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Original Article

Effects of low-intensity pulsed ultrasound on the infrapatellar fat pad in knee osteoarthritis: a randomized, double blind, placebo-controlled trial

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Abstract. [Purpose] We investigated the effects of low-intensity pulsed ultrasound (LIPUS) irradiation of the infrapatellar fat pad (IFP) combined with therapeutic exercise for management of knee osteoarthritis (knee OA). [Participants and Methods] The study included 26 patients with knee OA, who were randomized into the LIPUS group (patients underwent LIPUS+therapeutic exercise) and the therapeutic exercise group (patients underwent sham LIPUS+therapeutic exercise). We measured changes in the patellar tendon–tibial angle (PTTA) and in IFP thickness, IFP gliding, and IFP echo intensity after 10 treatment sessions to determine the effects of the aforementioned interventions. We additionally recorded changes in the visual analog scale, Timed Up and Go Test, the Western Ontario and McMaster Universities Osteoarthritis Index, and Kujala scores, as well as range of motion in each group at the same end-point. [Results] Compared with patients in the therapeutic exercise group, those in the LIPUS group showed significant post-treatment improvements in PTTA, VAS, and Kujala scores, as well as in range of motion. [Conclusion] The combined use of LIPUS irradiation of the IFP and therapeutic exercise is a safe and effective modality to reduce IFP swelling, relieve pain, and improve function in patients with knee OA.
Key words: Low-intensity pulsed ultrasound (LIPUS), Knee osteoarthritis, Adipose tissue

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INTRODUCTION

Knee osteoarthritis (knee OA) is the most common articular disorder characterized by pain and decreased function. In addition to functional decline, inhibition of Activities of Daily Living (ADL)[1] and decline in quality of life (QOL)[2] have also been reported. Conservative treatment of knee OA often includes physical therapy, orthosis, and therapeutic exercise, which is recommended in guidelines[3–5]. Ultrasound (US) therapy, a type of physical therapy, is also often used in clinical practice because it improves knee OA pain[6] and increases range of motion[7] by both thermal and non-thermal mechanisms

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(mechanical effects). Recent systematic reviews and meta-analyses suggest that pulsed US is superior to continuous wave in improving function[8], and that low-intensity pulsed US (LIPUS) is effective in improving knee function[9].

Low-intensity pulsed US therapy is a type of US therapy that uses a low intensity pulsed wave to stimulate a fracture and promote bone union. There have been positive reports on the effect of LIPUS on bone union[10–12], but there have also been negative reports in recent systematic reviews that concluded it has no effect on bone healing[13, 14]. Consequently, the effect of LIPUS on fracture treatment still needs to be discussed. Other effects of LIPUS, such as reduced inflammation[15], improved soft tissue microcirculation[16], increased expression of vascular endothelial growth factor (VEGF)[17], and improved hypoxic conditions[18] have also been reported. In a meta-analysis, the pain-relieving effect of LIPUS and improvements in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were reported[8]. In addition, physical therapy and therapeutic exercise are often used together in the clinical environment. In our systematic review of the combined effect of LIPUS and therapeutic exercise on knee OA, the effectiveness of LIPUS and therapeutic exercise was not confirmed. The reason for this is that the irradiation site and intensity were not consistent. Therefore, it is necessary to identify an effective irradiation site and intensity.

In recent years, the infrapatellar fat pad (IFP) has been attracting attention as a cause of pain in knee OA. The IFP is thought to play a role in supplying blood to the patellar tendon[19], regulating the inflammatory response around the knee[20] as a source of cytokines, absorbing shock during knee joint movement, and protecting tissues[21]. In a study using magnetic resonance imaging (MRI), it was reported that the volume of articular cartilage decreased and the volume of the IFP increased in knee OA[22]. In the IFP of patients with knee OA, repeated mechanical stress may cause bleeding and inflammation, resulting in fibrosis[23]. In other words, IFP dysfunction due to swelling and fibrosis is considered to be the cause of the onset of pain in knee OA. However, while there are some reports of morphological and histological changes in the IFP associated with knee OA, no effective treatment for IFP pathology can be confirmed.

Consequently, the purpose of this study was to verify the combined effect of LIPUS applied to the IFP together with therapeutic exercise with adjusted settings, focusing on the IFP, which is attracting attention as the causative tissue of knee pain in OA.

PARTICIPANTS AND METHODS

From July 2019 to October 2020, 26 out of 26 patients who visited an orthopedic clinic in Toyama Prefecture, Japan due to medial knee joint pain, with 26 knees that met the criteria, were targeted. The inclusion criteria were: age ≥45 years, with a diagnosis of knee OA based on physical and X-ray findings by one doctor, and with no anterior or medial knee joint pain. Exclusion criteria were: patellar tendonitis, rheumatoid arthritis, gouty arthritis, infectious arthritis, history of artificial knee joint replacement, history of nonsteroidal anti-inflammatory drug (NSAID) use, inhibition of exercise. Anyone with symptoms of gout, those who had undergone physical therapy or acupuncture in the preceding 6 months, or those who had used steroids orally or intra-articularly, were also excluded.

This single-center, prospective randomized placebo-controlled clinical trial was approved by the Ethical Review Board of Morinomiya University of Medical Sciences, on July 4, 2019 (approval no. 2019-035), and was conducted at the Clinic, Toyama city, Toyama prefecture, Japan between July 2019 and October 2020. The trial was also registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR ID: UMIN000038501). The study was explained to all participants, and all signed written informed consent.

This study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement[24]. The outline of this study procedure is shown in Fig. 1. All participants were randomly assigned at a 1:1 ratio into either the LIPUS group (LIPUS + therapeutic exercise) or the therapeutic exercise group (sham LIPUS + therapeutic exercise) in a double-blinded manner. Random numbers were generated on a computer and randomized using a random number table. The random number table was kept by the assigner, and participants, researchers, and outcome evaluators were blinded to treatment assignments during the study. In addition, treatment assignments were not disclosed when researchers collected and analyzed the data.

For all participants, quadriceps femoris muscle-strengthening exercise[25, 26] and hip abductor muscle-strengthening exercise[26] were advised as general exercise therapy for knee OA. The quadriceps muscle-strengthening exercise was performed in the supine position and used straight leg raising (SLR). Participants raised their heels 10 cm above the floor, held the position for 5 seconds, and then slowly lowered the leg (20 times; 1 set twice a day). In addition, isometric muscle-strengthening exercise (quadriceps femoris setting) of the quadriceps femoris was performed for 5 seconds in the knee joint extension position (20 times, 1 set twice a day). The hip abduction muscle-strengthening exercise was performed in the lateral decubitus position, with the participant slowly lifting their leg straight to the side of the body until level with the hip, holding it for 5 seconds, and then slowly lowering it.

A PHYSIO SONO (P-SONO, Sakai Medical. Co., Ltd., Tokyo, Japan) was used for LIPUS. In the LIPUS group, the knee was flexed 90° and a LIPUS probe was placed on the patellar tendon (Fig. 2). LIPUS was applied at a frequency of 3 MHz[27, 28] and an average spatial and temporal intensity of 120 mW/cm^2[2, 28–30] was applied for 20 minutes[28, 29], twice a week, a total of 10 times. The therapeutic exercise group went through the same procedure as for LIPUS but received no

irradiation. Therefore, participants and measurers were double-blinded so that they could not tell whether the participants were in the LIPUS group or the therapeutic exercise group. All treatments were performed on an outpatient basis.

The main outcomes were IFP functions: patellar tendon–tibial angle (PTTA), gliding, changes in thickness and echo intensity (histogram) of the IFP as an indicator of IFP fibrosis. IFP function was measured using a US diagnostic imaging system. US was performed in B mode using a 4 to18 MHz linear transducer (SNiBLE; Konica Minolta Inc., Tokyo, Japan). The patellar tendon and tibia were extracted and the angle between the lower end of the patellar tendon and the tibia (PTTA) was measured using the US measurement processing function (Fig. 3). Measurement of limb position was performed in the supine position, and knee flexion (KF) was measured in limb positions of 10°, 90°, and 120°. Gliding was calculated from the amount of change in the PTTA (KF 10° to 90° and KF 90° to 120°)[31]. In addition, the echo intensity (histogram) of the IFP was also measured using US[32]. For the rate of change in IFP thickness, the thickness of the superficial part of the IFP at knee flexion of 10° and 90° was measured in the sitting position according to the method described in a previous study[33]. The rate of change in IFP thickness between the two knee flexion angles was calculated.

Secondary outcomes were the visual analogue scale (VAS) for pain during walking, knee extension and flexion angle, knee extension strength, walking speed and locomotion ability (Timed Up & Go Test; TUG), and locomotion ability (Two-step test), QOL scale, WOMAC score, and Kujala score (KS). The VAS instrument consisted of a 10-cm horizontal line, the right end (0 cm) indicating very severe pain, and the left end (10 cm) indicating no pain[34]. Passive maximum flexion and maximum extension of the knee joint were measured using a goniometer with the participants in the supine position. Knee extension muscle strength was measured by isometric contraction using a Weltonic WTS-02 (Minato Medical Science Co. Ltd., Osaka, Japan). The TUG test measures the time it takes a participant to stand up from a chair, walk comfortably and

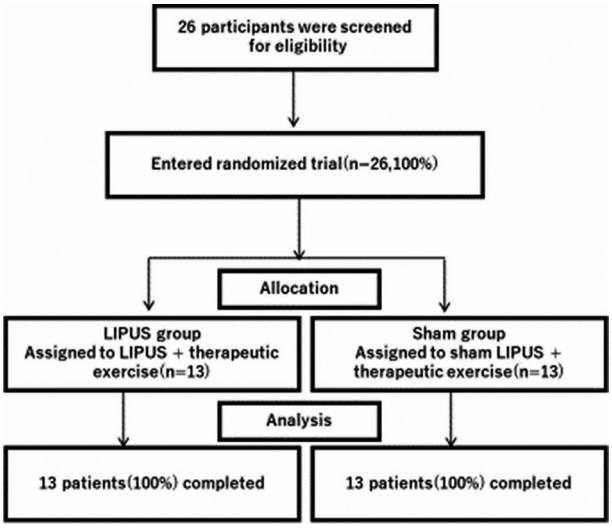

Fig. 1. CONSORT diagram showing the disposition of patients.
CONSORT: Consolidated Standards of Reporting Trials; LIPUS: low-intensity pulsed ultrasound.

Fig. 2. Application site of LIPUS. The LIPUS probe was placed just above the patellar tendon.

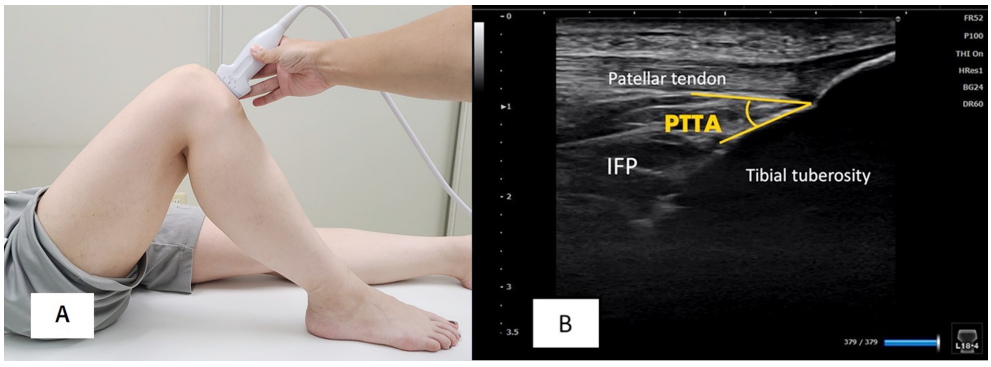

Fig. 3. A; Position of probe. B; Patellar tendon tibia angle (PTTA).
IFP: infrapatellar fat pad.

safely 3 meters, and then sit back in the chair again. The time it took participants to complete this task was measured with a stopwatch timed in 1/100 second increments by evaluators. The TUG test was administered twice and the average of the two recorded trials was used in data analysis. In the Two-step test[35], participants were instructed to align both toes to the starting line, walk two steps forward, taking as large strides as possible, and align both feet together. Participants were instructed to repeat the task if the other leg touched the floor or the tested leg wavered. The evaluator measured the length of the two steps and calculated the Two-step value (the ratio of the maximum length of the two steps to the height of the participants).

Outcomes were measured before treatment and at the end of the intervention (10th intervention).

A preliminary study was performed and sample size was calculated using G*power 3.1.9.7[36] (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Each group needed to contain at least 13 knees to identify differences between the groups.

Statistical analysis was performed using SPSS version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA). The Shapiro–Wilk test was used to confirm the normality of the main and secondary outcomes. All outcomes before treatment and after the 10th intervention were compared between groups using unpaired t-tests and the Mann–Whitney U test. The significance level was less than 5%. In the unpaired t-test, the t-value and the degree of freedom (df) were used, and the effect size r was calculated for each item from the following formula.

$$r = \sqrt{\frac{t^2}{t^2 + df}} \qquad (1)$$

The effect size r in the Mann–Whitney U test was calculated by converting each test statistic into Z and using the following formula based on the sample size (N).

$$r = Z/\sqrt{N} \qquad (2)$$

RESULTS

Twenty-six knee OA patients were screened for eligibility. All recruits participated in the study and were randomized. Participants were randomly assigned to the LIPUS group (n=13) or the exercise therapy group (n=13). All 26 completed a double-blind study. No adverse events due to LIPUS were reported in either group. The physical characteristics and clinical findings of the participants are listed in Table 1. There were no significant differences in height/weight/body mass index (BMI) between the LIPUS group and the exercise therapy group ($p>0.05$). However, the mean age of the LIPUS group was higher than that of the exercise therapy group ($p<0.05$).

For baseline comparisons, the main outcomes showed no significant differences in PTTA, brightness, or IFP thickness changes at any angle. On the other hand, there was no significant difference in gliding performance between KF 10° and 90°, but gliding performance in the exercise therapy group was significantly greater between KF 90° and 120° ($p<0.05$) (Table 2). Regarding secondary outcomes, there were no significant differences in VAS, knee range of motion, knee extension muscle strength, TUG, two-step test, WOMAC, or KS (Table 3).

At the 10th intervention, PTTA was significantly smaller in the LIPUS group at all angles ($p<0.01$). There were no significant differences in any other outcomes (Table 2).

In the comparison between the groups after the 10th intervention, the VAS score and KS were significantly improved in the LIPUS group compared to the exercise therapy group ($p<0.01$). In addition, the range of motion of the knee joint in extension was increased in the LIPUS group compared to the exercise therapy group after the 10th intervention ($p<0.05$). There were no significant differences in other outcomes (Table 3).

Table 1. Baseline demographic and clinical characteristics

Variable	LIPUS + Therapeutic exercise	Sham LIPUS + Therapeutic exercise
n	13	13
Gender (male/female)	3/10	2/10
Age (years)	63.5 ± 8.6	56.5 ± 7.5
Height (cm)	158.3 ± 8.7	158.8 ± 6.0
Weight (kg)	66.2 ± 9.7	60.5 ± 13.9
BMI (kg/m^2)	26.5 ± 4.3	24.0 ± 5.2
Kellgren & Lawrence class rating		
Grade II	13 (100%)	13 (100%)

Data are expressed as mean ± SD. LIPUS: low-intensity pulsed ultrasound; BMI: body mass index; SD: standard deviation.

Table 2. Main outcome

Variable	Baseline		After 10 treatments		
	LIPUS	Therapeutic exercise	LIPUS	Therapeutic exercise	Effect size
PTTA KF10, degrees	39.2 ± 4.0	40.8 ± 9.3	35.1 ± 4.0	39.4 ± 6.1**	0.397
PTTA KF90, degrees	18.8 ± 5.5	21.5 ± 6.6	13.4 ± 4.8	19.7 ± 4.7**	0.569
PTTA KF120, degrees	13.8 ± 5.2	14.2 ± 5.2	6.7 ± 3.6	13.2 ± 5.0**	0.614
Gliding KF10-90, degrees	20.4 ± 5.8	19.3 ± 7.3	21.7 ± 5.5	19.7 ± 4.5	0.202
Gliding KF 90-120, degrees	5.0 ± 3.4	7.2 ± 2.9*	6.7 ± 3.0	6.5 ± 4.0	0.033
Echo intensity 10	84.0 ± 15.4	92.9 ± 15.1	82.0 ± 20.0	89.2 ± 14.2	0.211
Echo intensity 90	78.5 ± 14.4	80.9 ± 12.7	71.6 ± 14.5	81.3 ± 15.9	0.315
Echo intensity 120	85.8 ± 16.1	87.0 ± 14.6	79.7 ± 16.3	86.5 ± 14.3	0.224
Thickness change ratio	130.0 ± 20.0	130.0 ± 20.0	150.0 ± 40.0	140.0 ± 20.0	0.232

Data expressed as mean ± SD. LIPUS: low-intensity pulsed ultrasound; PTTA: patellar tendon tibial angle; KF: knee flexion; SD: standard deviation.
*p<0.05, **p<0.01.

Table 3. Secondary outcomes

Variable	Baseline		After 10 treatments		
	LIPUS	Therapeutic exercise	LIPUS	Therapeutic exercise	Effect size
VAS, cm	5.3 ± 2.3	5.2 ± 2.2	0.8 ± 0.8	3.5 ± 2.8**	0.671
ROM flexion, degrees	139.1 ± 9.9	138.8 ± 6.8	145.1 ± 8.2	140.8 ± 8.7	0.252
ROM extension, degrees	−8.4 ± 5.5	−8.8 ± 4.6	−3.2 ± 3.7	−7.6 ± 3.4**	0.531
Muscle strength, N	249.2 ± 82.6	253.8 ± 103.7	361.5 ± 125.8	292.3 ± 99.8	0.302
TUG, sec	8.4 ± 1.2	8.9 ± 4.0	7.1 ± 1.2	7.6 ± 1.4	0.189
Two-step test	1.0 ± 0.1	0.9 ± 0.1	1.1 ± 0.1	1.0 ± 0.2	0.313
WOMAC	23.0 ± 13.5	20.6 ± 13.0	6.8 ± 6.9	7.2 ± 4.7	0.106
KS	68.6 ± 13.0	68.0 ± 16.0	91.4 ± 10.8	74.2 ± 15.8**	0.499

Data are expressed as mean ± SD. LIPUS: low-intensity pulsed ultrasound; VAS: visual analog scale; ROM: range of motion; TUG: timed up and go test; WOMAC: Western Ontario and McMaster Universities osteoarthritis index; KS: Kujala score; SD: standard deviation.
*p<0.05, **p<0.01.

DISCUSSION

The purpose of this study was to examine the combined effect of LIPUS and exercise therapy with adjusted settings by irradiating the IFP in patients with knee OA. The results showed that between the two groups after the 10th intervention, the LIPUS group had reduced PTTA at all angles of the knee joint compared to the exercise therapy group. In addition, it was revealed that VAS, knee joint extension angle, and KS were all improved.

Recently, the efficacy of LIPUS alone for knee OA has been reported[8]. On the other hand, the combined effect is controversial. Huang et al. used LIPUS at a mean temporal and spatial intensity of 500 mW/cm^2 three times a week for 8 weeks in the medial collateral ligament, anserine, and popliteal region in addition to therapeutic exercise, and reported that the combined LIPUS and therapeutic exercise group improved VAS and walking speed compared with the therapeutic exercise alone group[37]. Yildiz et al. reported that the group that received LIPUS irradiation to the anterior, medial, and lateral knee joints at an average temporal and spatial intensity of 300 mW/cm^2 five times a week for a total of two weeks in addition to therapeutic exercise had improved VAS compared to the therapeutic exercise alone group[38]. On the other hand, Cakir et al. reported no effect on VAS after irradiating the painful area with LIPUS at a mean temporal and spatial intensity of 250 mW/cm^2 five times a week for a total of two weeks in addition to quadriceps training, comparing the irradiated and non-irradiated groups[39].

In other words, there was a problem that the irradiation site, irradiation intensity, and frequency were not constant in previous studies. Furthermore, pain, walking speed, and QOL were used as outcomes, but functional evaluations such as knee joint range of motion were insufficient. Kitagawa et al. reported that LIPUS irradiation of IFP in a rat model of knee OA suppressed the activity of the transcription factor HIF-1α, which is activated during hypoxia, and suppressed fibrosis of IFP[28]. Therefore, in the present study, LIPUS was performed on IFP in a similar setting. As a result, changes were observed

in knee pain, extension limitation, and PTTA. In other words, this is the first study to demonstrate that LIPUS combined with exercise therapy for IFP improves functional impairment of knee OA.

The effects of LIPUS are known to be anti-inflammatory[15] and to suppress the expression and transcriptional activity of hypoxia-inducible factors[28]. We hypothesized that inflammation of the synovial membrane and increased transcriptional activity of hypoxia-inducible factors would promote fibrosis of IFP and decrease the amount of change in PTTA, which we considered an index of IFP gliding properties. However, the amount of change in PTTA did not change before and after treatment. The PTTA is the angle between the inferior border of the patellar tendon and the tibia. A decrease in PTTA may reflect a reduction in IFP swelling and anterior migration of the tibia. These possibilities are considered in the present results, as pain and limitation of extension were improved. However, the present study could not address what PTTA reflects, and future studies are needed.

No side effects or adverse events of LIPUS have been reported so far, and no adverse events occurred during or after LIPUS in this study. Therefore, it is suggested that LIPUS is very safe as a treatment method for knee OA. In addition, it can be an effective treatment method that can be performed without joint movement even for knee OA patients who experience strong pain during joint movement.

This study has some limitations. First, participants in this study were enrolled from a single institution and the sample size was small. Therefore, a larger population and multicenter clinical trials are needed. Second, age matching between the LIPUS group and the therapeutic exercise group could not be performed. It may therefore be necessary to adjust the age and conduct randomized controlled trials. Third, outcomes were evaluated only at the end of treatment, and outcomes could not be evaluated with a follow-up period after the intervention. Knee OA is a chronically advanced disease that can exacerbate symptoms and requires follow-up outcome assessment.

Conflict of interest

None of the authors has any conflict of interest to declare.

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