Original Article

# Effectiveness of Therapeutic Ultrasound on Clinical Parameters and Ultrasonographic Cartilage Thickness in Knee Osteoarthritis: A Double-Blind Trial

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## Abstract

**Objective:** A double-blind placebo-controlled randomized study was conducted to assess the effectiveness of therapeutic ultrasound (US) in knee OA. **Patients and Methods:** Thirty-three patients (mean age 54.7 ± 14.7) were randomized to receive either continuous US ($n$ = 15) or sham US ($n$ = 18) as a placebo. Continuous ultrasonic waves with 1 MHZ frequency and 1 watt/cm$^2$ power were applied for 5 min for 10 sessions. The primary outcome was pain on movement assessed by visual analog scale (VAS). The secondary outcomes were WOMAC scores and measurements of distal femoral cartilage thickness by imaging US. **Results:** Both groups showed reduced knee pain on movement following intervention. The VAS measurements improved significantly both in the treatment and the placebo group patients ($P < 0.05$ and $P < 0.05$). WOMAC scores improved statistically significant in all domains (pain, stiffness, physical function, and total score) in the treatment group ($P < 0.05$). All domains of WOMAC score showed statistically significant change when compared with the placebo group ($P < 0.05$). There was no change in the cartilage thickness measurements of medial femoral condyle, lateral femoral condyle, and intercondylar area in both groups after intervention. **Conclusion:** Results suggest that US is effective treatment modality in pain relief and improvement of function in patients with knee OA; however, US had no effect on cartilage repair.

**Keywords:** Cartilage repair, imaging ultrasound, knee, osteoarthritis, therapeutic ultrasound

## Introduction

Osteoarthritis (OA) is the most common joint disorder, and knee OA is one of the leading causes of disability with an increasing trend.[1] The current treatment of OA is oriented primarily to relieve pain and increase physical function. The basic pathologic element in OA is articular cartilage degeneration.[2] Patients with established knee OA are characterized by loss of articular cartilage and erosion. Previous studies have shown that during the course of knee OA, cartilage loss starts first locally at the medial area of the knee and progresses to diffuse lost.[1,2] New treatments (stem-cell therapies, mosaicplasty, etc.,) may modify disease progression by targeting cartilage repair; however, these procedures are invasive.[3] Ultrasound (US) is a technique that can be applied for both imaging – diagnostic and therapeutic purposes in knee OA.[4] Cartilage thickness is an important measure in the diagnosis of early OA and progression of the disease.[5] There have been studies which showed that US can be used to diagnose early OA, monitor progression of the disease, and evaluate the efficiency of treatment.[6,7]

We aim to use imaging US to evaluate the efficiency of therapeutic US in knee OA in this trial.

Therapeutic US, a deep-heating agent that converts mechanical energy into a form of sound waves which has thermal effects on tissues (increase of blood flow and acceleration of healing process) and nonthermal effects on cells (mechanical microstrain which stimulates biologic repair of cartilage),

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has been used widely as an effective nonpharmacological management option in patients with knee OA, both for pain relief and functional improvement.[8-10]

Besides these new invasive treatments (stem-cell therapies, mosaicplasty, etc.,) that modify OA progression, therapeutic US may be a noninvasive option to prevent the degeneration of articular cartilage. The effectiveness of therapeutic US has been assessed by clinical parameters in most studies, with only a few that sought to correlate clinical and US imaging findings in the involved knee.[7,11] To our knowledge, this is the first study that explored the effects of therapeutic US on cartilage measured by imaging US in patients with knee OA. In this double-blind controlled randomized study, we utilized clinical parameters and ultrasonographic cartilage thickness measurement to assess the effectiveness of therapeutic US in knee OA.

## Patients and Methods

The study was conducted at the Department of Physical Medicine and Rehabilitation of Istanbul Research and Education Hospital from September 2016 to January 2017. The study was approved by the local ethics committee, and informed consent was obtained from patients.

The study participants were recruited from among patients with newly diagnosed OA of the knee. Selection criteria were based on the clinical and radiological criteria defined by the American College of Rheumatology for knee OA.[12]

Patients were included if they were 45–65 years old; if they have had knee pain and limitation on most days of the past 6 months; and if the Kellgren-Lawrence[13] scores were III on radiological evaluation.[14] Patients were excluded from the study if they had any systemic illness or abnormal laboratory test result, any contraindication for physical therapy, and history of a knee operation, including lower limb arthroplasty; if they had been on any physiotherapy program before; or if they had received intra-articular knee injections or US therapy in the preceding year. Prior analgesic use was not an exclusion criterion.

All participants were initially screened over the phone with regard to selection criteria and those who fulfilled the criteria were invited to join the study. Patients were assessed by one of the three authors by history and detailed physical examination. All patients were initially questioned about age, sex, weight, height, duration of knee pain, and the target knee (the more symptomatic or painful knee). In patients in whom both knees were symptomatic, the more painful knee was chosen, or when symptoms were similar bilaterally, the right knee was chosen as the target knee. Laboratory analyses, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, hepatic enzyme tests, and renal function tests, were performed to rule out secondary causes of OA and other diseases.

The primary outcome was knee pain on movement over the past week assessed by visual analog scale (VAS) numbered in 1 cm intervals. Scores ranged from 0 to 10, with a score of 0 indicating no pain and 10 indicating extremely severe pain.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and distal femoral cartilage thickness measurements of the target knee were the secondary outcomes.

The WOMAC scores test pain, stiffness, and physical functioning[15] and consist of 24 items: 5 determine subjective global assessment of pain, 2 assess joint stiffness, and 17 assess physical functioning. WOMAC scores were recorded on a Likert scale of 0–4, where 0 = no pain/limitation; 1 = mild pain/limitation; 2 = moderate pain/limitation; 3 = severe pain/limitation; and 4 = very severe pain/limitation.

All measurements were by the same physiatrist using a 5–13 MHz linear probe (Esaote MyLab 5; Genova, Italy). Distal femoral cartilage thickness measurements were taken from the mid-points of medial femoral condyle (MFC), lateral femoral condyle (LFC) and the intercondylar area (ICA). The same protocol that Malas *et al*.[7] used for evaluating cartilage by US was applied in this study: patients flexed their knees in the maximum possible position while laying in a supine position. The transducer was placed axially above the patellar outer edge. Distal femoral cartilage thicknesses were assessed in longitudinal sagittal plane, and the distance between synovial space–cartilage and cartilage–bone interface was measured as the cartilage thickness. Cartilage thickness measurements were taken from the mid-points of MFC, LFC, and ICA. The distance between the thin hyperechoic line at the synovial space–cartilage interface and the sharp hyperechoic line at the cartilage–bone interface was measured as the cartilage thickness.

### Study design and assessment

Following baseline assessment, participants were randomized to receive either therapeutic US or placebo (sham US). An independent researcher not involved in the data assessment randomized the participants.

Patients were not permitted to use any analgesics 10 days before and during physiotherapy program (washout period). The physiotherapy program was conducted 5 times a week for 2 weeks, excluding weekends for a total of 10 sessions. Both the therapeutic US and the sham US application were performed by the same therapist, and patients were assessed by three blinded researchers before and at the end of therapy program.

### Interventions

No physiotherapy was prescribed before US treatment to either of the groups. In the treatment group, US was applied using an aqueous gel as a coupling medium in circular movements with the probe at right angles. The treatment area was 25 cm² and extended to both patellofemoral and tibiofemoral borders of the target knee on both the lateral and medial margins, avoiding the patella. Continuous ultrasonic waves with 1 MHZ frequency and 1 watt/cm2 power were applied with a 4-cm diameter applicator (Petson®.250 ultrasound equipment Petas, Turkey)

for 5 min in each session. To avoid the immediate effects of heat application, the outcome data evaluation was performed 2 days after completion of the last session.

In the placebo group, sham US (an applicator disconnected from the back to working US machine) was applied to the target knee in the same manner described above, using the same acoustic gel, 5 min per session. Patients were not able to see whether the cable was disconnected or not.

### Statistical analysis

IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY) for Windows package program was used for statistical analysis. Descriptive statistics are given as mean, standard deviation, and median for numerical variables and number and percentage for categorical variables. Distribution of variants was measured with Kolmogorov-Smirnov test. Mann–Whitney U-test was employed to compare outcome scores among treatment groups compared since the numerical variables did not make the normal distribution condition. Wilcoxon test was used to analyze dependent quantitative variables. Chi-square test was used to analyze qualitative variables. Fisher's exact test was used when Chi-square test could not be applied.

## Results

The number of patients enrolled in the treatment and the placebo groups was 15 and 18, respectively. The mean age of the patients in the treatment group and in the placebo group was 53.9 ± 17.2 and 55.5 ± 11.9, respectively. The majority of patients were female in the treatment group (56.3%) and male in the placebo group (64.7%). The demographic data and baseline characteristics of the patients are summarized in Table 1.

### Primary outcomes

The primary outcome was knee pain on movement over the past week assessed by VAS numbered in 1 cm intervals. Both groups showed reduced knee pain on movement following intervention. The VAS measurements improved significantly both in the treatment and the placebo group patients ($P < 0.05$ and $P < 0.05$). Both groups maintained this improvement in VAS scores 1 month after intervention. There was no statistically significant difference in VAS scores between groups before and after the intervention ($P > 0.05$) [Table 2].

### Secondary outcomes

McMaster Universities Osteoarthritis Index (WOMAC) scores and distal femoral cartilage thickness measurements of the target knee were the secondary outcomes. There was no statistically significant difference in WOMAC scores between groups before the intervention ($P > 0.05$) [Table 3]. WOMAC scores improved statistically significant in all domains (pain, stiffness, physical function, and total score) in the treatment group ($P < 0.05$) [Table 3]. All domains of WOMAC score showed statistically significant change when compared with the placebo group ($P < 0.05$) [Table 3]. There was no improvement in any domain of WOMAC score in the placebo group [Table 3].There was no difference in the cartilage thickness measurements between groups [Table 4]. There was no change in the cartilage thickness measurements of MFC, LFC, and ICA in both groups after intervention [Table 4].

**Table 1: Demographic characteristics of patients**

| Patient demographic characteristics | US, *n* (%) | | Placebo, *n* (%) | | *P* |
|---|---|---|---|---|---|
| Sex | | | | | |
| Female | 9 (60.0) | | 6 (33.3) | | 0.126 |
| Male | 6 (40.0) | | 12 (66.7) | | |
| Target knee | | | | | |
| Right | 8 (53.3) | | 10 (55.6) | | 0.898 |
| Left | 7 (46.7) | | 8 (44.4) | | |
| **Age (years)** | **US** | | **Placebo** | | ***P*** |
| **BMI (Kg/m²)** | **Mean±SD** | **Median** | **Mean±SD** | **Median** | |
| Age | 54.0±17.8 | 59 | 55.4±11.6 | 55 | 0.562 |
| BMI | 28.8±5.6 | 30.3 | 28.1±5.5 | 30.8 | 0.562 |

SD: Standard deviation, BMI: Body mass index, US: Ultrasound

**Table 2: Pre- and posttreatment visual analog scale measurements in the ultrasound and placebo groups are given as mean±standard deviation**

| VAS | US group | | Placebo | |
|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median |
| Pretreatment | 7.53±0.92 | 8 | 7.28±1.18 | 7 |
| Posttreatment | 5.93±0.80 | 6 | 5.89±0.68 | 6 |
| 1st month | 5.93±0.80 | 6 | 5.89±0.68 | 6 |
| *P* | <0.001 | | <0.001 | |

VAS: Visual analog scale, SD: Standard deviation, US: Ultrasound

## Discussion

In our current study, patients receiving the actual US treatment showed statistically significant improvement in all pain measurements (VAS and WOMAC scores) immediately after and 1 month after intervention. Pain is the predominant symptom of knee OA and could be due to intra-articular and periarticular problems.

US shows its biological action through thermal and nonthermal mechanisms. The thermal effects of US could relieve mechanical pain by increasing capillary permeability, pain threshold, tensile strength, and extensibility of periarticular soft tissue.[16,17]

The nonthermal mechanisms might change on signaling pathways that related with cartilage repair and attenuate the release of inflammatory mediators (prostaglandin E2 and nitric oxide).[18-20] Nonthermal mechanisms also may act in pain relief by stimulating tissue regeneration, changing cell membrane permeability, and increasing intracellular calcium in the nervous system and reduction in nociceptive inflammatory processing in the spinal cord.[16,21]

**Table 3: Pre- and posttreatment total McMaster Universities Osteoarthritis Index measurements in the ultrasound and placebo groups are given as mean±standard deviation**

| WOMAC (total) | US group | | Placebo | | *P* |
|---|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median | |
| Pretreatment | 73.6±8.1 | 71.9 | 75.4±8.1 | 73.4 | 0.55 |
| Posttreatment | 63.1±15.0 | 64.6 | 73.3±10.6 | 71.9 | 0.03 |
| 1st month | 45.3±14.1 | 49.0 | 75.6±8.2 | 71.4 | <0.001 |
| *P* | <0.001 | | 0.006 | | |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SD: Standard deviation, US: Ultrasound

**Table 4: Pre- and posttreatment measurements of cartilage thickness in the ultrasound and placebo groups are given as mean±standard deviation**

| US findings | US group | | Placebo | | *P* |
|---|---|---|---|---|---|
| | Mean±SD | Median | Mean±SD | Median | |
| LFC (mm) | | | | | |
| Pretreatment | 1.874±0.065 | 1.89 | 1.839±0.070 | 1.86 | 0.13 |
| Posttreatment | 1.875±0.065 | 1.89 | 1.839±0.070 | 1.86 | 0.128 |
| 1st month | 1.877±0.066 | 1.90 | 1.839±0.070 | 1.86 | 0.115 |
| *P* | 0.061 | | - | | |
| ICA (mm) | | | | | |
| Pretreatment | 1.839±0.089 | 1.88 | 1.836±0.087 | 1.86 | 0.771 |
| Posttreatment | 1.843±0.091 | 1.88 | 1.835±0.087 | 1.86 | 0.561 |
| 1st month | 1.845±0.091 | 1.88 | 1.835±0.087 | 1.86 | 0.434 |
| *P* | 0.005 | | 0.135 | | |
| MFC (mm) | | | | | |
| Pretreatment | 1.845±0.091 | 1.88 | 1.835±0.087 | 1.86 | 0.434 |
| Posttreatment | 1.845±0.091 | 1.88 | 1.835±0.087 | 1.86 | 0.434 |
| 1st month | 1.847±0.091 | 1.88 | 1.835±0.087 | 1.86 | 0.383 |
| *P* | 0.135 | | - | | |

ICA: Intercondylar area, LFC: Lateral femoral condyle, MFC: Medial femoral condyle, US: Ultrasound, SD: Standard deviation

In the placebo group, there was an improvement in pain scores which might be due to placebo response; however, there was no improvement in WOMAC scores in the placebo group, and there was a statistically significant improvement in all domains of WOMAC scores immediately after intervention and 1 month after intervention in the treatment group when compared with placebo group. WOMAC index evaluates not only pain but also stiffness and physical function which are more objective parameters than pain. Studies have shown improvement in knee OA with placebo, ranging from 16% to 40% which may be due to attention to patient, concerns by the doctor, the strength of doctor–patient relationship, and intense monitoring. In a recent meta-analysis of studies involving patients with knee OA, the placebo effect increased based on its application type. The analgesic effect of intra-articular and topical placebo was found to be superior than oral placebo. In our study, we applied sham US to the target knee for 5 min per session.[22-24] Although knee OA affects the entire joint (articular cartilage, periarticular structures, ligaments, tendons, subcondral bones, and joint capsule), the primary problem is articular cartilage degeneration. Patients with established knee OA are characterized by loss of articular cartilage and erosion. Previous studies have shown that during the course of knee OA, cartilage loss starts first locally at the medial area of the knee and is more pronounced in the medial and lateral tibiofemoral areas compared to the intercondylar region and progresses to diffuse loss.[1,2,29,30]

Ultrasonic features of OA cartilage loss are loss of margin sharpness, loss of clarity of cartilage band, and thickness reduction.[3-5] Previous studies have shown that US can be used to diagnose early onset of OA, monitor progression of the disease, and evaluate efficiency of treatment by measuring cartilage thickness of knee.[4] In our study, there was no change in the cartilage thickness measurements of MFC, LFC, and ICA in both groups after intervention. In animal studies, US treatment was found to be effective in preventing cartilage damage by increasing type 2 collagen and affecting signaling pathways of cartilage repair. Another animal study of pulsed and continuous US showed increased chondrogenesis through the increase of HSP 70 and chondrogenesis-related mRNA expressions in rat articular cartilage. The hypothesis of these studies was that US may stimulate mechanotransduction pathway in which living cells respond mechanical stimulus and give biochemical responses. These biologic responses may cause regulation of structures acting in the pathogenesis of OA.[19,25-28] In

addition to the mechanical effect, heating effect of US may accelerate healing in damaged cartilage by increasing local circulation and metabolism. One study conducted in human subjects demonstrated a positive effect of US on the cartilage repair in patients with knee OA.[25] In that study, investigators assessed the effect of US on osteoarthritic knee cartilage by magnetic resonance imaging in a double-blinded randomized placebo-controlled study. They administered low-intensity pulsed US for 24 sessions to patients with mild OA. Only participants who attended 20 sessions or more showed an increase in medial tibial cartilage thickness in the active US treatment group.[25] In our study, we used continuous US and made only 10 sessions in patients with severe OA. While we observed no change in cartilage thickness measurement in treatment group, the dose and duration of US treatment might not be enough for increase in cartilage thickness of the knee, or there would be irreversible damage in these areas that US treatment had no effect.

### Limitations

The absence of a pure control group that did not receive any treatment at all may be considered a limitation of this study; however, a double-blind placebo-controlled randomization design renders it unfeasible to allocate a group of participants into a nonintervention group. What is more, for most patients presenting with knee OA, nonintervention may be an unacceptable option and may lead to dropouts. A nonintervention group may not even be necessary as double-blind randomization minimizes bias and statistical analysis attempts to ascertain to what degree the changes seen in study samples could be ascribed to random change alone. Dose, intensity, mode, or application techniques may influence cartilage repair effect of US. The duration and severity of OA also may be the factors influence effect of US on cartilage. New studies are needed to investigate optimal dose and application techniques.

## Conclusion

The current study revealed that US is safe and effective treatment modality in pain relief and improvement of function in patients with knee OA; however, we did not find any positive effects of US on cartilage repair which may due to frequency, duration, dose, and intensity of therapeutic US we used. We need new studies that compare different application parameters of US to establish the optimal dose and treatment period.

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### Conflicts of interest

There are no conflicts of interest.

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