Ultrasonographic echo intensity in the medial femoral cartilage is enhanced prior to cartilage thinning in women with early mild knee osteoarthritis

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Abstract

Purpose: We aimed to determine whether altered cartilage echo intensity is associated with knee osteoarthritis (OA) severity and whether the alteration occurs before thinning of the femoral cartilage in knee OA.

Methods: The medial femoral cartilage thickness and echo intensity of 118 women aged ≥50 years were assessed using an ultrasound imaging device. Based on the Kellgren–Lawrence (KL) grade and knee symptoms, participants were classified into five groups: control (asymptomatic grades 0–1), early OA (symptomatic grade 1), grade 2, grade 3, and grade 4. Analysis of covariance, with adjusted age and height, and the Sidak post hoc test were used to assess the differences in cartilage thickness and echo intensity in knees with varying OA severity.

Results: The echo intensity on longitudinal images, equivalent to the tibiofemoral weight-bearing surface, was significantly higher in the grade 2 group than that in the control group ($p = 0.049$). However, no significant difference was noted in cartilage thickness (n.s.). In the grades 3 and 4 groups, cartilage thickness became thinner as OA progressed ($p < 0.001$ and $p < 0.001$, respectively). However, the cartilage echo intensity was not significantly enhanced compared with that of the grade 2 group (n.s.). There were no significant differences in the cartilage thickness and echo intensity between the early OA and control groups on the longitudinal images (n.s.).

Conclusions: The echo intensity of the medial femoral cartilage was high in patients with KL grade 2, without decreased thickness. Our findings suggested that higher echo intensity is a feature of early cartilage degeneration in mild knee OA. Further studies are needed to establish this feature as a useful screening parameter of early cartilage degeneration in knee OA.

Level of evidence: Level Ⅲ

Keywords

Knee; osteoarthritis; cartilage; echo intensity; thickness; ultrasound; degeneration

Introduction

Knee osteoarthritis (OA) is a chronic disease characterized by cartilage degeneration, which begins prior to symptom onset [8, 18, 22]. The cartilage in the knee typically becomes thinner as OA progresses [23]. However, in the early stages of OA, even without observable cartilage thinning, there is a decline in cartilage quality; this includes proteoglycan loss, change in the collagen fiber orientation, and increase in the water content [6, 7]. Thus, to detect cartilage degeneration in the early stages of knee OA, it is necessary to assess the cartilage quality in addition to its quantity.

Although magnetic resonance imaging (MRI) with T2 or T1ρ mapping is a well-established method for assessing early cartilage degeneration in knee OA [1, 6, 9], more accessible and inexpensive methods are required [19]. Cartilage echo intensity measurement using B-mode ultrasonography has attracted attention as a potential qualitative indicator of degeneration. One study determined that increased echo intensity is a feature of early cartilage degeneration in patients with knee OA [14]. Another study identified low-echo intensity in the cartilage of young participants with arthroscopically confirmed cartilage damage after anterior cruciate ligament injury than in the cartilage of healthy young participants [3]. However, to the best of our knowledge, no study has quantified both cartilage thickness and echo intensity for each grade of knee OA severity. It is necessary to determine the echo intensity associated with cartilage degeneration and whether this alteration is an indicator of early cartilage degeneration prior to cartilage thinning. Determining echo intensity could be a foothold to establishing a useful clinical screening parameter of early cartilage degeneration prior to cartilage thinning in knee OA.

We aimed to determine how cartilage echo intensity differs with knee OA severity and whether medial femoral cartilage echo intensity is altered prior to its thinning. We hypothesized that the cartilage echo intensity in patients with early mild knee OA is more enhanced than that in healthy controls and occurs before cartilage thinning.

Material and Methods

A total of 126 women aged ≥50 years, who lived independently, and who could visit the research facilities were recruited from two community orthopedic clinics and local communities in Kyoto and other peripheral cities. The exclusion criteria were as follows: (1) history of surgery of the lower limbs, (2) lateral knee OA, (3) rheumatoid

arthritis, and (4) cardiovascular and neurological diseases. Additionally, patients in whom all measurements could not be obtained were excluded. Finally, 118 individuals were included in our analyses (age, 71.9±8.9 years; height, 154.3±5.9 cm; body weight, 54.9±9.2 kg; and body mass index [BMI], 23.0±3.4 kg/m^2).

Knee radiographs were obtained in the standing position, and the OA severity of the tibiofemoral joint was determined by two orthopedic surgeons using the Kellgren–Lawrence (KL) grading scale. To determine the interobserver reliability of this assessment, a pilot study was conducted with 10 patients who were selected randomly from the study participants. The kappa coefficient of the two surgeons was 0.73, confirming substantial interobserver reliability [5]. Intraobserver reliability of these orthopedic surgeons had already been confirmed in a previous study [24]. Ultrasonographic variables were measured in the right knee for participants without radiographic evidence of OA and in the knee with a greater KL grade on radiographs with evidence of OA. If the KL grades were the same, the variables on the more painful side were measured.

All participants provided written informed consents after a study overview was provided. This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine (R3014) and was conducted in accordance with the principles of the Declaration of Helsinki.

1. Assessment of the knee symptoms and classification of the OA severity

The knee symptoms were assessed using the Knee Society Score 2011 Japanese Edition (KSS symptom score) [16, 21]. The KSS symptom score consists of questions on knee pain during walking and climbing stairs and knee stiffness. The scores range from 25 to 0, with lower scores indicating more severe pain or stiffness. A score of 23 or higher was defined as asymptomatic[20].

Based on the KL grade and KSS symptom score, participants were classified into five groups: control (asymptomatic KL grades 0–1), early OA (symptomatic KL grade 1), grade 2 (KL grade 2), grade 3 (KL grade 3), and grade 4 (KL grade 4).

2. Measurement of knee range of motion

The knee range of motion (ROM) was measured in the supine position using a goniometer. The angle was measured between a line connecting the greater trochanter and lateral condyle of the femur and a line connecting the head of the fibula and lateral malleolus in 1° increments.

3. Ultrasound imaging of the medial femoral cartilage

B-mode images of the medial femoral cartilage were obtained using an ultrasound imaging device, with a 5–18 MHz linear transducer (Noblus; Hitachi Aloka Medical Systems, Tokyo, Japan). After the participants had rested in the supine position for 15 min, longitudinal and transverse B-mode images of the femoral cartilage were acquired at maximum knee flexion (Fig.1). The same examiner performed the ultrasonographic examination in all patients. The longitudinal images captured at maximum knee flexion were used to assess the tibiofemoral weight-bearing surface [11]. The transverse images above the patella were used to assess the femoral trochlea within the patellofemoral joint [3]. The probe was placed at a point midway between the medial patellar edge and medial femoral epicondyle when assessing the longitudinal images [15]. The probe was placed in line with the medial and lateral femoral condyles above the superior patellar edge when assessing the transverse images [2]. Before capturing the images, the probe tilt was adjusted to ensure that the two white bands (the synovium–cartilage and cartilage–bone interfaces) were sharp. The measurement reliability was evaluated in 10 older women randomly selected from among the study participants (age, 74.7±8.4 years; height 152.0±4.6 cm; weight, 55.5±4.6 kg; BMI, 24.0±1.8 kg/m^2; and KL grades: grade 1, n=4; grade 2, n=2; grade 3, n=1; and grade 4, n=2). The two examiners were blinded to the degree of cartilage degeneration. We used a free software to generate random numbers for the selection of the pilot study participants. The longitudinal and transverse B-mode images of the femoral cartilage were acquired the same way as that used in the main experiment. The same procedures were repeated twice, with the probe away from the knee. Intraclass coefficients (ICC [1,1] and ICC [2,1]) were calculated for the longitudinal and transverse image ultrasonographic variables [4]. The ICCs (1,1) of the cartilage thickness were 0.99 and 0.97 in the longitudinal and transverse images, respectively, and those of the cartilage echo intensity were 0.95 and 0.99, respectively. The ICCs (2,1) of the cartilage thickness were 0.92 and 0.83 in the longitudinal and transverse images, respectively, and those of the cartilage echo intensity were 0.81 and 0.88, respectively. This validated acquiring only one femoral cartilage image in the main study.

4. Ultrasonographic image analysis

All the images were analyzed using Image J (https://imagej.nih.gov/). An examiner, who had not performed any measurements and was blinded to the OA severity, evaluated the cartilage thickness and echo intensity. The cartilage was manually segmented in the transverse images above the patella [3], and the medial compartment alone was analyzed.

The average distance between the synovium-cartilage and cartilage-bone interfaces at three random points was calculated as the cartilage thickness in each image [15]. To calculate the cartilage echo intensity, the region of interest in the cartilage band was magnified; interfaces with other tissues or blurry areas were excluded. The signal intensity ranged from 0 (black) to 255 (white), and the average signal intensity was calculated as the echo intensity [12]. The cartilage thickness and echo intensity were calculated using the longitudinal and transverse images.

Statistical analysis

The required sample size of patients for comparing the ultrasonographic femoral cartilage variables among knee OA of varying severities using one-way analysis of covariance (ANCOVA) ($\alpha = 0.05$, power = 0.80, and effect size F-value = 0.40) was calculated using G*Power (version 3.1; Heinrich Heine University, Düsseldorf, Germany). The required sample size was 111.

All statistical analyses were performed using IBM SPSS Statistics version 22(IBM SPSS, Armonk, NY, USA). First, analysis of variance and the Sidak post hoc test were used to compare the physical characteristics between the groups. Second, ANCOVA, with adjusted age and height, and the Sidak post hoc test were used to determine the differences in thickness and echo intensity of the medial femoral cartilage between the groups. The statistical significance of all analyses was set at 5%.

Results

The study participants were classified as follows: 18, 12, 39, 24, and 25 in the control, early OA, grade 2, grade 3, and grade 4 groups, respectively. There were significant differences in the participants' demographic characteristics, such as age, weight, and knee ROM, between the groups (Table 1).

The unadjusted results for cartilage thickness and echo intensity for each group are shown in Figure 2, and the results of the ANCOVA with adjusted age and height are shown in Table 2. The ANCOVA results revealed significant main effects of the groups on all ultrasonographic variables, excluding echo intensity in the transverse images above the patella. The Sidak post hoc analysis of the cartilage on the longitudinal images indicated that the cartilage thicknesses of participants in the grades 3 and 4 groups were thinner than those of the participants in the control and early OA groups. Additionally, patients of the grade 4 group had thinner cartilages than those in the grade 2 group. On the transverse images above the patella, participants in the grades 2, 3, and 4 groups had thinner cartilages than those in the control group. Additionally, participants in the grade 4 group had thinner cartilages than those in the other groups.

The post hoc analysis of the cartilage echo intensity on the longitudinal images revealed that the cartilage echo intensity of the participants in the grades 2, 3, and 4 groups was higher than that of those in the control group, and the cartilage echo intensity of the grade 3 group was higher than that of the early OA group. The detailed the post hoc test results are shown in Supplemental File 1.

Discussion

The most important finding of our study was that the medial femoral cartilage echo intensity was enhanced in patients with early mild knee OA before cartilage thinning had begun. Our results differed between the longitudinal images, representative of the tibiofemoral weight-bearing surface, and the transverse images above the patella, representative of the femoral trochlea within the patellofemoral joint. The cartilage echo intensity on longitudinal images was higher in patients with knee OA (KL grades 2–4) than in asymptomatic patients with KL grades 0–1. Furthermore, the echo intensity was enhanced even in participants with mild OA severity (KL grade 2) without cartilage thinning. However, the cartilage echo intensity on transverse images showed no significant differences despite cartilage thinning in patients with mild-to-severe knee OA.

Although only participants with KL grades 3 and 4 OA had thinner cartilages than those in the control group on longitudinal images, the echo intensity was higher than that of the control group even in participants with KL grade 2. Cartilage quality decreases with progression of knee OA severity [6, 7]. In addition, quantitative magnetic resonance imaging (T2 mapping) confirms that the cartilage in KL grade 2 knee OA has increased water content, which is characteristic of the loss of cartilage quality [6]. Conversely, the cartilage volume decreases in the mid-severe knee OA [1] but not in patients with KL grade 2 OA [13] Collectively, these results indicate that enhanced echo intensity could be a feature of cartilage quality loss and can be detected before cartilage thinning begins.

The medial femoral cartilage echo intensity on longitudinal images was higher in patients with knee OA (KL grades 2-4) than in those with asymptomatic healthy control, which supported our hypothesis. These results are in accordance those of a previous study whose evaluation criterion adopted increased echo intensity as a characteristic findings of early cartilage degeneration [14]. Conversely, another study, which compared the femoral cartilage of young participants after anterior cruciate ligament injury with those of healthy participants, reported that decreased echo intensity was a feature of cartilage degeneration [3]. However, healthy cartilage is almost anechoic [10]; thus, cartilage degeneration is unlikely to lower echo intensity. This discrepancy between our and the previous studies [3] may be attributed to the difference in the participants' age or pathogenesis of the cartilage damage.

No significant difference was noted in the cartilage echo intensity in knees of varying OA severities on transverse images above the patella. Stefanik et al. [17] showed that the progression of cartilage degeneration differs between the tibiofemoral and patellofemoral joints. In this study, as we classified participants based on their tibiofemoral OA severity, participants with different patellofemoral joint OA severity might belong to the same groups. Thus, further studies are needed to evaluate the association between cartilage degeneration and echo intensity when participants are classified based on their patellofemoral OA severity.

This study had some limitations. First, we could not determine the cut-off value of cartilage echo intensity to diagnose cartilage degeneration. This is because echo intensity varies based on device settings, such as frequency, gain, and focus. Second, we could only partially unify the cartilage assessment location because of variations in the maximum knee flexion angle between participant. However, no participant in our study had severe loss of knee flexion. Thus, our results might reflect the variations of the measured cartilage portion, as well as the association between cartilage degeneration and knee OA severity. Finally, the participants in this study were only middle-aged and older women with medial knee OA. Further studies are required to determine whether our study results can be applied to other populations, including men, patients with lateral knee OA, and patients with severely limited knee flexion.

Our results have potential clinical relevance. The association between enhanced echo intensity and knee OA severity that was determined in our study suggests that echo intensity may be a useful screening indicator of cartilage condition. Enhanced echo intensity was observed even in patients with KL grade 2 knee OA without decreased thickness, and the degenerated cartilage could be easily distinguished from the healthy cartilage. Thus, ultrasonographic echo intensity of the cartilage would be a useful alternative to MRI scans for the detection of early cartilage degeneration in daily clinical practice. After establishing an echo intensity cut-off to definitively detect cartilage degeneration, our findings would become a significant contribution to the early detection of cartilage degeneration in knee OA.

Conclusions

Echo intensity in the medial femoral cartilage was high in patients with KL grade 2 knee OA without decreased cartilage thickness. These findings suggest that higher echo intensity may be a feature of early cartilage degeneration in mild knee OA. However, further studies are required to determine whether this feature can be used a useful screening parameter of early cartilage degeneration in knee OA.

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Tables

Table 1 Participant demographic characteristics

	Age, y			Height, cm			Weight, kg			Knee ROM, °		
Control	68.3±11.0	vs eOA	n.s.	154.3±5.9	vs eOA	n.s.	47.8±4.5	vs eOA	n.s.	151.0±6.0	vs eOA	n.s.
		vs 2	n.s.		vs 2	n.s.		**vs 2**	**p=0.033**		vs 2	n.s.
		vs 3	n.s.		vs 3	n.s.		**vs 3**	**p=0.014**		**vs 3**	**p=0.001**
		vs 4	**p=0.045**		vs 4	n.s.		**vs 4**	**p=0.008**		**vs 4**	**p<0.001**
Early OA	66.3±11.4	vs 2	n.s.	153.4±4.0	vs 2	n.s.	54.8±8.9	vs 2	n.s.	146.4±6.5	vs 2	n.s.
		vs 3	n.s.		vs 3	n.s.		vs 3	n.s.		vs 3	n.s.
		vs 4	**p=0.018**		vs 4	n.s.		vs 4	n.s.		**vs 4**	**p<0.001**
Grade 2	72.4±8.4	vs 3	n.s.	155.0±5.7	vs 3	n.s.	55.3±8.7	vs 3	n.s.	145.4±7.4	vs 3	n.s.
		vs 4	n.s.		vs 4	n.s.		vs 4	n.s.		**vs 4**	**p<0.001**
Grade 3	72.6±7.3	vs 4	n.s.	155.3±5.5	vs 4	n.s.	56.8±9.7	vs 4	n.s.	140.3±7.4	**vs 4**	**p<0.001**
Grade 4	75.9±8.9	-		152.6±7.1	-		57.2±10.5	-		129.2±11.3	-	
Total	71.9±8.9			154.3±5.9			54.8±9.3			141.9±11.1		

Data are presented as mean ± standard deviation. Bold text indicates a significant difference in the Sidak post hoc test.

OA: osteoarthritis, ROM: range of motion, eOA: early OA, 2: grade 2, 3: grade 3, 4: grade 4, n.s.: not significant

Table 2 Comparison of the femoral cartilage ultrasonographic outcomes between knees with varying OA grades

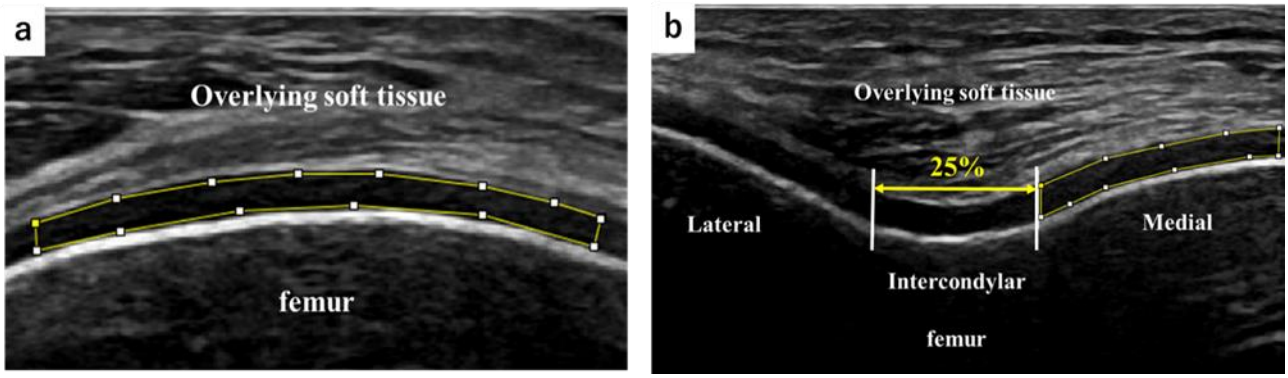
	LS thickness, mm			LS echo intensity, a.u.			ST thickness, mm			ST echo intensity, a.u.		
Control	1.4±0.1	vs eOA	n.s.	23.5±2.4	vs eOA	n.s.	1.6±0.1	vs eOA	n.s.	26.5±2.4	vs eOA	n.s.
		vs 2	n.s.		**vs 2**	**p=0.049**		**vs 2**	**p=0.02**		vs 2	n.s.
		vs 3	**p=0.001**		**vs 3**	**p=0.001**		**vs 3**	**p=0.04**		vs 3	n.s.
		vs 4	**p<0.001**		**vs 4**	**p=0.009**		**vs 4**	**p<0.001**		vs 4	n.s.
Early OA	1.4±0.1	vs 2	n.s.	24.5±3.0	vs 2	n.s.	1.5±0.1	vs 2	n.s.	29.7±2.9	vs 2	n.s.
		vs 3	**p=0.003**		**vs 3**	**p=0.015**		vs 3	n.s.		vs 3	n.s.
		vs 4	**p=<0.001**		vs 4	n.s.		**vs 4**	**p<0.001**		vs 4	n.s.
Grade 2	1.2±0.1	vs 3	n.s.	31.9±1.7	vs 3	n.s.	1.3±0.1	vs 3	n.s.	32.0±1.6	vs 3	n.s.
		vs 4	**p<0.001**		vs 4	n.s.		**vs 4**	**p<0.001**		vs 4	n.s.
Grade 3	1.0±0.1	vs 4	n.s.	36.5±2.1	vs 4	n.s.	1.3±0.1	**vs 4**	**p=0.004**	32.1±2.1	vs 4	n.s.
Grade 4	0.8±0.1	-		34.6±2.1	-		0.9±0.1	-		32.0±2.2	-	

Data are shown as mean ± standard error. Bold text indicates a significant difference in the Sidak post hoc test.

OA: osteoarthritis, LS: longitudinal sagittal, ST: suprapatellar transverse, eOA: early OA, 2: grade 2, 3: grade 3, 4: grade 4, n.s.: not significant, a.u.: arbitrary unit

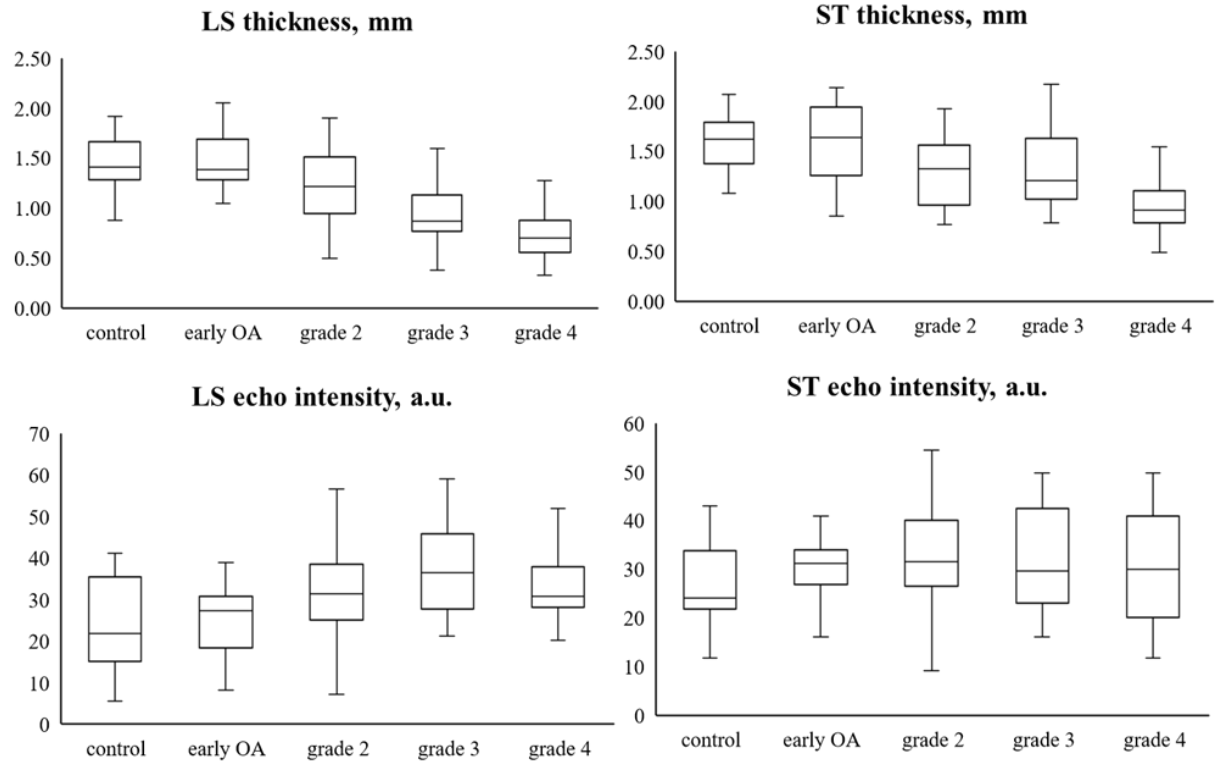
Figures

Fig. 1 Ultrasonographic image of the femoral cartilage



a. Longitudinal and b. transverse images. The region inside the yellow line represents the area analyzed. The transverse images were manually segmented using a previously described method [3]. The intercondylar zone was defined as the middle 25% of the image, centered at the deepest point of the intercondylar notch. The medial femoral zone was defined as the portion to the right side of the intercondylar zone. In this study, we analyzed only the medial compartment.

Fig. 2 Unadjusted thickness and echo intensity of the femoral medial cartilage in each group



The top and bottom line represent the maximum and minimum values of cartilage thickness and echo intensity, respectively. The top and bottom line of the boxes represent the third and first quartiles, and the line in the boxes represent the median. LS : longitudinal sagittal, ST : suprapatellar transverse

Supplemental file 1 Differences of femoral cartilage ultrasound outcomes between knee OA grade

		LS thickness, mm			LS echo intensity, a.u.			ST thickness, mm			ST echo intensity, a.u.		
		difference	95% CI	P value	difference	95% CI	P value	difference	95% CI	P value	difference	95% CI	P value
vs control	early OA	0.02	-0.33 to 0.38	>0.99	0.99	-9.84 to 11.81	>0.99	-0.08	-0.44 to 0.28	>0.99	3.15	-7.44 to 13.75	0.99
	grade 2	-0.21	-0.48 to 0.07	0.28	**8.44**	**0.05 to 16.87**	**0.049**	**-0.31**	**-0.59 to -0.03**	**0.02**	5.43	-2.79 to 13.65	0.47
	grade 3	**-0.43**	**-0.73 to -0.13**	**0.001**	**13.05**	**3.86 to 22.24**	**0.001**	**-0.31**	**-0.62 to -0.006**	**0.04**	5.57	-3.48 to 14.62	0.57
	grade 4	**-0.66**	**-0.97 to -0.36**	**<0.001**	**11.11**	**1.84 to 20.38**	**0.009**	**-0.68**	**-0.99 to -0.37**	**<0.001**	5.45	-3.85 to 14.75	0.64
vs early OA	grade 2	-0.24	-0.56 to 0.09	0.35	7.45	-2.46 to 17.36	0.29	-0.23	-0.56 to 0.10	0.37	2.28	-7.40 to 11.95	>0.99
	grade 3	**-0.45**	**-0.80 to -0.10**	**0.003**	**12.06**	**1.49 to 22.64**	**0.015**	-0.24	-0.59 to 0.12	0.44	2.42	-7.97 to 12.81	>0.99
	grade 4	**-0.69**	**-1.04 to -0.33**	**<0.001**	10.13	-0.52 to 20.77	0.07	**-0.61**	**-0.97 to -0.25**	**<0.001**	2.30	-8.32 to 12.91	>0.99
vs grade 2	grade 3	-0.22	-0.47 to 0.03	0.13	4.61	-2.94 to 12.16	0.58	-0.004	-0.26 to 0.25	>0.99	0.14	-7.59 to 7.31	>0.99
	grade 4	**-0.45**	**-0.70 to -0.20**	**<0.001**	2.67	-4.90 to 10.25	0.98	**-0.37**	**-0.63 to -0.11**	**0.001**	0.02	-7.64 to 7.68	>0.99
vs grade 3	grade 4	-0.23	-0.51 to 0.04	0.17	-1.94	-10.32 to 6.44	>0.99	**-0.37**	**-0.66 to -0.08**	**0.004**	-0.12	-8.68 to 8.44	>0.99

Post hoc analyses with the Sidak correction after the general linear model were performed to compare cartilage thickness and echo intensity in two portions of the femoral medial condyle among knee OA grades. Bold font indicates a statistically significant difference. OA: osteoarthritis; LS: longitudinal-sagittal; ST: suprapatellar transverse; difference: adjusted mean difference; CI: confidence interval