total cartilage volume and tibial plateau area change per year, Amin et al. [51] determined that quadriceps strength had no influence on cartilage loss at the tibiofemoral joint. In the present study, both groups received a moderate exercise program including aerobic, isometric isotonic and flexibility exercises. Since both groups showed significant increase in quadriceps strength, the protection of cartilage may be due to the gain in the muscle strength.

Measurement of changes in joint space width is currently the gold standard in evaluation of structure modifying drugs in OA [52]. Comparative data from the MRI and x-rays indicate that the MRI is a more comprehensive tool for studying cartilage changes earlier and identifying factors that are predictive of the progression of the disease [47,53]. Therefore, we used MRI to evaluate the alterations in the cartilage volume and thickness. In the literature there are limited studies investigating the effects of different therapy modalities on cartilage thickness with MRI. In a recent study, Loyola-Sanchez et al. [54] evaluated the effect of low intensity pulsed ultrasound on the cartilage repair, and the authors found

an increase in medial tibia cartilage thickness in the active US therapy group attended 20 sessions or more. In another study, the impact of weight loss on knee cartilage thickness and composition was assessed and weight loss was found to be associated with quantity of medial articular cartilage [55].

Our study has some limitations. Firstly, exclusion of a group receiving no treatment due to ethical reasons may be considered a limitation. Secondly, since the patients were only evaluated after the therapy, this time may not be enough to observe the DMOAD effects of glucosamine. Also, there are studies evaluating the effects of glucosamine with larger populations for longer period in the literature. However, in the present study, we also aimed to evaluate the effects of exercise on cartilage progression. So, both groups received an exercise program supervised by a physiatrist and it is not possible to continue a supervised exercise program for a longer period.

In the literature, there are limited studies about the effects of glucosamine and exercise on joint space narrowing evaluated with MRI. We found that glucosamine in addition to an exercise program seems to have no further significant effect in terms of joint space narrowing, pain, disability, muscle strength, walking distance, depression and QOL and in patients with knee OA. Considering its cost-effectivity, exercise therapy alone is effective in protection of articular cartilage and improvement of clinical symptoms in a short period in the patients with knee OA.

Acknowledgements

This study was supported by the Ondokuz Mayıs University Research Fund (T-529).

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