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Ultrasonographic Changes of the Knee Joint Reflect Symptoms of Early Knee Osteoarthritis in General Population; The Nagahama Study

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Abstract

Objective. Radiographic changes in knee osteoarthritis (OA) are not always associated with symptoms, especially in its early stages. Ultrasonography (US) can detect early changes in the knee joint, but the changes that reflect symptoms have not been fully elucidated. This study aimed to identify US-detectable changes in the knee that are often associated with knee symptoms and demonstrate the feasibility of early diagnosis in symptomatic knee OA using US. *Design.* In this cross-sectional community-based study, 1,667 participants aged ≥60 years (1,103 women [66%]) were included. All participants concurrently underwent US and radiography of the knee and completed the Knee Society Knee Scoring System (KSS) questionnaire. Simple and multiple regression analyses were used to examine the associations between US findings and KSS symptom subscales. *Results.* Among all participants, medial meniscus protrusion and medial osteophytes, age, and body mass index showed significant associations with KSS symptom scores. Among 894 participants with Kellgren-Lawrence (KL) grade ≤1, medial osteophytes and age were significantly associated with KSS symptom score. US measures were more related to KSS symptoms than KL grades. *Conclusions.* Among the knee US-detectable changes, medial osteophytes were strongly associated with knee symptoms. Osteophytes are reliable predictors of symptomatic early knee OA, even in participants with few radiographic OA changes.

Keywords

ultrasonography, osteoarthritis, early knee osteoarthritis, knee symptoms, community-based study

Introduction

Knee osteoarthritis (OA) is a common destructive joint disease that primarily affects the elderly population and severely impairs locomotion in the end stage of the disease.[1] To date, there are no effective disease-modifying treatments for knee OA, which impose a significant socioeconomic burden on societies. Therefore, there has been a drive to proactively detect knee OA to initiate therapeutic interventions at an earlier stage.[2]

Although conventional radiography is still widely used to diagnose the earlier stage of knee OA and to evaluate disease severity in epidemiological and clinical studies, structural pathologies observed on radiographs, such as bone abnormalities and joint space narrowing, are noted at a relatively later stage of the disease.[3] In addition, OA is a disease not merely affecting bones and cartilages, but the whole joint, including soft tissues such as the synovia and menisci.[4] In contrast to conventional radiography, in this regard, ultrasonography (US) can detect earlier, subtle changes of synovia and menisci as well as osteochondral tissues such as osteophytes and articular cartilage, of which structural changes are a well-known feature of knee OA.[5] Indeed, an observational study using an ultrasound-based semiquantitative scoring system revealed that femoral osteophytes and medial meniscus extrusion were assessable in the presence or absence of symptomatic knee OA,[6] and osteophytes measured by US reportedly have a greater sensitivity than those measured by radiography.[7] Furthermore, it has been reported that femoral cartilage thickness measured by US strongly

correlates with cartilage thickness assessed macroscopically.[8,9] However, how effectively US can reflect symptoms has not been explored in a comparative manner with radiographic evaluations. Conversely, magnetic resonance imaging (MRI) enables the evaluation of all articular and periarticular structures, including bone marrow lesions, subchondral cysts, synovitis, and effusion; therefore, it seems to be an essential imaging modality for clinical practice and related research;[3,10] however, MRI unfortunately costs more in terms of time and money, with specialized immovable equipment, making it difficult to utilize in a large community-based screening and/or research. Although US cannot visualize whole joint structures, especially deep tissues, its noninvasive, inexpensive, repeatable, and prompt examination makes it a useful tool for the evaluation of individuals in a large-scale population.[11]

The symptoms in knee OA have multifactorial etiologies, and one of them is structural pathology with intra-articular risk factors such as cartilage thinning, meniscus protrusion, osteophytes, and effusion.[12,13] In the past decade, many epidemiological studies on knee OA patients have reported an association between knee structural abnormalities evaluated by US and knee symptoms, but the sample sizes were fairly limited, and their findings have been inconsistent.[14-17] In particular, to the best of our knowledge, no studies have investigated the association between structural pathologies and knee symptoms in the whole stages of knee OA, including asymptomatic and/or no degenerative participants evaluated by US. If any structural changes strongly related to knee symptoms are identified, they would provide extremely useful information for screening in the general population, evaluations in symptomatic patients, therapeutic research in disease-modifying drugs, and understanding of pathological associations between structures and symptoms.

Therefore, we aimed to determine symptom-related, intra-articular findings among quantitatively measured structural changes using US, especially in the early stages of radiographic knee OA, in a population-based study. We hypothesized that minimal structural changes that can be detected by US are significantly correlated with symptoms, even in participants with fewer radiographic OA findings. We especially focused on earlier changes of knee OA in one of the largest population-based cohorts in the world, including participants with no to severe symptoms and structural damage to their knees.

Materials and Methods

Participants

The participants of this cross-sectional study were recruited from the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama study). The Nagahama study, which is an ongoing community-based study, consisting of 9,850 middle-aged to elderly citizens who were recruited from 2013 to 2016 from the general population of Nagahama City, a rural city of 125,000 inhabitants located in central Japan, to elucidate the pathogenesis and etiology of various diseases by integrating and analyzing a wide range of health-, environment-, and habit-related information. An overview of the Nagahama study has been described in previous studies.[18-20] Among the participants in the second survey, those of the current study were included to match the following criteria: (1) age over 60 years old, (2) having the ability to participate in the health examinations independently, (3) having no communication problems, and (4) voluntarily deciding to participate in the project. Except for age, we did not establish any exclusion criteria for this study. A total of 1,758 residents agreed to participate in this study. When any clinical or ultrasound data were missing, the participants were excluded from the analyses. After excluding 91 participants, 1,667 participants were included in the final analyses (**Fig. 1**). This study was designed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of Kyoto University Graduate School of Medicine and by the Nagahama Municipal Review Board (No. C278). Written informed consent for this study was obtained from all participants.

US Assessments

All US examinations and measurements were performed as previously described.[21] Briefly, five independent orthopedic

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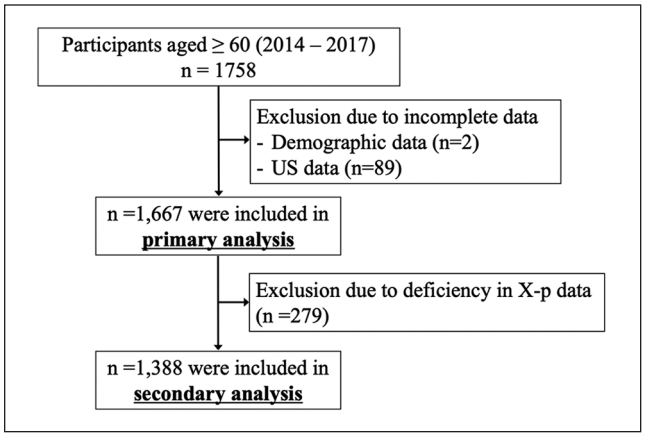

Figure 1. Flowchart of available data in this study. Secondary analysis was performed to demonstrate the correlation between knee symptom and structural changes in pre-/early radiographic knee osteoarthritis.

surgeons well-trained in US technique for the knee joint, who were blinded to the clinical findings, performed US examinations in both knees of each participant using B-mode US (Noblus US; Hitachi Aloka Medical, Tokyo, Japan). All scanning protocols were determined according to standardized methods (Fig. 2).[9,22,23] First, the participant was placed in a supine position with the knee fully extended. The suprapatellar pouch on the anterior longitudinal aspect of the knee was detected, and suprapatellar effusion (SPE) and suprapatellar synovial hypertrophy (SPSH) were observed. Second, without changing the position of the knee, the probe was set at the medial and lateral joint space, and medial meniscus protrusion (MMP), medial recess synovial hypertrophy (MRSH), medial femoral/tibial osteophytes, and lateral recess synovial hypertrophy (LRSH) were detected in the medial and lateral longitudinal views of the knee. Finally, the participant remained in the supine position with the knee as fully flexed as possible, and cartilage thickness of distal medial femoral condyle (CTh-MFC) was detected in the longitudinal and transverse planes, respectively. As shown in **Supplementary** Figure 1, in all US images, each US parameter was quantified by 2 trained orthopedic surgeons (M.S. and A.O.) using ImageJ software (National Institutes of Health, Bethesda, MD). Specifically, SPE was measured as the maximum diameter of the abnormal anechoic or hypoechoic area. The depth of synovial hypertrophy was measured as the maximum diameter of each site. Medial osteophytes were measured as the length of the cortical protrusion at the joint margin in the femoral or tibial sites. MMP was defined as the perpendicular distance from the outer edge of the meniscus to the line of the femoral and tibial cortical margins, excluding osteophytes. Cartilage thickness was defined as the average of the measurements divided by the anechoic band lining the superior surface of the bone into 3 areas. With regard to the left/right selection of the knee, the worse measurements in each US finding were adopted for analysis (ie, a larger value of SPE, SPSH, MMP, MRSH, LRSH, and medial osteophytes, or a smaller value of CTh-MFC). All US findings were measured in a blinded manner. To evaluate intraobserver intraclass correlation coefficient (ICC), 1 trained orthopedic surgeon (M.S.) performed 2 separate measurements with a 4-week interval. To evaluate interobserver ICC, 2 trained orthopedic surgeons (M.S. and A.O.) performed 2 separate measurements without informing each other of the results. In the current study, the ICCs for the interobserver (0.60-0.92) and intraobserver (0.82-0.92) reliabilities of each US measurement were good to excellent in all parameters (**Supplementary** Table S1).

Assessment of Knee Pain

In the Nagahama study, the new Knee Society Knee Scoring System® (KSS 2011) was translated into Japanese and used to assess the participants' knee symptoms and function.[24] The KSS 2011 is a self-administered questionnaire comprising the following four subcategories: symptom, patient satisfaction, functional activities, and expectation. As the knee surgeries were likely unplanned, the subcategory "expectation" was excluded.[19] In this study, the subcategory "symptom" (3 questions, 0–25 points; 0 = severe, 25 = none) was used to analyze the association between knee pain and US findings.

Radiographic Assessments

In the Nagahama study, weight-bearing anteroposterior radiography of both knees was performed by participants on a voluntary basis. Among the study population, radiographic data of the knee were available in 1,388 participants (83%), who were included in the secondary analysis (**Fig. 1**). All such data were independently evaluated by 2 registered orthopedic surgeons (H.I. and T.K.), who were blinded to the participants' information, using the Kellgren-Lawrence (KL) grades (0-4; 0 = none, 4 = severe),[25] and the higher score from the bilateral knee joints was used for analysis. Knees with KL ≤1 were defined as pre-/early radiographic OA on the basis of previous studies.[26,27] With regard to the left/right selection of the knee, the side with the worse KL grade was adopted for analysis.

Statistical Analysis

Statistical analyses were performed using JMP Pro version 13 (SAS Institute Inc., Tokyo, Japan), except for ICCs, which were calculated using IBM SPSS Statistics version

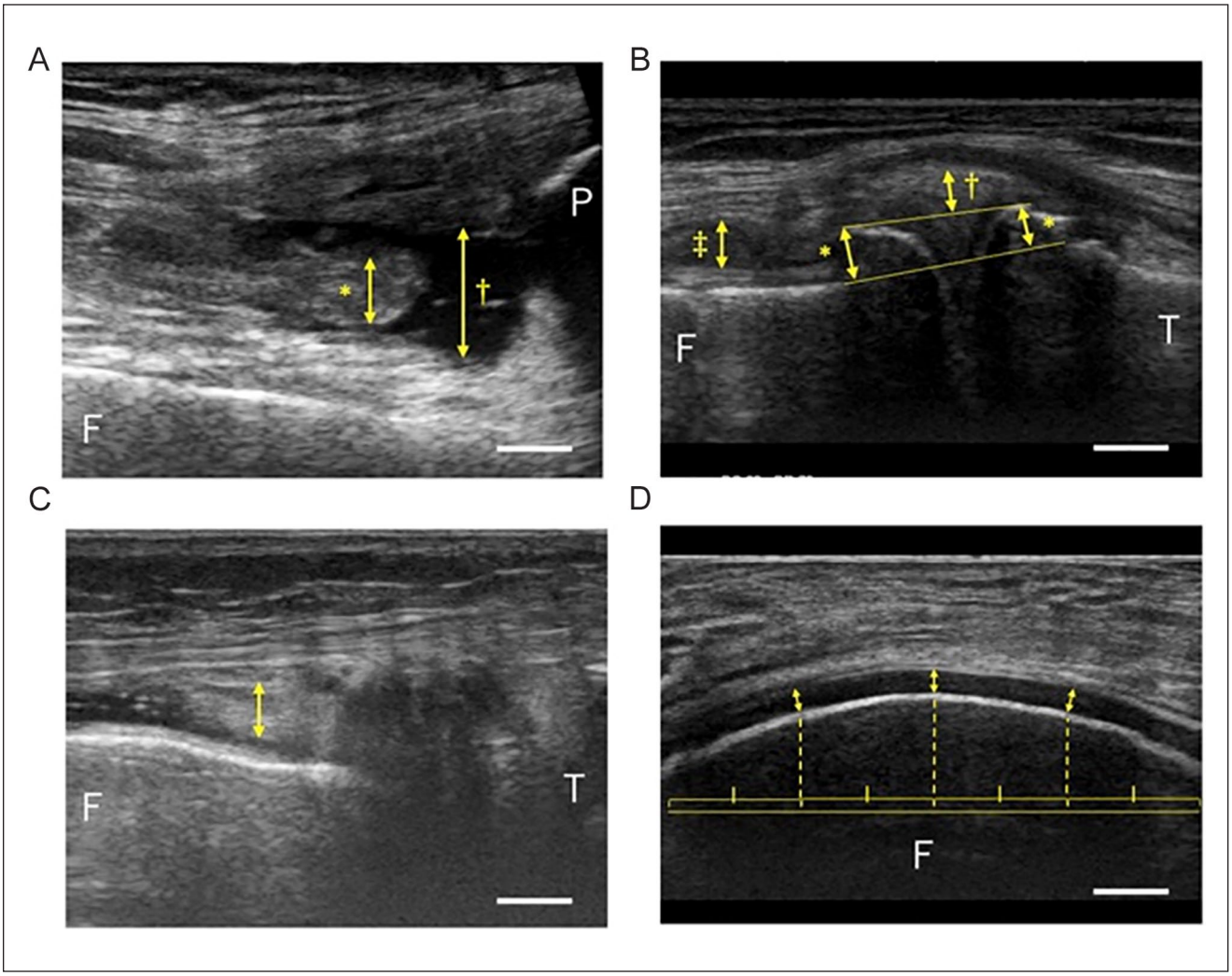

Figure 2. Representative ultrasonography images of each site. The yellow 2-way arrows indicate the measurement of distance for ultrasonographic parameters. (**A**) Image at the suprapatellar pouch. * and † indicate the length of SPE and SPSH, respectively. (**B**) Image at the medial recess. *, †, and ‡ indicate the length of MMP, osteophytes, and MRSH, respectively. (**C**) Image at the lateral recess. Yellow double-headed allow indicate the length of LRSH (**D**) Image at the medial condylar cartilage. The dotted line equally divides a segment into four parts and indicates the measurement points. Scale bar represents 5 mm. P = patella; F = femur; T = tibia.

24 (IBM, NY). Intra-observer and inter-observer reliabilities of the US measurement between the 2 observers were evaluated by calculating ICCs. The normality was examined by Shapiro-Wilk test. Spearman's rank correlation coefficient was calculated in the univariate association analyses between continuous and ordinal variables that were not normally distributed. For between-group comparison, categorical variables were compared using Fisher's exact test, and continuous variables were compared using Student's t-test, if normally distributed, and the Mann-Whitney U test, if not normally distributed. Statistical significance was set at $P < 0.05$. Multiple linear regression analysis with the forced entry method was used to identify variables associated with the KSS 2011 symptom score. Categorical variables (sex) were coded as 0 (male) or 1 (female). The unstandardized *beta* (*B*), standard error for the unstandardized *beta* (*SE B*), standardized *beta* (β), tolerance, variance inflation factor (VIF), and probability value (*P*) were calculated for the multiple linear regression analysis. Moreover, we divided participants into 2 groups according to the KL grade to evaluate whether US captures the minimal changes in radiography. We defined KL ≤1 as pre-/early knee OA and analyzed the association between KSS 2011 symptom score of the participants with KL ≤1 and US findings using

multiple linear regression analysis with the forced entry method. The bootstrap method was used to compare the correlation coefficients for knee symptoms.

Results

Primary Analysis

In the primary analysis, 1,677 participants were included. Clinical and ultrasound parameters, including the primary analysis, are summarized in Table 1. In this group, the mean age was 68 (standard deviation; SD = 5.3) years; women accounted for 66%; the mean body mass index (BMI) was 22.3 (SD = 3.0); the mean KSS symptom score was 23 (interquartile range [IQR] = 20-25). As shown in Table 2, there were unanimous and significant correlations among the US findings, especially between nearby structures such as medial femoral and tibial osteophytes (ρ = 0.80, $P < 0.01$), as expected. It is of note that there are also significant correlations among separated structural changes such as those between SPE and MRSH (ρ = 0.21), between MMP and femoral osteophytes (ρ = 0.37), and between tibial osteophytes and CTh-MFC (ρ = –0.21). Correlation of US findings with KL grade yielded universal significance in all of the assessed findings, especially moderately or strongly in MMP, MRSH, femoral osteophytes and tibial osteophytes (ρ = 0.35, 0.42, 0.64, and 0.58, respectively). The crucial findings of this analysis are that all structural changes were weakly but significantly correlated with symptoms. In particular, femoral and tibial osteophytes were both single-handedly correlated with the symptoms at a similar level compared with that of the KL grade (ρ = –0.26, and –0.28 versus –0.28), indicating the usefulness of the changes detected by US. We then conducted multivariate regression analysis to identify independent changes in all assessments and found that the explanatory factors of worse KSS symptom score were older age, higher BMI, larger MMP, and medial osteophytes (Table 3).

Secondary Analysis

In the secondary analysis, a total of 1,388 participants with radiographic data available were included. There were no significant differences in demographic and clinical data, including US findings, between participants with and without radiographic data (data not shown). Among the participants with KL ≤1, the mean age was 67.3 (SD = 5.2) years, females accounted for 56%; the mean BMI was 21.9 (SD = 2.8),and the mean KSS symptom score was 24 (IQR = 21-25) (**Supplementary** Table S2). In participants with KL ≤1, there were weak but significant correlations between KSS symptoms and SPSH or tibial osteophytes, indicating early changes leading to symptoms in the knee joint (**Supplementary** Table S3). Furthermore, we conducted multivariate regression analysis with only the KL ≤1 group and found that the explanatory factors of worse KSS symptom score were older age and larger tibial osteophytes, indicating that early changes especially in osteophytes likely lead to the symptoms (Table 4).

Table 1. Characteristics of the Participants in Primary Analysis.

Variables	Participants (n = 1,667)
Age (years)	68.0 ± 5.3 [60-81]
Women	1103 (66)
BMI (kg/m^2)	22.3 ± 3.0 [14.7-34.6]
KSS symptom (points)	23, 20-25 [0-25]
US findings (mm)	
SPE	0, 0-2.2 [0-13.6]
SPSH	0, 0-1.0 [0-6.4]
MMP	2.3, 1.9-2.9 [0.7-6.3]
MRSH	1.7, 1.2-2.2 [0-7.4]
Femoral osteophyte	0, 0-1.1 [0-8.9]
Tibial osteophyte	0, 0-1.1 [0-9.2]
LRSH	2.3, 1.8-3.0 [0.7-7.4]
CTh- FMC	1.3, 1.1-1.5 [0.2-2.9]

Data for continuous variables are expressed as mean ± SD [minimum–maximum] except for KSS score and US findings (median, inter-quartile range [minimum–maximum]), and data for categorical variables are expressed as numbers and percentages. BMI = body mass index; KSS = knee society score; US = ultrasound; SPE = suprapatellar effusion; SPSH = suprapatellar synovial hypertrophy; MMP = medial meniscus protrusion; MRSH = medial recess synovial hypertrophy; LRSH = lateral recess synovial hypertrophy; CTh-MFC = cartilage thickness of distal medial femoral condyle.

Discussion

In this large-scale population-based study, we found that knee symptoms, evaluated by patient-reported outcome measures, were more prominently correlated with the size of medial osteophytes measured by US than the other measurements. Interestingly, even in the pre-/early radiographic knee OA participants, larger osteophytes were significantly correlated with the severity of knee symptoms. Considering the knee with KL ≤1 is defined as the knee with no obvious osteophytes,[25] minimal structural changes of the knee, detected by US rather than radiography, may predict the degree of knee symptoms.

The focus on early knee OA has been growing while the number of OA patients has gradually increased worldwide, as early intervention has the potential to prevent or delay the progression of the disease, which may lead to reduce socioeconomic burden of knee OA.[1,2] Another advantage is that early detection of the knee OA could help control knee symptoms before acute pain turns into chronic pain.[28] It has been demonstrated that persistent chronic pain could develop pain sensitization even though structural

Table 2. Associations Among US Parameters, KSS Score, and KL Grade in Primary Analysis.

	SPE	SPSH	MMP	MRSH	Femoral osteophyte	Tibial osteophyte	LRSH	CTh-MFC	KL Grade	KSS symptom
SPE	-	0.63**	0.13**	0.21**	0.21**	0.20**	0.19**	-0.06*	0.19**	-0.14**
SPSH		-	0.08**	0.13**	0.22**	0.17**	0.03	-0.07**	0.13**	-0.13**
MMP			-	0.38**	0.37**	0.40**	0.21**	-0.08**	0.35**	-0.17**
MRSH				-	0.43**	0.40**	0.38**	-0.07*	0.42**	-0.18**
Femoral osteophyte					-	0.80**	0.15**	-0.23**	0.64**	-0.26**
Tibial osteophyte						-	0.15**	-0.21**	0.58**	-0.28**
LRSH							-	-0.007	0.18**	-0.06**
CTh-MFC								-	-0.17**	0.12**
KL grade									-	-0.28**

US = ultrasound; KSS = knee society score; KL = Kellgren-Lawrence; SPE = suprapatellar effusion; SPSH = suprapatellar synovial hypertrophy; MMP = medial meniscus protrusion; MRSH = medial recess synovial hypertrophy; LRSH = lateral recess synovial hypertrophy; CTh-MFC = cartilage thickness of distal medial femoral condyle.
*$P < 0.05$. **$P < 0.01$.

pathologies is undetectable via radiography.[29] Furthermore, the pain mechanism of OA is very complicated and inherent in multifactorial contributors, and also the degree of knee pain does not always correspond to the radiographic severity of knee OA or disease duration.[30] Therefore, detecting minimal structural changes using US would enable a clinician to persuasively instruct moderate exercise load and management of obesity to symptomatic patients even without radiographic OA evidence in order to prevent from further exaggerating arthritis as well as developing chronic pain phenotypes at an earlier stage than the conventional clinical works.

Over the last decade, many studies have been conducted to determine the association between structural pathologies and knee pain or function.[13] Although several studies using US have reported that synovitis and synovial thickness or meniscal protrusion correlate well with knee pain in patients with knee OA, no significant correlation was observed between them in the current study.[15-17] One probable reason is that the populations of previous studies differ from that of our study in terms of the class of recruited patients; those studies included only patients with apparent radiographic knee OA. As shown in Table 1, most of our cohort comprised participants with KL ≤ 1, and few participants reported definite joint effusion and synovial thickness. This is probably why there was no correlation between joint effusion or synovial thickness and knee pain in the current study. However, this study does not deny any possible correlations, and further studies are needed.

With regard to knee osteophytes, some studies have shown that, among structural pathologies of the knee joint, osteophytes are especially associated with knee pain even at the early phase of knee OA using MRI[31,32] or US.[14,15] Although the relationship between osteophytes and knee pain remains to be fully elucidated, it has been speculated by the presence of periostitis[13] or sensory nerve growth.[33] In a previous study examining the innervation in osteophytes using tibia samples from patients undergone total knee replacement, it was shown that sensory nerve and sympathetic nerve were localized within the marrow cavities of the tibial osteophytes.[34] Sensory nerve innervation may explain why the size of osteophytes is significantly correlated with knee symptoms in the current study. To our knowledge, no study investigated that the direct treatment targeted to sublet osteophytes which are undetectable by radiography, therefore, future investigation may be proposed in this regard.

In the current study, we attempted to compare radiography alone and US findings to demonstrate the diagnostic ability of US for early knee OA. As shown in Table 5, US findings were more significantly associated with knee symptoms compared to radiography. Although conventional radiography is able to detect osteophytes formation, joint space narrowing, subchondral bone thickness, and cyst formation, these radiographic hallmarks are not highly correlated with knee pain.[35] In fact, there are no consistent results in published studies investigating the relationship between conventional radiography and knee symptoms even though psychosocial factors are adjusted.[36,37] A previous large-scale study using radiography and MRI showed that several pathological changes were detected by MRI in patients without radiographic evidence of knee OA.[38,39] Indeed, MRI has a possibility to detect early stage knee OA by visualizing soft tissue changes that occur prior to radiographic changes. However, MRI has also several limitations such as a high cost and long scanning time for daily practice.[27] Compared to MRI, US may be useful in the preliminary diagnosis of early knee OA due to its readily availability in routine clinical practice and its ability to aid in the interpretation of radiographic images.

This study had several limitations. First, because it was based on a cross-sectional observation, a causal relationship

Table 3. Multiple Linear Regression Analysis in the Primary Analysis.

Independent Variables	Dependent Variable: KSS Symptom Sore						R^2	Adjusted R^2
	B	SE	B	*P* Value	Tolerance	VIF		
SPE							0.143	0.130
0	ref							
0< X <1	-0.304	1.159	-0.006	0.793	0.963	1.039		
1≤ X <2	0.395	0.403	0.028	0.327	0.657	1.522		
2≤	-0.539	0.323	-0.052	0.096	0.544	1.837		
SPSH								
0	ref							
0< X <1	0.486	0.875	0.014	0.578	0.882	1.134		
1≤	-0.486	0.340	-0.045	0.153	0.536	1.865		
MMP								
<2	ref							
2≤ X <2.5	-0.081	0.284	-0.008	0.774	0.677	1.476		
2.5≤ X <3	-0.068	0.322	-0.006	0.834	0.691	1.447		
3≤	-0.793	0.352	-0.068	**0.025**	0.569	1.757		
MRSH								
<1	ref							
1≤ X <1.5	-0.007	0.375	-0.001	0.984	0.392	2.549		
1.5≤ X <2	-0.150	0.393	-0.014	0.703	0.402	2.490		
2≤	-0.369	0.411	-0.037	0.369	0.306	3.269		
Femoral osteophyte								
0	ref							
0< X <1	0.345	0.393	0.027	0.381	0.554	1.806		
1≤	-1.107	0.409	-0.105	**0.007**	0.348	2.872		
Tibial osteophyte								
0	ref							
0< X <1	-0.298	0.362	-0.026	0.411	0.524	1.909		
1≤	-1.293	0.405	-0.125	**0.001**	0.343	2.917		
LRSH								
<2	ref							
2≤ X <2.5	0.057	0.294	0.005	0.846	0.747	1.339		
2.5≤ X <3	-0.235	0.333	-0.019	0.480	0.756	1.323		
3≤	0.069	0.304	0.006	0.820	0.652	1.534		
CTh-MFC								
<1	-0.948	1.062	-0.068	0.372	0.090	11.071		
1≤ X <1.5	-0.142	1.025	-0.015	0.890	0.046	21.650		
1.5≤ X <2	0.198	1.037	0.018	0.848	0.057	17.396		
2≤	ref							
Age	-0.093	0.021	-0.106	**0.000**	0.909	1.100		
BMI	-0.119	0.039	-0.076	**0.002**	0.853	1.172		
Sex	-0.045	0.248	-0.005	0.855	0.835	1.197		

KSS = knee society score; B = regression coefficient; β = standardized regression coefficient; VIF = variance inflation factor; SPE = suprapatellar effusion; SPSH = suprapatellar synovial hypertrophy; MMP = medial meniscus protrusion; MRSH; medial recess synovial hypertrophy; LRSH = lateral recess synovial hypertrophy; CTh-MFC = cartilage thickness of distal medial femoral condyle; BMI = body mass index. Bold values indicate statistical significance.

between structural changes and knee pain could not be demonstrated. Second, we did not include information regarding whether participants were taking analgesics or pain modifiers. Third, for the assessment of synovitis, power Doppler signals were not examined in this study.[22] Fourth, diagnostic examinations and on-site assessments by medical personnel were lacking. Specifically, the knee joint instability caused by anterior cruciate ligament or meniscal injuries could largely affect development of osteophytes. Nevertheless, physical examination of valgus-varus and anterior-posterior instability were performed in 1,469 participants (90%) in this study, and only 3 knees in the valgus and varus stress test and 8 knees in the anterior and posterior drawer test had noticeably laxity (0.2% and 0.5%,

Table 4. Multiple Linear Regression Analysis in the Secondary Analysis.

Independent Variables	Dependent Variable: KSS Symptom Sore						R^2	Adjusted R^2
	B	SE	B	*P* value	Tolerance	VIF		
SPE							0.035	0.009
0	ref							
0< X <1	-0.652	1.491	-0.015	0.662	0.964	1.037		
1≤ X <2	0.205	0.477	0.017	0.667	0.679	1.473		
2≤	-0.042	0.398	-0.005	0.916	0.588	1.702		
SPSH								
0	ref							
0< X <1	-0.593	1.016	-0.021	0.560	0.865	1.157		
1≤	-0.695	0.429	-0.072	0.105	0.568	1.760		
MMP								
<2	ref							
2≤ X <2.5	-0.181	0.322	-0.022	0.574	0.737	1.357		
2.5≤ X <3	-0.037	0.371	-0.004	0.920	0.738	1.355		
3≤	-0.242	0.453	-0.021	0.593	0.724	1.381		
MRSH								
<1	ref							
1≤ X <1.5	-0.163	0.416	-0.020	0.695	0.428	2.339		
1.5≤ X <2	-0.479	0.438	-0.055	0.275	0.441	2.267		
2≤	-0.290	0.469	-0.032	0.537	0.406	2.463		
Femoral osteophyte								
0	ref							
0< X <1	0.751	0.466	0.073	0.107	0.535	1.870		
1≤	0.307	0.555	0.026	0.580	0.521	1.919		
Tibial osteophyte								
0	ref							
0< X <1	-0.614	0.429	-0.066	0.153	0.514	1.944		
1≤	-1.087	0.492	-0.102	**0.027**	0.521	1.918		
LRSH								
<2	ref							
2≤ X <2.5	0.194	0.347	0.021	0.576	0.769	1.300		
2.5≤ X <3	-0.128	0.407	-0.012	0.752	0.799	1.252		
3≤	-0.181	0.365	-0.020	0.620	0.683	1.465		
CTh-MFC								
<1	0.797	1.447	0.060	0.582	0.094	10.595		
1≤ X <1.5	0.421	1.390	0.052	0.762	0.037	26.840		
1.5≤ X <2	0.924	1.401	0.105	0.510	0.044	22.723		
2≤	ref							
Age	-0.064	0.026	-0.085	**0.015**	0.901	1.110		
BMI	-0.051	0.049	-0.037	0.302	0.868	1.152		
Sex	0.249	0.294	0.032	0.398	0.799	1.252		

KSS = knee society score; B = regression coefficient; β = standardized regression coefficient; VIF = variance inflation factor; SPE = suprapatellar effusion; SPSH = suprapatellar synovial hypertrophy; MMP = medial meniscus protrusion; MRSH; medial recess synovial hypertrophy; LRSH = lateral recess synovial hypertrophy; CTh-MFC = cartilage thickness of distal medial femoral condyle; BMI = body mass index. Bold values indicate statistical significance.

respectively). Therefore, it was assumed that the impact of knee instabilities on the results was minimal. Fifth, US has a potential problem of lacking objectivity, since all US examinations are dependent on the skill of examiners, and it is difficult for other examiners to re-evaluate findings in motion. In order to ensure the objectivity as much as possible, in the current study, we selected only well-trained orthopedic surgeons as the examiners. Finally, we recruited individuals from a single ethnic community, and the results may not apply to other ethnic populations. Despite these limitations, we believe that this large community-based study, will provide clinicians with a more accurate understanding of the relationship between knee pain and structural changes in the knee.

Table 5. Comparison of Regression Coefficient Between KL Grade and US Findings.

	Dependent Variable: KSS Symptom								Difference (Model 2—Model 1)		
Independent Variables	B	SE	β	*P* Value	Tolerance	VIF	R^2	Adjusted R^2	Adjusted R^2	95%CI	*P* Value
Model 1							0.108	0.108			
KL grade	-2.210	0.170	-0.329	<**0.001**	1.000	1.000					
Model 2							0.153	0.149	0.041	0.003-0.066	**0.01**
SPE	-0.168	0.080	-0.062	**0.036**	0.584	1.712					
SPSH	-0.257	0.126	-0.059	**0.041**	0.621	1.611					
MMP	-0.335	0.168	-0.054	**0.047**	0.707	1.414					
MRSH	-0.149	0.154	-0.028	0.331	0.601	1.663					
Femoral osteophyte	-0.793	0.158	-0.211	<**0.001**	0.290	3.447					
Tibial osteophyte	-0.413	0.174	-0.095	**0.018**	0.320	3.129					
LRSH	0.110	0.124	0.022	0.372	0.835	1.198					
CTh-MFC	0.615	0.363	0.040	0.091	0.913	1.095					

KL = Kellgren-Lawrence; US = ultrasound; KSS = knee society score; B = regression coefficient; β = standardized regression coefficient; VIF = variance inflation factor; CI = confidence interval; SPE = suprapatellar effusion; SPSH = suprapatellar synovial hypertrophy; MMP = medial meniscus protrusion; MRSH; medial recess synovial hypertrophy; LRSH = lateral recess synovial hypertrophy; CTh-MFC = cartilage thickness of distal medial femoral condyle. Bold values indicate statistical significance.

In conclusion, in this large, population-based study using US, we found that medial osteophytes were strongly associated with knee symptom scores, even in participants with no or few radiological changes. The current results suggest that patients with osteophytes detected by US tend to have knee symptoms despite exhibiting few radiographic OA changes, and US can provide clinicians with informative findings at the earlier phase of knee OA.

Authors' Contributions

H.I., Y.T., F.M., and S.M. designed the study. M.S. and H.I. wrote the manuscript. M.S., H.I., A.O., M.F., K.N., S.K., S.N., T.K., T.I., Y.T., and S.M. collected data and information of the subjects. H.I. and T.K. analyzed radiography. M.S. and A.O. performed the statistical analyses. H.I., T.M., T.T., N.I., Y.T., F.M., and S.M. collected fundings. F.M. and S.M. supervised the works. All authors read and approved the final manuscript.

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Declaration of Conflicting Interests

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Ethics Approval and Consent to Participate

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of Kyoto University Graduate School of Medicine and by the

Nagahama Municipal Review Board (No. C278). Written informed consent was obtained from all participants.

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