

# Effect of Different Intensity Ultrasound on Femoral Cartilage Thickness and Symptomatic Relief in Knee Osteoarthritis: A Randomized, Controlled Double-Blind Study

## Diz Osteoartritinde Farklı Yoğunluklu Ultrasonun Femur Kıkırdak Kalınlığı ve Semptomatik Rahatlama Üzerine Etkisi: Randomize, Kontrollü Çift Kör Çalışma

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**ABSTRACT Objective:** Therapeutic ultrasound is a noninvasive and easily applicable treatment method used for musculoskeletal pain. The aim of this randomized, double-blind, controlled study is to evaluate the effects of different ultrasound intensities on pain and function in patients with knee osteoarthritis. **Material and Methods:** This single-center, prospective, randomized, double-blind, controlled study included 90 patients diagnosed with knee osteoarthritis (Kellgren-Lawrence stage II–III) according to ACR criteria and experiencing moderate-to-severe knee pain. Patients were randomly assigned to three groups (n = 30) using a computer-generated random number table. All patients received a standard exercise program combined with hot pack, TENS, and continuous ultrasound therapy for 3 weeks (5 days per week, totaling 15 sessions). Pain (VAS), function (Western Ontario and McMaster Universities Arthritis Index (WOMAC), Lequesne index), and femoral cartilage thickness (ultrasonography) were measured by a blinded evaluator before treatment, at the end of treatment, and at 1 month. Ultrasound wave frequencies were set at 1 MHz, 1 W/cm<sup>2</sup> for the first group; 1.5 W/cm<sup>2</sup> for the second group; and 2 W/cm<sup>2</sup> for the third group. **Results:** There were no demographic differences between the groups (p>0.05). In all groups, significant improvement was observed in VAS, WOMAC subscores, Lequesne index, and femoral cartilage thickness at both the end of treatment and 1 month after treatment compared to baseline (p<0.001). However, no statistically significant differences were found between the three groups in terms of clinical scores and cartilage thickness changes (p>0.05). **Conclusion:** Long-term low-intensity ultrasound significantly reduced pain and improved joint function in patients

**ÖZET Amaç:** Terapötik ultrason, musculoskeletal ağrı için kullanılan, invaziv olmayan ve kolay uygulanabilir bir tedavi yöntemidir. Bu randomize, çift-kör, kontrollü çalışmanın amacı, diz osteoartriti olan hastalarda farklı ultrason yoğunluklarının ağrı ve fonksiyon üzerindeki etkilerini değerlendirmektir. **Gereç ve Yöntemler:** Tek merkezli, prospektif, randomize, çift kör, kontrollü planlanan bu çalışmaya ACR kriterlerine göre diz osteoartriti (Kellgren-Lawrence evre II–III) tanısı alan, orta-şiddetli diz ağrısı bulunan 90 hasta dahil edildi. Bilgisayar destekli rastgele sayı tablosu ile üç gruba (n=30) ayrıldı. Tüm hastalara 3 hafta boyunca haftada 5 gün (toplam 15 seans) sıcak paket, TENS ve sürekli ultrason tedavisi ile standart egzersiz programı uygulandı. Ağrı (VAS), fonksiyon (Batı Ontario ve McMaster Üniversitesi Artrit İndeksi (WOMAC), Lequesne indeksi) ve femoral kıkırdak kalınlığı (ultrasonografi) tedavi öncesi, bitiminde ve 1. ayda kör değerlendirici tarafından ölçüldü. Ultrason dalga frekansları: birinci grup için 1 MHz, 1 W/cm<sup>2</sup>; ikinci grup için 1.5 W/cm<sup>2</sup>; üçüncü grup için 2 W/cm<sup>2</sup> olarak belirlenmiştir. **Bulgular:** Gruplar arasında demografik fark yoktu (p>0.05). Tüm gruplarda VAS, WOMAC alt skorları, Lequesne indeksi ve femoral kıkırdak kalınlığında tedavi öncesine göre hem bitimde hem 1. ayda anlamlı iyileşme görüldü (p<0.001). Ancak, klinik skorlar ve kıkırdak kalınlığı değişimleri açısından üç grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (p>0.05). **Sonuç:** Uzun süreli düşük yoğunluklu ultrason, hastalarda ağrıyı önemli ölçüde azaltmış ve eklem fonksiyonunu iyileştirmiştir.

**Keywords:** Osteoarthritis of knee; ultrasound therapy

**Anahtar Kelimeler:** Diz osteoartriti; ultrason tedavisi

Osteoarthritis (OA) is an important and strenuous health problem affecting nearly one in three adults.<sup>1,2</sup> The incidence of OA increases with age and obesity rates, and it typically affects the knees. This condition is a degenerative disease characterized by progressive cartilage destruction in the joints, osteophyte formation and subchondral sclerosis along with

the inflammatory process.<sup>3</sup> OA causes a large economic burden on the healthcare system.<sup>4,5</sup>

Analgesics and non-steroidal anti-inflammatory drugs are frequently used for treating OA.<sup>1</sup> These drugs have gastrointestinal and cardiovascular side effects. Intra-articular hyaluronic acid injection may be an alternative, but painful interventional procedures may be

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less preferred by patients.<sup>6</sup> Noninvasive and safe physical therapy methods can be used for treating OA.<sup>7</sup>

Ultrasound (US) therapy, which has a low side effect profile, has been used for a long time for treating OA, but there are conflicting studies regarding its effectiveness. There are clinical studies supporting that US reduces pain and functional limitation and is superior to placebo controls.<sup>8-11</sup> However, no study so far has mentioned a standardized method of applying US therapy.

Our purpose was to determine the effect of different US intensity therapies on ultrasonographic cartilage measurement and clinical results in Knee Osteoarthritis (KNO).

## MATERIAL AND METHODS

This study was designed as a single-center, double-blinded, prospective, randomized, controlled study.

The Ethics Committee approved the study with a 2017/329 protocol number (date: October 23, 2017, no: 2017/329). This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

### PARTICIPANTS

A total of 90 patients who were diagnosed with knee osteoarthritis (KOA) according to the American College of Rheumatology classification criteria were included in the study.<sup>12</sup> The inclusion criteria for this study were as follows: (1) grade 2-3 KOA patients according to the Kellgren-Lawrance classification; (2) being aged between 45 and 70 years; (3) having knee pain for at least 6 months; and (4) the visual analog scale (VAS) score being at least 3 or more.<sup>13</sup> The exclusion criteria were as follows: (1) those who had a history of surgery or traumatic knee injury; (2) those who had inflammatory rheumatic diseases; (3) those who underwent intra-articular injection in the knee in the last 6 months; (4) having a history of cancer, bleeding diathesis, and behavioral problems; (5) those who had a disease that would limit their contribution in the physical therapy program; (6) those who had problems in the lower extremity; and (7) those who had participated in similar physical therapy program in the last 3 months.

### RANDOMIZATION

A total of 90 (73 males, 17 females, mean age of  $58.09 \pm 6.2$  years, range: 45-70 years) out of 136 patients who were diagnosed with grade 2 or 3 KOA were included. Forty-six patients were excluded according to the exclusion criteria of our study before the randomization process.

A total of 90 patients who met the inclusion criteria were randomly assigned to 3 equal groups ( $n=30$ ) using the sealed opaque envelope method. The randomization process was performed by an independent researcher not involved in the study, using a computer-generated random number table prepared in advance. Each allocation was placed in sequentially numbered, opaque, sealed envelopes, and after eligibility confirmation, one envelope was opened to determine the group assignment for each participant. Ninety patients were divided into 3 groups: 1<sup>st</sup> group with 1 W/cm<sup>2</sup> intensity ( $n=30$ ); 2<sup>nd</sup> group with 1.5 W/cm<sup>2</sup> intensity ( $n=30$ ); and 3<sup>rd</sup> group with 2 W/cm<sup>2</sup> intensity ( $n=30$ ). Randomization was performed using the random envelope-pulling method. The study flow chart is shown in [Figure 1](#).

### Assessment Tools

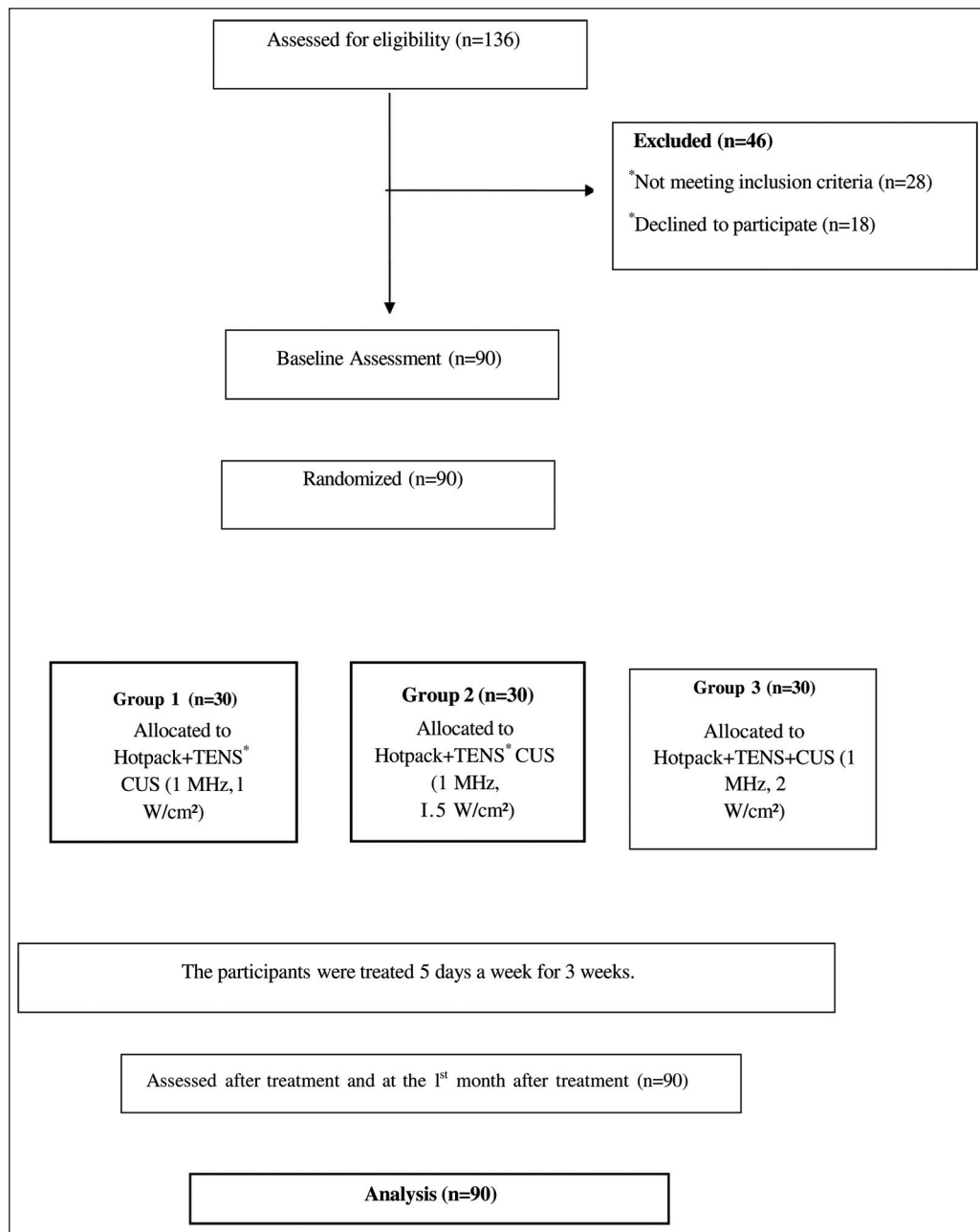
Sociodemographic features such as age, gender, disease duration, height, and weight were questioned and recorded for all participants.

### Assessment of Pain

Pain intensity was measured using VAS, which is commonly used to determine pain level in clinical studies. Patients were asked to determine the severity of pain with a value between 0 and 10 points.<sup>14</sup>

### Functional Assessment

The functional adequacy of the patients was evaluated with the Ontario and McMaster University Arthritis Index (WOMAC) scale. WOMAC is a questionnaire consisting of 3 separate parts that evaluate pain, stiffness, and physical function. The functional adequacy of the patients was evaluated with the WOMAC scale. WOMAC is a questionnaire consisting of 3 separate parts that evaluate pain, stiffness, and physical function. High WOMAC scores are directly proportional to the severity of functional dis-



**FIGURE 1:** CONSORT flow diagram of the study. Ninety patients with KOA who met the inclusion and exclusion criteria were included in the study. There was no dropout during the treatment and follow-up, and 90 patients were analyzed at the end of the study. TENS: Transcutaneous electrical nerve stimulation; CUS: Continuous; KOA: Knee osteoarthritis

ability, pain, and stiffness.<sup>15</sup> The LequesneAlgo-functional knee index consists of 10 questions , with 3 separate headings (pain or discomfort, maximum walking distance, daily life activities). The Lequesne index results are expressed in a value between 0 and 24 points.<sup>15</sup>

### Ultrasonographic Measurements

The femoral cartilage thickness was evaluated ultrasonographically with a linear probe (7-12 MHz Logiq P5, GE Medical Systems, WI, USA) by the senior physician. For femoral cartilage thickness measurements, the patients had to lay in a supine

position on the testing table, their knees positioned in maximum flexion and a comfortable position, and the probe was placed on the suprapatellar zone and in an axial position. The space between the thin hyperechoic line at the synovial space/cartilage interface and the sharp hyperechoic line at the cartilage-bone interface was defined as the cartilage thickness. The femoral cartilage thickness was quantified at three alternative points at the lateral condyle, intercondylar range, and medial condyle level.

## TREATMENT PROTOCOL

### Exercises

A standard exercise program was designated for the patients by the same researcher. The exercise program comprised range of motion (ROM) exercises, stretching, strengthening, and flexibility exercises. The exercise program was started with active ROM exercises. ROM exercises for the knee joints in the supine and prone positions were conducted in a pain-free range. The exercises were sustained with straight leg raising, quad sets, pillow squeeze, heel raising, one-leg balance, step-up, and exercises for quadriceps strengthening. Each exercise was conducted as 10 times/set for 2 sets. The patients were trained and advised to maintain the same program at home.

### ULTRASOUND THERAPY

The duration of treatment was arranged for each patient for 15 sessions, 5 days a week, for 3 weeks. The treatment program was applied to all patients by the same therapist. All clinical evaluations and measurements were conducted by a blinded investigator on the treatment.

In the 3 patient groups, hot packs (hydro collar hot packs, Chattanooga, California, USA) were heated to 42° C, and subsequently applied over the knees for 20 min. Symmetrical, 100 MHz frequency and constant current, transcutaneous electrical nerve stimulation (TENS) (Intellect Advanced Combo, Chattanooga, California, USA) were applied to both knees at a dose that the patient could tolerate at the current intensity for 20 min. Then, the continuous US was applied for 10 min in total, with 1 MHz frequency and 1 W/cm<sup>2</sup> intensity in the 1<sup>st</sup> group, 1 MHz frequency and 1.5 W/cm<sup>2</sup> intensity in the 2<sup>nd</sup> group,

and 1 MHz frequency and 2 W/cm<sup>2</sup> intensity in the 3<sup>rd</sup> group. This therapeutic US was applied to the patients in the supine position, after application of the gel to the knee (without using any pharmacological agents), which was applied at right angles with 5 cm diameter circular movements (BTL-4000 combined therapy device, Ankara, Türkiye). All patients were given an isometric exercise program. Clinical outcome evaluations were made 2 days after the end of treatment to avoid the acute effects of heat.

## STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 22.0, SSPS Inc., Chicago, Illinois, USA). The analysis results of some demographic variables were given with the help of descriptive statistics (mean, standard deviation). One-way analysis of variance (ANOVA) was used to compare patient groups according to demographic characteristics. One-way repeated measurement variance analysis was used to compare the variables before treatment, after treatment, and after the first month after treatment. Two-way repeated measurement variance analysis was used to compare the variables before treatment, after treatment, and after the first month after treatment according to the groups. Probability values of  $p < 0.05$  were considered statistically significant. Power analysis was conducted using G\*Power version 3.1 (Heinrich-Heine-Universität Düsseldorf, Germany).. For the analysis, the total number of people required to find a statistically significant effect size expectation (Cohen  $f = 0.40$ ), in terms of medial measurements after treatment in the 3 groups, was calculated as 66 ( $\alpha = 0.05$ ,  $1 - \beta = 0.80$ ).

## RESULTS

A total of 90 patients were included in the study. All patients completed the study. 73 (81.1%) of these patients were female and 17 (18.9%) were male. The mean age of the patients was  $58.09 \pm 6.2$  years. When demographic characteristics were compared, there was no statistically significant difference between the 3 groups in terms of age, weight, height, and body mass index ( $p > 0.05$ ). The sociodemographic data of the patients are summarized in [Table 1](#).

**TABLE 1:** Demographic characteristics of the patients

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	
Patient demographic characteristics	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	p value
Age (years)	57.03 $\pm$ 7.08	58.07 $\pm$ 5.22	59.17 $\pm$ 6.19	0.410*
BMI (kg/m <sup>2</sup> )	32.57 $\pm$ 4.92	31.10 $\pm$ 3.87	32.15 $\pm$ 5.28	0.460*
Duration of illness (months)	33.50 $\pm$ 30.70	39.80 $\pm$ 30.19	54.77 $\pm$ 38.82	0.460*

\*One-way ANOVA test; SD: Standard deviation; BMI: Body mass index

Statistically significant decreases were detected in VAS, WOMAC-pain, WOMAC-function, WOMAC-stiffness, and WOMAC-total values at the end of the treatment (in week 3), compared to the baseline in the 3 groups ( $p < 0.001$ ). The femur medial, intercondylar, and lateral cartilage thickness increased at statistically considerable levels in all groups compared with the pre-treatment period ( $p < 0.001$ ). There were significant improvements from baseline to the end of the treatment in all groups with respect to the Lequesne scores ( $p < 0.001$ ).

There were no statistically significant differences among the 3 groups in terms of VAS, WOMAC, and Lequesne scores ( $p > 0.05$ ). It was determined that different US intensities were not superior to each other in terms of recovery (Table 2). There was a significant increase in femoral cartilage thickness in all groups after the treatment period ( $p < 0.001$ , for all interviews). Changes in femoral cartilage thickness were compared among the 3 groups, and there were no significant differences found in terms of cartilage thickness among the groups ( $p > 0.05$ ) (Table 3, Table 4).

## DISCUSSION

This study was conducted to compare the effects of different intensities of US therapy on pain, function, and femoral cartilage thickness in patients with KOA. The results of the study determined that continuous US therapy application reduced pain, function, and femoral cartilage thickness. However, it was observed that the effects of different intensities of US therapy on clinical and sonographic findings were not superior to each other. As far as we know, this is the first prospective, randomized study performed on this topic.

**TABLE 2:** Pre- and post-treatment VAS, Lequesne index and total McMaster Universities Osteoarthritis Index measurements in all groups

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
Measurements	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
VAS			
Pretreatment	7.90 $\pm$ 1.40	4.70 $\pm$ 2.22	4.17 $\pm$ 2.74
Post-treatment	7.93 $\pm$ 1.51	5.03 $\pm$ 2.40	4.77 $\pm$ 2.86
1 <sup>st</sup> month	7.90 $\pm$ 1.49	4.93 $\pm$ 2.38	5.00 $\pm$ 2.26
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.689**	
Lequesne index			
Pretreatment	11.87 $\pm$ 2.78	11.97 $\pm$ 2.67	12.93 $\pm$ 3.10
Post-treatment	9.53 $\pm$ 3.00	8.33 $\pm$ 3.89	8.70 $\pm$ 3.19
1 <sup>st</sup> month	9.10 $\pm$ 3.64	8.83 $\pm$ 4.24	9.63 $\pm$ 3.47
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.649**	
WOMAC (Total)			
Pretreatment	52.20 $\pm$ 13.69	53.94 $\pm$ 11.68	57.38 $\pm$ 15.09
Post-treatment	40.46 $\pm$ 15.65	35.80 $\pm$ 17.32	3.697 $\pm$ 14.02
1 <sup>st</sup> month	38.27 $\pm$ 16.85	35.38 $\pm$ 18.70	39.55 $\pm$ 16.49
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.720**	

\*One-way repeated measurement variance analysis; \*\*Two-way repeated measurement variance analysis; SD: Standard deviation; VAS: Visual Analog Scale; WOMAC: McMaster Universities Osteoarthritis Index

**TABLE 3:** Pre- and post-treatment measurements of right knee cartilage thickness in all groups

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
US findings	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
LFC (mm)			
Pretreatment	0.24 $\pm$ 0.47	0.23 $\pm$ 0.43	0.22 $\pm$ 0.65
Post-treatment	0.26 $\pm$ 0.03	0.26 $\pm$ 0.04	0.26 $\pm$ 0.06
1 <sup>st</sup> month	0.25 $\pm$ 0.04	0.26 $\pm$ 0.04	0.25 $\pm$ 0.05
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.602**	
ICA (mm)			
Pretreatment	0.22 $\pm$ 0.05	0.24 $\pm$ 0.06	0.23 $\pm$ 0.07
Post-treatment	0.24 $\pm$ 0.04	0.26 $\pm$ 0.06	0.26 $\pm$ 0.07
1 <sup>st</sup> month	0.23 $\pm$ 0.04	0.26 $\pm$ 0.05	0.25 $\pm$ 0.06
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.156**	
MFC (mm)			
Pretreatment	0.23 $\pm$ 0.48	0.23 $\pm$ 0.06	0.23 $\pm$ 0.06
Post-treatment	0.24 $\pm$ 0.04	0.25 $\pm$ 0.06	0.28 $\pm$ 0.06
1 <sup>st</sup> month	0.23 $\pm$ 0.04	0.25 $\pm$ 0.05	0.25 $\pm$ 0.05
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.212**	

\*One-way repeated measurement variance analysis; \*\*Two-way repeated measurement variance analysis; US: Ultrasound; SD: Standard deviation; LFC: Lateral femoral condyle; ICA: Intercondylar area; MFC: Medial femoral condyle



**TABLE 4:** Pre- and post-treatment measurements of left knee cartilage thickness in all groups

	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)
US findings	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
LFC (mm)			
Pretreatment	0.22±0.03	0.23±0.05	0.21±0.07
Post-treatment	0.24±0.04	0.25±0.05	0.26±0.06
1 <sup>st</sup> month	0.23±0.04	0.25±0.04	0.23±0.05
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.537**	
ICA (mm)			
Pretreatment	0.23±0.06	0.24±0.06	0.24±0.07
Post-treatment	0.24±0.06	0.25±0.06	0.27±0.07
1 <sup>st</sup> month	0.24±0.06	0.26±0.06	0.25±0.07
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.525**	
MFC (mm)			
Pretreatment	0.23±0.05	0.25±0.07	0.22±0.06
Post-treatment	0.24±0.04	0.26±0.06	0.26±0.06
1 <sup>st</sup> month	0.24±0.04	0.26±0.06	0.26±0.06
p value	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>	<b>&lt;0.001*</b>
		0.344**	

\*One-way repeated measurement variance analysis; \*\*Two-way repeated measurement variance analysis; US: Ultrasound; SD: Standard deviation; LFC: Lateral femoral condyle; ICA: Intercondylar area; MFC: Medial femoral condyle

US therapy is used in many musculoskeletal system problems, and the number of studies investigating the effectiveness of US therapy in KOA is increasing daily. However, there are insufficient data on how to standardize different US intensities in KOA.<sup>16</sup> US intensities between 1 W/cm<sup>2</sup>-3 W/cm<sup>2</sup> were used in most of the studies about KOA and were reported as effective.<sup>17</sup> In our study, there was a significant improvement in the VAS, WOMAC, and Lequesne values in all 3 groups after treatment. In this study, we applied 3 different US intensities and evaluated their superiority. We found that 1 W/cm<sup>2</sup> US application provided a similar clinical and sonographic improvement in KOA as compared with 1.5 W/cm<sup>2</sup> and 2 W/cm<sup>2</sup> applications. It has been considered that the application of US therapy at the lowest intensity could provide sufficient improvement and could be preferable to other high intensities. Thus, the potential side effects may be less likely with a lower intensity.

Our study showed that US therapy could reduce the severity of the disease and furthermore could increase the femoral cartilage thickness. We thought

that US therapy could be the approach for not only providing symptomatic relief but also for treating disease progression, degeneration, or destruction. These promising data on the potential slowdown of disease progression with the US treatment strategy warrant further study.

When the literature was examined, it was seen in animal studies that pulse and continuous US therapy could contribute to cartilage repair.<sup>18,19</sup> However, it has been observed that studies investigating the effectiveness of continuous US on humans are limited.<sup>16</sup> With this study, the effects of continuous US on humans were investigated and it is thought that it will contribute to the literature in the missing field.

A limitation of our study is that we did not evaluate the patients' comorbid diseases and the medications they used. Another limitation of this study is the absence of an untreated control group. The 3 study groups were considered each other's control. In this regard, we accepted this study as a preliminary study and planned to continue the long-term follow-up of our current patients with clinical and sonographic data. Future studies with various clinical and sonographic measurements should include larger sample sizes.

## CONCLUSION

In conclusion, different intensities of therapeutic continuous US application in KOA have a positive effect on pain, functionality and cartilage regeneration, but are not superior to each other. This may be because we measured the femoral cartilage thickness in a short period after treatment. Longer follow-up studies are needed. Our study revealed that the therapeutic US showed the expected treatment efficacy even at low intensity (1 W/cm<sup>2</sup>). In addition, our study might be a guide for standardization in the application of one of the frequently used modalities, US in KOA. There is a need for multicenter, randomized controlled trials with larger patient groups and longer follow-up periods.

## Source of Finance

*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.*

### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

bers of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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