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Pain in patients with equal radiographic grades of osteoarthritis in both knees: the value of gray scale ultrasound

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SUMMARY

Objectives: To investigate the association of ultrasound (US) features with pain and the functional scores in patients with equal radiographic grades of osteoarthritis (OA) in both knees.
Methods: Fifty-six consecutive patients with knee OA: 85 symptomatic knees (81 knees with medial pain) and 27 asymptomatic knees, and 10 healthy patients without knee OA as a control were enrolled. US was done by two ultrasonographers blinded to patient diagnoses. US features were semiquantitatively scored (0–3) when appropriate.
Results: In the OA group, common US findings were marginal osteophyte, suprapatellar synovitis, suprapatellar effusion (SPE), medial meniscus protrusion, medial compartment synovitis (MCS), lateral compartment synovitis, and Baker's cyst. Only SPE and MCS were significantly associated with knee pain. Visual analog pain scale (VAS) scores on motion were positively linearly associated with SPE and MCS ($P < 0.01$). Only MCS was degree-dependently associated with VAS scores at rest, the Western Ontario and McMaster Universities pain subscale, and the presence of medial knee pain ($P < 0.01$) after adjustments for age, gender, body mass index (BMI), radiographic grade, and other US features. In the control group, no US features were associated with knee pain.
Conclusions: US inflammation features, including SPE and MCS, were positively linearly associated with knee pain in motion. MCS was also degree-dependently associated with pain at rest and the presence of medial knee pain. These findings show that synovitis was one important predictive factor of pain. Further studies to confirm the association of US features and pain are warranted.

Introduction

Arthritis is the most common cause of pain in the elderly, and knee pain is the major clinical symptom of knee osteoarthritis (OA)[1]. The cause of pain in knee OA is not yet fully understood. General practitioners, rheumatologists, and orthopedists usually use knee radiography, which visualizes only bony structures, as a first-line diagnostic tool for knee OA. Community-based studies[2–4] have shown that severe radiographic knee OA is associated with greater pain; however, there is a high degree of discordance between clinical and radiographic knee OA[5–8]. In clinical practice, a patient with equal radiographic grades of OA in both knees usually presents with unequal visual analog pain scale (VAS) pain scores, and sometimes even with pain in only one knee. The reason for the discrepancy between pain and radiographic structure lesions is probably that the origin of pain is multifactorial[3,9].

Ultrasound (US) is an easy noninvasive procedure with minimal discomfort for patients, and seems useful in evaluating joint effusion and synovitis, the features of inflammation[10–14]. There are a few studies that have demonstrated the correlation of sonographic findings, such as suprapatellar effusion (SPE) and medial meniscus protrusion (MMP), and symptomatic OA[11,15–17]. However,

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in our daily practice, synovitis in the medial knee recess revealed on an US examination seems to correspond well to knee pain in patients with OA, especially to medial knee pain. Our hypothesis was that synovitis, either in the medial knee recess or in the suprapatellar pouch, is important in the mechanism of OA knee pain. Although the radiographic grade is not well-correlated with clinical symptoms, it is still a possible confounding factor. Otherwise, pain is self-reported and depends on personal factors that are difficult to assess and quantify. Comparing the degree of pain in both knees of the same patient can minimize the individual variance in the perception of pain. To minimize the confounding factors, our study aim was to investigate the association of US features with the pain and function in patients with equal radiographic grades of OA in both knees.

Materials and methods

One hundred fifty-six consecutive patients with bilateral primary knee OA were recruited from the orthopedics outpatient clinic of our university medical center, a consultation center of the region, from December 2009 to May 2012. All patients consulted for intra-articular (IA) hyaluronate (HA) injection therapy were at least 45 years old and met the American College of Rheumatology (ACR) criteria for knee OA[18]. The inclusion criterion was equal radiographic K–L (Kellgren and Lawrence) grades of OA in both knees. Exclusion criteria were: (1) secondary knee OA following Group for the Respect of Ethics and Excellence in Science (GREES) criteria[19]; (2) a history of knee surgery; and (3) a history of arthrocentesis and an IA steroid or hyaluronic acid injection 3 months before the study. Otherwise, 10 patients presenting unilateral/bilateral knee pain without knee OA, other systemic inflammatory disease, or a previous knee trauma history were enrolled as the control group. Our institutional ethics committee for studies on human subjects approved the protocol. Informed consent was obtained from all patients before the clinical, US, and radiographic evaluation. All enrolled patients received clinical assessment, radiographic assessment, US assessment, and finally US-guided injection of HA in order if indicated.

Clinical assessment

Demographic characteristics were collected using standard questionnaires. Body mass index (BMI), a 100-mm VAS in motion and at rest, and the Western Ontario and McMaster Universities (WOMAC) OA Index of pain, stiffness, and function subscales over the preceding 48 h were obtained from all patients. Bothersome knee pain (symptomatic) was defined as a VAS above 40 mm while walking[10]. Both knees were clinically evaluated by the same orthopedic surgeon (IMJ), who also recorded the duration of symptoms, knee alignment, presence of spontaneous medial knee pain, and tenderness at the pes anserinus insertion (PAI). Tenderness at the PAI was assessed by applying firm digital pressure at the anteromedial aspect of the proximal tibia (2.5–3.0 cm distal to the medial femorotibial joint line)[17]. No anagelsics were allowed for 72 h preceding the clinical and US assessment[13].

Radiographic assessment

Weight-bearing anteroposterior (AP) and lateral knee radiographs were read by two orthopedic surgeons (TCC and KCW), who, blinded to the clinical and US findings, assessed the severity of the OA using the K–L radiographic scale (grades I–IV)[18] and patellofemoral (PF) signs of degeneration. Grading discrepancies were resolved by consensus. Patients with the same K–L grade for both knees were enrolled for the study.

US procedure

Within 5 days of the clinical evaluation, US (MicroMaxx; SonoSite, Bothell, WA) was done, using an HFL38 (6–13 MHz) linear array transducer, on the suprapatellar pouch, medial knee recess, PAI, lateral knee recess, and posterior aspect of the knee, in that order, by two ultrasonographers (PTW and CJS) blinded to the patients' diagnoses. Both longitudinal and transverse scans were done using a standardized method[7,16,17]. US diagnostic criteria for tendon and ligament lesions, bursitis, and panniculitis were based on those described in the literature[17,20,21]. Synovitis was defined as hypoechoic synovial hypertrophy. In the suprapatellar recess, synovial hypertrophy ≥4 mm thick on the median longitudinal plane was defined as synovitis (Fig. 1)[11]. In the medial and lateral knee recesses, synovitis was defined as a thickening of the normally very thin hypoechoic line[10]. Effusion was identified as an anechoic or hypoechoic compressible material seen in two perpendicular planes (Fig. 2)[11,17,22]. The synovium and amount of effusion at the maximum depth observed in the longitudinal scan were measured. Effusion in the suprapatellar recess was recorded as present if it was ≥4 mm deep[7]. The cutoffs for grading effusion and synovial hypertrophy in the suprapatellar recess were modified based on a previous study (Table II)[23]. A hypertrophied synovium in the medial and lateral knee recesses is difficult to distinguish clearly from the fluid. Therefore, in the medial and lateral recesses, the depths of the synovium and effusion were measured together. Abnormal synovial hypertrophy and effusion accumulation >2 mm deep in the medial/lateral recess was defined as synovitis of the medial/lateral compartment [medial compartment synovitis (MCS)/lateral compartment synovitis (LCS), Table II]. Marginal osteophytsis (MO) was assessed over the suprapatellar, medial and lateral knee recess. The size of the largest osteophyte was recorded and scored with a modified semiquantitative system (Table II)[24]. Baker's cyst was identified when the gastrocnemius-semimembranosus bursa filled with hypoechoic material showed a transverse diameter >4 mm[17].

Protrusion of the meniscus was defined as a distance between the peripheral border of the meniscus and the outline of the tibial plateau >3 mm[25]. The distance of protrusion was measured and graded as 0–3 (<3 mm, 3 to <5, 5 to <8, ≥8) (Table II).

Intraobserver variability of the US features was tested by doing a second US scan in 20% of the patients (randomly chosen) on the same day. In between, at least one other US assessment was done. The consistency of the intraobservers for radiographic K–L grades

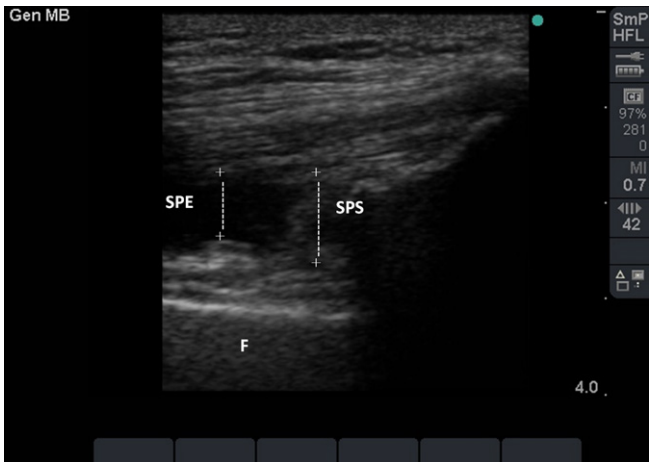

Fig. 1. Suprapatellar recess. Accumulated hypoechoic fluid and hypertrophied synovium were measured and recorded. F = femur.

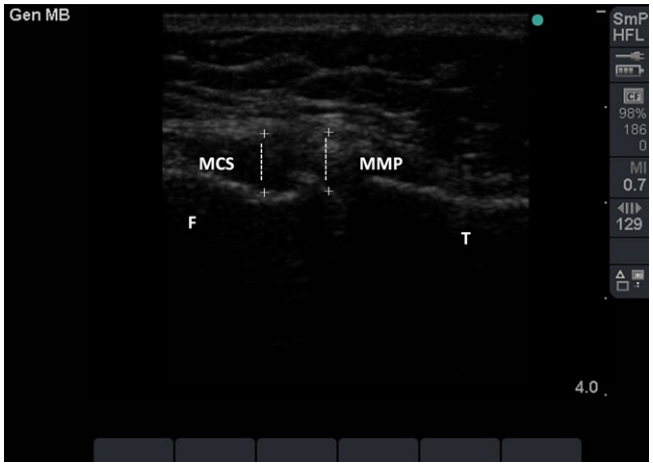

Fig. 2. Medial knee recess. Protruding medial meniscus and hypertrophied synovium mixed with effusion were measured and recorded. F = femur, T = tibia.

was examined with a second reading in 20% of the patients (randomly chosen) within 5 days after the first clinic visit. Interobserver agreement on US features and radiographic K–L grades was done by re-reading the stored images. All US feature assessments were done. Assessment discrepancies were resolved by consensus.

Intraobserver variability, evaluated using the κ value, was 0.80 for suprapatellar synovitis (SPS), 0.78 for suprapatellar effusion (SPE), 0.73 for MMP, 0.75 for MCS, 0.78 for LCS, 0.89 for MO, and 0.73 for K–L grade. Interobserver agreement, also evaluated using the κ value, was 0.79 for SPS, 0.74 for SPE, 0.72 for MMP, 0.75 for MCS, 0.77 for LCS, 0.85 for MO, and 0.72 for K–L grade.

Statistical analysis

Because of the relatively small number of asymptomatic knees, differences between knee symptoms were analyzed using a χ^2 test for the proportion of the variables and a Mann–Whitney *U* test for parametric variables. Since every enrolled subject received evaluations of their bilateral knees, the general linear regression model with the generalized estimating equation (GEE) method was used to investigate the association of pain with the selected US features, including VAS in motion, VAS at rest, the WOMAC pain subscale, and the WOMAC index. The GEE uses robust standard error estimates to take into account within–subjects correlations of the pain score[26]. Otherwise, the degree of medial knee pain was difficult to quantify with the independence of knee pain, we assessed the spontaneous medial knee pain with a binary question. The association of medial knee pain and the selected US features in the medial recess (MCS and MMP) was analyzed using the multivariant logistic regression model with the GEE method. Both regression analyses were adjusted for age, gender, BMI, K–L grade, and other US features. Additionally, one of the US feature in the medial recess, MO, was not included in the logistic regression model because of its high correlation with K–L grade ($R = 0.54$). Inclusion of MO in the multivariate analyses would cause the statistical problem of multicollinearity. Data were analyzed using SAS for Windows 9.2.

Table I
Clinical and radiographic findings in patients with equal radiographic grades of OA in both knees and the control group

	Bilateral equal grades of OA group	Control group
Clinical data		
Number of patients	56	10
Age (years) (mean, SD)	62.9 ± 8.2	41.9 ± 12.7
Gender		
Male (*n*, %)	14 (25.0%)	3 (30.0%)
Female (*n*, %)	42 (75.0%)	7 (70.0%)
BMI (mean, SD)	24.7 ± 3.3	23.2 ± 2.0
Knee alignment		
Normal (*n*, %)	42 (37.5%)	10 (100%)
Genu varus (*n*, %)	70 (62.5%)	0 (0%)
Genu valgus (*n*, %)	0	0
Radiographic finding		
K–L grade		
0 (*n*, %)	0	10 (100%)
I (*n*, %)	1 (1.8%)	0
II (*n*, %)	5 (8.9%)	0
III (*n*, %)	27 (48.2%)	0
IV (*n*, %)	23 (41.1%)	0
Radiographic PF degenerative signs (*n*, %)	80 (72.7%)	0 (0%)

Table II
Clinical, radiographic, and US findings in symptomatic and asymptomatic knees with OA

	Symptomatic knee ($n = 85$)	Asymptomatic knee ($n = 27$)	*P*-value
VAS on motion [mean (95% CI)]	74.0 (71.0, 77.0)	24.8 (20.1, 29.6)	<0.001
VAS at rest [mean (95% CI)]	20.8 (17.3, 24.3)	3.0 (0.9, 5.0)	<0.001
WOMAC [mean (95% CI)]	42.2 (38.8, 45.6)	13.7 (9.3, 18.0)	<0.001
Medial knee pain (*n*, %)	81 (95.3%)	0	
US features			
Marginal osteophyte (*n*, %)	84 (98.8%)	26 (96.3%)	0.939
Grade 0 (<1 mm)	9 (10.6%)	3 (11.1%)	
Grade 1 (1∼2 mm)	26 (30.6%)	8 (29.6%)	
Grade 2 (2∼5 mm)	40 (47.1%)	15 (55.6%)	
Grade 3 (>5 mm)	10 (11.8%)	1 (3.7%)	
SPS (*n*, %)	79 (92.9%)	15 (63.0%)	<0.001
Grade 0 (<4 mm)	6 (7.1%)	10 (37.0%)	
Grade 1 (4∼<8 mm)	44 (51.8%)	12 (44.4%)	
Grade 2 (8∼<11 mm)	25 (29.4%)	4 (14.8%)	
Grade 3 (≧11 mm)	10 (11.8%)	1 (3.7%)	
SPE (*n*, %)	28 (32.9%)	3 (11.1%)	0.016
Grade 0 (<4 mm)	57 (67.1%)	24 (88.9%)	
Grade 1 (4∼<8 mm)	20 (23.5%)	3 (11.1%)	
Grade 2 (8∼<11 mm)	7 (8.2%)	0	
Grade 3 (≧11 mm)	1 (1.2%)	0	
Protrusion of medial meniscus (MMP) (*n*, %)	74 (87.1%)	19 (70.4%)	0.067
Grade 0 (<3 mm)	11 (12.9%)	8 (29.6%)	
Grade 1 (3∼<5 mm)	30 (35.3%)	13 (48.1%)	
Grade 2 (5∼<8 mm)	32 (37.6%)	5 (18.5%)	
Grade 3 (≧8 mm)	12 (14.1%)	1 (3.7%)	
MCS (*n*, %)	75 (94.1%)	15 (55.6%)	<0.001
Grade 0 (<2 mm)	5 (5.9%)	12 (44.4%)	
Grade 1 (2∼<5 mm)	51 (60.0%)	15 (55.6%)	
Grade 2 (5∼<8 mm)	24 (28.2%)	0	
Grade 3 (≧8 mm)	5 (5.9%)	0	
LCS (*n*, %)	50 (58.8%%)	11 (40.7%)	0.597
Grade 0 (<2 mm)	35 (41.2%)	16 (59.3%)	
Grade 1 (2∼<5 mm)	46 (54.1%)	11 (40.7%)	
Grade 2 (5∼<8 mm)	4 (4.7%)	0	
Grade 3 (≧8 mm)	0 (6.2%)	0	
Baker's cyst (*n*, %)	21 (24.7%)	4 (14.8%)	0.282
Radiographic finding			
K–L grade			0.090
I (*n*, %)	1 (1.2%)	1 (3.7%)	
II (*n*, %)	5 (5.9%)	5 (18.5%)	
III (*n*, %)	40 (47.1%)	14 (51.9%)	
IV (*n*, %)	39 (45.9%)	7 (25.9%)	

K–L grade: Kellgren and Lawrence grade of OA.

Table III
Association between US features and visual analog scale (VAS) pain scores in motion, VAS at rest, the WOMAC index, and the WOMAC pain subscale in 56 patients with equal radiographic grades of OA in both knees

	SPS	SPE	MMP	MCS	LCS	MO
VAS in motion						
β-coefficients	0.22	2.21	−1.19	5.47	−1.30	−0.82
95% CI	(−9.88, 21.88)	(6.142, 39.92)	(−27.63, 5.65)	(31.08, 76.70)	(−46.11, 26.73)	(−31.00, 12.19)
P-value	0.459	0.008	0.195	<0.001	0.602	0.393
VAS at rest						
β-coefficients	−0.78	0.86	−0.56	3.05	−0.78	0.56
95% CI	(−17.42, 3.15)	(−4.60, 21.37)	(−19.73, 7.98)	(12.26, 46.34)	(−34.06, 21.04)	(−19.29, 30.40)
P-value	0.174	0.206	0.406	<0.001	0.643	0.661
WOMAC pain						
β-coefficients	0.23	0.10	−0.18	0.94	0.07	−0.21
95% CI	(−1.19, 5.80)	(−2.54, 4.74)	(−5.14, 1.47)	(4.00, 14.69)	(−5.25, 7.09)	(−8.46, 3.89)
P-value	0.196	0.555	0.276	<0.001	0.770	0.468
WOMAC						
β-coefficients	1.07	0.47	−1.14	1.56	−0.11	1.31
95% CI	(−0.57, 25.18)	(−9.14, 19.12)	(−22.81, 2.00)	(−3.54, 37.42)	(−25.97, 23.61)	(−10.56, 34.81)
P-value	0.061	0.489	0.100	0.105	0.926	0.295

The β-coefficients and the corresponding 95% CI were estimated from the general linear regression model with the GEE method and were adjusted for age, gender, BMI, radiologic OA grade, and other US features.
MMP: protrusion of medial meniscus.
Units for all US variables were expressed in millimeter (mm).

Results

Study population

Finally, 56 patients [42 (75.0%) women, and 14 men; mean age: 62.9 ± 8.2 years] were included in our OA group (Table I). There was no patient with a lateral compartment affected predominantly with OA. Most patients had radiographic K–L grade III or IV OA (Table I). There were 85 symptomatic knees and 27 asymptomatic knees. Eighty-one (95.3%) symptomatic knees had spontaneous medial knee pain and 78 (91.8%) symptomatic knees had PAI tenderness on physical examination. In the control group, there were 7 (70%) women and three men (mean age: 41.9 ± 12.7 years, Table I), and 12 symptomatic knees and eight asymptomatic knees. 6 (50%) symptomatic knees had spontaneous knee pain and 8 (66.7%) symptomatic knees had PAI tenderness on physical examination.

Prevalence of US features

In patients with bilateral equal grades of knee OA, there were significant differences between the symptomatic and asymptomatic knees in three of the six US features: SPS (79 vs 15; $P < 0.001$), SPE (28 vs 3; $P = 0.016$), and MCS (75 vs 15; $P < 0.001$) (Table II). All three features were correlated with knee pain. Differences between the knees in MO, MMP, LCS, and Baker's cyst showed no association with knee pain. In the control group, all six US features were not correlated with knee pain. In either OA group or control group, no knee showed US pes anserinus tendino-bursitis, tendon lesions, prepatellar or infrapatellar bursitis, a ligament rupture, lateral collateral ligament lesions, or panniculitis of the medial knee fat.

Association of US features with VAS scores, the WOMAC index, and medial knee pain

In the OA group, of all US features, only MCS had significant positive linear associations with VAS scores in motion, VAS at rest, and the WOMAC pain subscale after adjustments for age, gender, BMI, K–L grade, the site of affected knees and other US features (Table III). Of the other US features, only SPE was associated with VAS scores in motion. For the WOMAC index, all US features showed no association. Otherwise, the K–L grade showed significantly associated with VAS at rest, WOMAC pain subscale, and WOMAC index (data not shown). In the presence of medial knee pain, MCS showed a significant association after adjustments for age, gender, BMI, K–L grade, and MMP: odds ratio (OR) (95% confidence interval (CI)) for grade 1 MCS 6.1 (1.8–20.6) and grade 2 + 3 MCS 41.3 (2.8–598.8). MMP showed no association (Table IV). In the control group, no US features was associated with VAS score (either in motion or at rest), WOMAC index, or medial knee pain.

Discussion

This is the first study that has examined the association between pain and US features in patients with equal radiographic grades of OA in both knees. The majority of our symptomatic OA knees showed inflammation over both the suprapatellar recess and medial recess. In individual OA knees, we showed a dose-dependent association between sonographic inflammation features, including SPE and MCS, and pain. SPE and MCS were independently associated with VAS in motion, but other features were not. In addition, MCS was also associated with VAS at rest, the WOMAC pain subscale, and medial knee pain. In knees without OA, no US feature was correlated with knee pain or associated with VAS score, WOMAC index, or medial knee pain.

Effusion, synovitis, and bone marrow lesions have been the principal findings associated with knee pain in MRI and US studies

Table IV
Association of US features and spontaneous medial knee pain in 56 patients with equal radiographic grades of OA in both knees

US feature grade	*N*	*P*-value	Adjusted OR* (95% CI)
MCS			
0	17		1
1	66	0.004	6.1 (1.8–20.6)
2 + 3	24 + 5	0.006	41.3 (2.8–598.8)
MMP			
0	19		
1	43	0.334	2.4 (0.4–13.7)
2	37	0.198	3.4 (0.5–21.4)
3	13	0.221	4.4 (0.4–46.1)

The adjusted OR were estimated from the multivariate logistic regression model with the GEE method and were adjusted for age, gender, BMI, radiologic OA grade, and another US feature.
MMP: protrusion of medial meniscus.

of knee OA[10,15–17,27–29]. Prior US studies[11–13] showed that a higher BMI and some US features such as SPE, SPS, MMP with medial collateral ligament displacement (MCLD), and Baker's cyst are associated with pain in knee OA. A high incidence of sonographic inflammation features and MMP with MCLD were detected in our patients, especially in symptomatic knees. However, only SPE and MCS were associated with knee pain. We also found MMP in most asymptomatic patients. It was believed that MMP created a condition similar to the aftermath of a meniscectomy, which has been shown to predispose patients to OA[30]. The degree of MMP was correlated with the severity of the K–L grade[25]. Therefore, MMP was regarded as an important risk factor for knee pain in OA[16,17,25]. However, in our study, MMP was not associated with OA knee pain. As implied by Breitenseher *et al.*[31], our finding suggests that subluxation is associated with the development of structural OA and does not necessarily induce symptoms in those with structural OA[27].

In individual OA knee joints, we showed a degree-dependent association between inflammation features and pain. SPE was degree-dependently associated only with pain in motion. MCS was clearly associated with mechanical pain, pain at rest, and the WOMAC pain subscale. We also found that in most patients with medial knee pain, hypertrophied synovium mixed with effusion over the medial knee recess was clearly revealed on US, and that MCS was significantly associated with medial knee pain with a high OR in advanced inflammation (grades 2 and 3) after adjustment. The importance of synovitis in OA progression is well recognized[32–36]. OA knee joints usually show signs of synovitis, even in the early stage of the disease[37,38]. MR imaging in patients who either have or are at risk for knee OA showed that high-grade synovitis was associated with knee pain compared with those with no or low-grade synovitis[39,40]. There is evidence that synovitis is not only a secondary phenomenon in individuals with knee OA, but is also involved in the progression of cartilage loss[34]. However, MCS has rarely been discussed in the literature. Ayral *et al.*[34] reported that remarkable medial focal synovitis is a common feature of painful medial knee OA, associated with more severe medial chondropathy. Only the inflammatory synovitis group showed an association of cartilage loss at the 1-year follow-up. Furthermore, medial synovial tissue taken from patients with medial compartment OA showed more remarkable inflammation and more frequent incidence of pain-related neuropeptides (substance P and calcitonin gene related peptide), which may modulate the pain pathway in OA, than did those from the lateral and suprapatellar regions[41]. Therefore, medial synovial inflammation possibly contributes to pain, especially to medial knee pain, in patients with knee OA. In our study, the association between MCS and pain suggested that MCS is an important predictive factor of pain, and even medial knee pain, in patients with knee OA. However, the factors that induce MCS are still unclear. In contrast, neither US synovitis features nor other US features were associated with knee pain in knees without OA. The results reflect the importance of synovitis in OA knee pain and the multifactorial origins of pain.

This study has some limitations. First, the study population was small and predominant in advanced stage of OA (K–L grade III and IV), because the patients with equal radiographic grades of OA in both knees were relatively fewer in our outpatient department. Otherwise, the fact that all our patients were referred to us, or consulted with us, for IA–HA injection therapy may have contributed to the tendency of advanced OA stage in our patient population. The asymmetric population distribution may lead to the unclear association between synovial inflammation and knee pain in early stage of OA (K–L grade I and II) and control group. However, this study clearly showed that US-detected synovial inflammation, especially MCS, was positively linearly associated with OA knee pain. Our finding that synovitis is significantly associated with OA knee pain is similar to that of prior studies[16,17,27,39,40]. Second, there was no patient with predominantly lateral compartment OA, although predominantly medial compartment OA is typical in patients with knee OA. In our study, MCS was associated with the presence of medial knee pain and high VAS pain scores, but LCS was not. However, the question of whether LCS is related to knee pain or lateral knee pain in predominantly lateral compartment OA or not is unclear. Third, only gray-scale US was used to assess synovitis in this study. Power Doppler sonography (PDS) and contrast-enhanced (CE) US are more sensitive in detecting synovitis associated with OA[23,42]. However, PDS is highly machine-dependent in detecting synovial inflammation[43], and CE–US is more facility-dependent. In contrast, gray-scale US is more available and can consistently depict the morphology of inflammation[11,44]. We found that B-mode US adequately delineated the inflammation features and demonstrated their association with pain. Additional studies using US techniques that are more sensitive are necessary to confirm our results. Fourth, because of the busy clinic work, intraobserver variability of the US features was tested for the same patient on the same day, and interobserver agreement was done by re-reading the stored US images. Both methodologies possibly lead to the evaluation bias. Fifth, pain is multifactorial. This study was designed to verify the role of synovitis in OA knee pain. Therefore, US parameters with regard to the structure damage, such as thickness of femoral articular cartilage or of quadriceps tendon, were not evaluated comprehensively in our study.

In this study, US inflammation features, including SPE and MCS, were positively linearly associated with knee pain in motion in patients with equal radiographic grades of OA in both knees. MCS was also positively linearly associated with pain at rest and the WOMAC pain subscale, and degree-dependently associated with the presence of medial knee pain. These findings show that synovitis is one of the important predictive factors of pain. This knowledge may give rise to further research for therapeutic strategies. However, further studies to confirm the association of US features and pain in OA knees are needed.

Author contributions

All authors were involved in drafting and critically reading the manuscript for important content, and all authors approved the final version. Dr I-Ming Jou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. PT Wu, CJ Shao, TC Chern, IM Jou.

Acquisition of data. PT Wu, CJ Shao, KC Wu, TT Wu, IM Jou.

Analysis and interpretation of data. PT Wu, LC Kuo, IM Jou, LC Kuo.

Conflict of interest statement

All authors declare that they have no commercial interests or other types of conflicts of interest related to the manuscript.

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