Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, radiographic and MRI findings?

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Running title: Ultrasound in Knee Osteoarthritis

Abstract

Objectives

To investigate the associations of Outcome Measures in Rheumatology (OMERACT) ultrasound scores for knee osteoarthritis (OA) with pain severity, other symptoms, and OA severity on radiographs and magnetic resonance imaging (MRI).

Methods

Participants with symptomatic and mild-moderate radiographic knee OA underwent baseline dynamic ultrasound assessment according to standardized OMERACT scanning protocol. Using the published ultrasound image atlas, a physician operator obtained semi-quantitative or binary scores for ultrasound pathologies. Clinical severity was measured on Numerical Rating Score (NRS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) symptoms and pain sub-scores. OA severity was assessed using the Kellgren-Lawrence grade (KLG) on X-rays and MRI osteoarthritis knee score (MOAKS) on non-contrast-enhanced MRI. Separate linear regression models were used to determine associations of ultrasound OA pathologies with pain and KOOS sub-scores, and Spearman's correlations were used for ultrasound scores with KLG and MOAKS.

Results

Eighty-nine participants were included. Greater synovial hypertrophy, power Doppler (PD) and meniscal extrusion scores were associated with worse NRS pain (*B*=0.92,95% confidence interval CI 0.25,1.58); *B*=0.73(95% CI 0.11,1.35) and *B*=1.01(95% CI 0.22,1.80). All greater ultrasound scores except for cartilage grade demonstrated significant associations with worse KOOS symptoms while only PD and meniscal extrusion were associated with worse KOOS pain. All ultrasound scores except for PD were significantly correlated with KLG. Ultrasound pathologies except for cartilage revealed moderate to good correlation with their MOAKS

counterparts with ultrasound synovitis having the greatest correlation {0.69(95% CI 0.60, 0.78}.

Conclusion

OMERACT ultrasound scores revealed significant associations with pain severity, KLG and MOAKS.

Keywords

Osteoarthritis; Musculoskeletal ultrasound; Imaging; Association

Introduction

Osteoarthritis (OA) is one of the most prevalent chronic health conditions causing pain and disability among elderly adults (1). Approximately 15.4% of the adult population have symptomatic OA (2). By 2030, OA is predicted to be the single greatest cause of disability globally, with an estimated 35% prevalence (3).

The pathophysiology of knee OA is complex and involves multiple-tissue pathologies affecting the whole joint structure (4). Pathologies include synovitis, synovial hypertrophy, effusion, power Doppler (PD) signals, meniscal damage, cartilage loss and bony osteophyte (5, 6). Imaging tools are used to visualize the severity of these pathologies, but each has its own limitations (7). The plain radiograph involves radiation and can view only the bony structure while MRI is expensive and not readily accessible in clinical practice (4). Ultrasound is a non-invasive imaging tool that can detect soft tissues as well as the bony cortex including osteophytes in OA (6).

One concern expressed about ultrasound has been observer-dependence. As such, the Outcome Measures in Rheumatology (OMERACT) group (8) used international consensus and reliability testing to develop standardized knee ultrasound scanning methods and grading scores for synovitis, synovial hypertrophy, effusion, power Doppler (PD), cartilage thinning, osteophyte and meniscal extrusion; however, the validity of these grading scores has not been tested. Therefore, the objective of this study is to examine the associations of the OMERACT knee OA ultrasound grading scores by testing their relationship with pain severity, clinical symptoms, and severity on plain radiograph and MRI findings.

Methods

Study design and participant selection

This is a cross-sectional analysis using baseline data from the Sydney, Australia site of the ongoing RESTORE (platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR knee ostEoarthritis) clinical trial (Trial registration No: ACTRN12617000853347) (9). Inclusion and exclusion criteria were the same as for the RESTORE study (9). Briefly, eligible participants met the following inclusion criteria.

(i) aged>50 years;

(ii) knee pain on most days in the last month;

(iii) osteophytes on x-ray; and

(iv) A minimum pain score of 4 on an 11-point numeric rating scale (NRS) for the last week

The exclusion criteria included (i) Kellgren and Lawrence (KL) grade 1 or grade 4; (ii) predominant lateral tibiofemoral disease; (iii) systemic or inflammatory joint disease; (iv) history of crystalline or neuropathic arthropathy; (v) be unwilling to discontinue NSAID and other analgesic usage for knee pain, except for paracetamol for rescue pain relief, from 2 weeks prior to baseline assessment.

For those participants with bilaterally eligible knees, the most symptomatic knee was deemed the study knee. The cohort included here is a convenience sample recruited from the baseline visit, and all participants available for an ultrasound visit between September 2017 and February 2019 were included.

Participants' demographic data such as age, gender, height, weight and symptom duration were collected as previously described (9). Body mass index (BMI) was calculated using height and weight (kg/m2). This study was approved by the Northern Sydney Local Health Districts Human Research Ethics Committee (HREC/16/HAWKE/430).

Clinical assessment

On the same day of the ultrasound scan, average overall knee pain severity over the last week was measured using an 11-point NRS with terminal descriptors 'no pain' (score 0) and 'worst pain possible' (score 10), with the highest scrores denoting the worst pain, and this outcome measure is recommended to be included in knee OA clinical trials by the Osteoarthritis Research Society International (10). The Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and other symptoms sub-scores were collected. The KOOS is a knee-specific self-report outcome measure with high test-retest reliability, internally consistent and face and content validity [12]. Likert responses range from None to Extreme, and scores range from 0 to 100, with lower scores indicating worse symptoms. The KOOS pain subscale is scored from 9 questions about knee pain frequency experienced in the last week, and the amount of knee pain experienced during specific activities such as twisting, bending and walking. The KOOS other symptoms subscale is scored from 7 questions regarding other symptoms experienced in the last week, such as swelling, restricted range of motion and mechanical symptoms.

Radiological Assessment

Participants underwent bilateral weight-bearing posteroanterior radiography ([Model R-20 J] Shimadzu Corporation, Nakagyo-ku, Kyoto, Japan) before ultrasound and MRI examinations. Kellgren and Lawrence grade was assessed by a rheumatologist (SY, 7 years of experience in grading radiograph of knee OA) who was blinded to clinical, ultrasound and MRI scores.

Ultrasound evaluation

physician operator (WMO, 6 years of musculoskeletal ultrasound experience and certified with musculoskeletal ultrasound in rheumatology (RhMSUS) by the American

College of Rheumatology) blinded to clinical, radiograph and MRI findings, performed and scored the ultrasound scans of the study knee (11). These were done dynamically and extensively in a wide area with a multi-frequency linear 14L5 transducer (using 10MHz) of Aplio Platinum 500 machine, Toshiba, Japan, according to the standardized OMERACT scanning protocol (8). The ultrasound scores for seven disease manifestations were then graded by the same operator using the OMERACT knee ultrasound OA atlas: semi-quantitative scores for (i) synovitis (0-3) (combined synovial hypertrophy and effusion), binary scores (0-1) for (ii) synovial hypertrophy ≥ 4mm, (iii) effusion ≥ 4mm (12), and (iv) PD signals separately from suprapatellar recess in a longitudinal plane, medial and lateral para-patella recesses in a transverse plane, semi-quantitative scores for (v) osteophytes (0-3) from the medial and lateral joint aspects in a longitudinal plane and (vi) meniscal extrusion (0-2) (only the medial joint aspects) in longitudinal plane, and for (vii) cartilage abnormalities (0-3) in transverse plane on a maximally flexed knee. (**supplementary file 1**). The application specialist from Toshiba machine settings optimised the machine setting, providing grey scale gain=85%, probe frequency=10 MHz, doppler frequency=6Mhz, doppler gain=40%, pulse repetition frequency=14.8kHz and wall filter=5. The ultrasound operator was not allowed to change these, except for depth and focus, through the study.

The maximum score approach (i.e, the highest score of the same ultrasound features such as synovitis, osteophyte, etc from different scanned sites was taken as the final score of the whole knee) (13) was then used to correlate with clinical and radiographic and MRI data of the study knee. For the whole knee scan for these seven disease manifestations, it took around 8 minutes for scanning and about 13 minutes for scoring.

Inter-rater and intra-rater reliability

Testing of inter-rater reliability testing was limited to supra-patellar synovitis and PD, medial osteophyte and medial meniscal extrusion. A second trained reader (DP, 8 years of musculoskeletal ultrasound experience) independently performed the ultrasound scans of the study knee in 20 patients after the first ultrasound operator finished scanning, and provided the independent grading. To evaluate intra-rater reliability of all seven ultrasound OA manifestations, the same operator (WMO) re-scanned 10 patients one week later and calculated ultrasound scores whilst blinded to the previous scores.

MRI evaluation

On the same day as the ultrasound scanning, the study knee was imaged with a 3T MRI scanner (Siemens Skyra, Siemens Healthcare, Erlangen, Germany) using a 15-channel transmit/ receive knee coil. The following 5 MRI sequences were performed:

1) sagittal T2-weighted dual-echo steady-state

2) sagittal proton-density-weighted fat-suppressed non-contrast turbo spin-echo (TSE)

3) coronal proton-density-weighted TSE

4) coronal proton-density-weighted fat-suppressed TSE

5) axial proton-density-weighted fat-suppressed TSE.

Technical details of the sequences can be found in **supplementary file 2**.

The semiquantitative MOAKS grading involves evaluation of the cartilage loss (any or full-thickness) from patellofemoral, medial and lateral tibiofemoral compartments, osteophyte from 12 different sites, medial meniscal extrusion, effusion-synovitis over the supra-patellar and parapatellar areas, and Hoffa's synovitis over the Hoffa's fat pad at the infra-patellar area as described by Hunter *et al* (13). The maximum score of the same MRI features such as cartilage loss (any or full-thickness), and osteophyte from all sites was taken as the whole knee score for that MRI feature.

Inter-rater and intra-rater reliability of MRI

Scoring of the MOAKS was performed by W.M.O., who obtained imaging training from an experienced musculoskeletal radiologist (J.M.L., 25 y of experience in musculoskeletal MRI). Both readers independently scored the MRI images of 10 consecutive participants. The readers were blinded to clinical features and symptoms and radiograph and ultrasound scores. WMO also performed the second reading of all MRI images one month apart to obtain the intra-rater reliability.

Statistics

Descriptive statistics of categorical variables were expressed as frequencies and percentages. Descriptive statistics of continuous variables were calculated as mean and standard deviation (SD) for normally distributed data, and median and range for non-normally distributed data. Although it might seem that "the OMERACT US scoring system" is 1 single scoring system, in fact, it consists of 7 US scoring systems, covering both structural and inflammatory features present in knee OA. For all these scoring systems, relationship has to be assessed separately. To investigate whether these ultrasound features were associated with pain and other symptoms, separate linear regression models were fit with each ultrasound feature as predictor, adjusting for age, gender, BMI, duration of disease and radiographic KLG. Spearman's correlations were calculated to determine the relationship of ultrasound features with radiographic KLG and MRI MOAKS scores. Correlation coefficients were interpreted according to the Evans' classification (14), <0.20:very weak; 0.20-0.39:weak; 0.40-0.59:moderate; 0.60-0.79;strong and >0.80:very strong. The study was powered for the association of the seven ultrasound pathologies with VAS joint pain. With 7 potential predictors, testing at the 5% significance level with 80% power, and assuming a minimum R^2 of 0.3, 42 patients were required to show that the ultrasound scores explain a statistically

significant amount of the variation in joint pain. All statistics were conducted with SPSS version 23 and a significant association/correlation was defined as a p-value less than 0.05.

Results

Demographic, clinical characteristics, ultrasound and MRI findings

Eighty-nine participants were included in this study with 48 (53.9%) females, BMI of 27.5±6.4), pain of 5.8±1.5 on an NRS scale, 59.6% of participants having KLG III, and 95.5% and 47.0% showing ultrasound synovitis grade ≥1 and PD signals respectively. However, synovial hypertrophy and effusion on ultrasound were present in 47.2% and 59.6% of the participants using quantitative cut-offs of 4 mm. All participants had osteophytes and meniscal extrusion on ultrasound, with 95.5% having cartilage abnormalities. **Table 2.** demonstrates the other characteristics in detail.

Reliability for ultrasound scores

The kappa statistics for inter-rater reliability ranged from 0.55 to 0.88 indicating moderate to excellent agreement and the kappa statistics for intra-rater reliability ranged from 0.63 to 1.00 indicating good to excellent reliability (**Table 1**).

Reliability for MOAKS score

The kappa statistics for the inter-rater reliability ranged from 0.42 to 0.90 indicating moderate to excellent agreement for individual MRI lesions while intra-rater reliability was mostly good to excellent as shown by kappa statistics ranging from 0.62 to 0.92 (**Supplementary file 3**).

Association of ultrasound findings with clinical symptoms

After adjusting for the confounders, only OMERACT scores of synovial hypertrophy, PD signals and meniscal extrusion scores were significantly associated with pain severity on NRS (Table 3). For example, when power Doppler was present (0-1), the pain NRS increased by 0.54 units (Beta coefficient 0.54, 95% CI [0.11, 0.96]).

All OMERACT scores except for cartilage grade demonstrated significant associations with KOOS other symptoms (Table 3). For example, when PD signals were present (0-1), the KOOS other symptoms score decreased (worsened) by 6.1 units (Beta coefficient -6.12, 95% CI [-10.93, -1.31]). Only meniscal extrusion and PD signals were significantly associated with KOOS pain (Table 3). For example, for a one unit increase on meniscal extrusion grade (0 to 2 on a semi-quantitative score), knee pain on the KOOS score decreased (worsened) by 10.8 units (Beta coefficient -10.84, 95% CI [-18.57, -3.10]).

Association of ultrasound findings with radiographic KLG

The ultrasonographic synovitis, synovial hypertrophy, effusion, osteophyte and meniscal extrusion were significantly correlated with KLG except for PD signals and cartilage scores (**Figure 1**).

Association of ultrasound findings with MOAKS scores

The associations between ultrasound features and their MRI counterparts are presented in **figure 2.** Synovitis, synovial hypertrophy, effusion, PD signals, osteophyte and meniscal extrusion on ultrasound were significantly associated with their respective MRI counterparts with the largest correlation for ultrasound synovitis (**Figure 3**). Measures of osteophytes and meniscal extrusion showed significant associations between the two imaging modalities while ultrasound cartilage thickness showed a significant but weak relationship with MRI cartilage thickness (any or full) on MRI.

Discussion

This is the first study examining the associations of OMERACT knee ultrasound scores against pain severity and other symptoms using well-validated self-reported questionnaires, and standard imaging tools widely used in the OA clinical and research setting. We found significant associations of ultrasound scores such as PD signal, synovial hypertrophy and meniscal extrusion with NRS pain and KOOS pain sub-score as well as KOOS symptoms. Significant associations with radiographic severity were detected in all ultrasound pathologies except for PD signals and cartilage grades, with meniscal extrusion showing the highest associations. Ultrasound synovial and structural disorders had significant associations with their MRI counterparts with moderate to strong correlation for synovitis, synovial hypertrophy, PD signals, meniscal extrusion and osteophyte. Thus, our findings further support the use of the OMERACT ultrasound scores in the knee OA research setting. The OMERACT scanning protocol involved scanning over a wide area as well as multiple sites instead of a single predefined location. This can increase the chance of detecting more pathologies, if present, compared to a single predefined scan, due to the capability of scanning the entire joint. In addition, the maximum score of a certain ultrasound pathology from different scanning sites was used as a single final score in our study instead of adding them because the semi-quantitative score is an ordinal and not an interval scale (15). This method is commonly used in MRI research (13, 16). It might provide better coverage of pathologies present in the whole knee compared to single location-specific score. As an example, out of 16 patients with grade 0 synovitis in supra-patella recess in our study, 8 people demonstrated ≥ grade 1 synovitis in medial parapatellar recess. This is also supported by the fact that the prevalence of MRI effusion-synovitis which takes into account synovitis in all synovial recesses on axial MRI scan is almost the same in our study (93.3%).

Reliability of ultrasound scores

The reliability was done in medial compartment because our study participants had predominant medial OA. On comparison with OMERACT reliability exercises which reported moderate to good agreement across two rounds (kappa= 0.52 and 0.51 for synovitis, kappa=0.54 and 0.58 for meniscal extrusion, and kappa=57 and 0.62 for osteophyte), our results were comparable for synovitis (kappa=0.55) and meniscal extrusion (kappa=0.55) while we have better agreement for osteophyte (kappa=0.88). In addition, in this study, we have recruited the sonographer to perform and score the ultrasound scan independently in 20 patients (only 22% of the whole study sample). In order to get away from the conception of operator-dependency in ultrasound, it would be helpful in future studies to also have an uninvolved reader assess the US images and determine the agreement between those two US readers, which could support the lack of operator-dependency.

Association of ultrasound synovitis grade with clinical and other imaging sco

The prevalence of synovitis, when assessed using the OMERACT atlas maximum score approach (8), is high (more than 95%). However, for synovial hypertrophy and effusion which used the strict criteria of 4mm cut-offs (for which there is no published atlas), the prevalence of these synovial disorders reduces to about 50%, in agreement with a meta-analysis report in knee OA {49% (95% CI 30.5,67.6)} (17). This may indicate that OMERACT atlas for grade 1 synovitis might include people with normal physiological fluid which can be up to 3mm thick as the semi-quantitative grading score is visually based on the amount of distension of knee recesses using the standardized atlas (12).

The association of synovial pathologies with pain and symptoms did not show consistent results in the literature. Some authors reported significant associations (18-21) while others determined no association (22-25). This may be due to using different cut-offs (4mm in vs 2mm for synovial hypertrophy), different grading methods (semi-quantitative or

qualitative), and application of varying case-definitions and inclusion of different disease severity in the study protocols. The utilisation of standardized OMERACT ultrasound knee score in future studies will help minimise heterogeneity of such scanning protocols and grading methods. Our study using the OMERACT synovitis atlas and quantitative cut-off (4 mm) for synovial hypertrophy demonstrated significant correlation.

Ultrasound synovitis is strongly correlated with MRI effusion-synovitis. This finding further supports the symptom-structure discordance widely recognized in the OA imaging literature (26). This is due to the fact that pain is a very subjective phenomenon (27), and psychosocial factors and neurobiological mechanism such as pain sensitization (28) can influence the association. Although synovial hypertrophy has significant correlations with NRS pain, KOOS symptoms and KOOS pain, it had only a moderate correlation with MRI synovitis. As a note, MRI is not contrast-enhanced in our study and so not optimal for detecting the synovial hypertrophy (29), thereby placing MRI at a disadvantage on the level of association. Our magnitude of association is consistent with the report by two studies (20, 30) although they utilized different ultrasound scanning methods and grading definitions (different quantitative cut-offs for semi-quantitative scores) for both MRI and ultrasound scores.

Association of ultrasound power Doppler grade with clinical and other imaging scores Only PD signals and meniscal extrusion are important predictors for NRS pain. This finding is reinforced by the significant associations of these ultrasound pathologies with KOOS pain, a different composite measure of pain characteristics involving pain frequency and amount of pain during specific activities. Although PD signals had been a focus of interest in rheumatoid arthritis (31), there is a paucity of publications which reported the isolated association of PD signals with pain severity due to very low prevalence of PD observations in the studies (19, 23, 32) or because the extent of association was based on total inflammatory score combining synovitis and PD signals (33, 34) or the scanning protocol did not include

evaluation of PD signals. Iagnocco *et al* (32) observe PD signals in only one patient in their sample (n=17) while Hall *et al* obtain 10 observations in 62 patients with symptomatic knee OA (23), leading to lack of power to detect any significant associations. Song *et al* reported that PD signals revealed the significant association of PD signals with pain (r=0.37,p=0.02) (20), which is confirmed by our study.

As expected, PD is not a significant predictor of KL grade perhaps due to the fact that PD is a sensitive and reliable marker only for acute and active inflammatory phase of arthritis (35, 36). However, knee OA is recognized as off-and-on disease with exacerbation and remission (27) while KLG reflects the collective structural outcome accumulated over long-term disease process and focused on change in the bone (37, 38).

Association of ultrasound meniscal extrusion grade with clinical and other imaging scores

Discordant results were reported for the association of meniscal extrusion with pain; some with significant results (22, 39) and other with negative results (21, 40, 41). Chan *et al* (22) reported that medial meniscal extrusion measured in mm showed significant association with extent of pain during stair-climbing while the degree of meniscal extrusion was significantly increased in painful knee OA compared with painless knee (39). On the other hand, significant association was not detected between presence of meniscal extrusion (cut-off >3mm) with pain severity in a case-control design (40, 41). In a recent study, Kijima *et al* reported that meniscal extrusion >4.3mm cut-off provided high sensitivity (85%) and specificity (85%) for presence of knee pain in the general population(42). In MRI studies, meniscal extrusion plays a crucial role in OA pathogenesis, progression and symptom genesis (43, 44).

The meniscal extrusion showed the strongest association with KLG perhaps due to the fact that our sample was limited only to KLG 2 and 3 the difference of which is only joint

space narrowing (JSN). Hunter *et al* reported that the meniscus accounts for a substantial proportion of the variance explained in JSN (45).

Association of ultrasound cartilage grade with clinical and other imaging scores

Unexpectedly, cartilage grade did not reveal a significant association with KLG. Several reasons might contribute to this: 1) the location where cartilage ultrasound measures were taken might not exactly represent the actual maximal weight-bearing area on standing and 2) cartilage thinning might be on the tibial cartilage which is inaccessible to ultrasound. However, further analysis after dichotomising the cartilage (cartilage thinning present or not by combining grade 0 and 1, and grade 2 and 3 respectively) is non-significant. The authors of the OMERACT ultrasound OA atlas discussed that ultrasound cartilage grade needs further research due to assessment problems (8). Ultrasound cartilage grade also failed to show a significant association with all other outcome measures except for MRI cartilage loss which revealed a significant but weak association. In the MRI literature, the associations between cartilage abnormalities and symptoms are not consistent (46, 47).

While it is important to standardize outcome tools in clinical trials, and this study does provide the usefulness of OMERACT ultrasound knee OA protocol as a scoring system, the utility of this US scoring tool for a meaningful clinical practice needs further research for several reasons. Cartilage loss correlated with nothing but MRI, PD did correlate with NRS pain, but as yet, anti-synovial/ anti-inflammatory therapies haven't been very promising in knee OA, and baseline inflammation hasn't consistently been shown to predict response to anti-inflammatory/anti synovial therapies (48, 49)

Limitations of the study

We did not include psychosocial factors which can have an impact on the level of symptom-structure association. However, the important known confounders are adjusted in our

analysis. Another limitation is that the anatomical site of ultrasound scoring might take place in a different location from measurements on an MRI in the absence of invasive marker as in the cartilage and osteophyte scores. Similarly, the x-rays were obtained in weight-bearing position while the ultrasound and MRI were obtained with a person lying supine. The last limitation is that the study relies mainly on results of linear regression and correlation analyses. Therefore, the lack of correlation between variables may not necessarily represent a lack of a relationship as some relationships may be non-linear.

Conclusion

In conclusion, most of OMERACT ultrasound OA scores had a significant but modest association with symptoms and imaging scores from radiographs and MRI. These results support the construct validity of the OMERACT ultrasound scores and their use in future ultrasound studies as a useful outcome. As this is a cross-sectional study, longitudinal studies are required to determine its responsiveness to change to further determine its value as an outcome measure in interventional studies.

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Conflict of Interest: DJH provides consulting services to Pfizer, Lilly, Merck Serono, TLC bio. Other authors declared no conflict of interest.

Data Availability: Data are available from the corresponding author on reasonable request.

Author contributions

WMO, DJH and JML conceived and designed the study. WMO, DJH, JML, KLB, DP and SY contributed to acquisition of clinical data of this study. WMO had full access to all the data and analysis and drafted the first manuscript. All authors revised the manuscript and gave final approval of the article for submission.

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Figures:

Figure 1. The association of OMERACT ultrasound OA scores with KLG on radiograph

CI= Confidence interval; KLG= Kellgren and Lawrence grade; MME=Medial Meniscal Extrusion; PD=Power Doppler; SH= Synovial Hypertrophy; US=ultrasound

Figure 2. The association of OMERACT ultrasound OA scores with MOAKS on magnetic resonance imaging

CI= Confidence interval; MME=Medial Meniscal Extrusion; MOAKS= Magnetic Resonance Imaging Osteoarthritis Knee Score; MRI= Magnetic Resonance Imaging; PD=Power Doppler; SH= Synovial Hypertrophy; US=ultrasound

Figure 3. The demonstration of ultrasound and MRI synovitis from three synovial recesses of the knee in the same patient. **A.** OMERACT Grade 3 synovitis at the suprapatellar recess on a longitudinal scan. **B.** OMERACT Grade 3 synovitis at the medial parapatellar recess on a transverse scan **C.** OMERACT Grade 3 synovitis at the lateral parapatellar recess on a transverse scan **D.** MOAKS grade 3 effusion-synovitis on the axial non-contrast-enhanced MRI scan

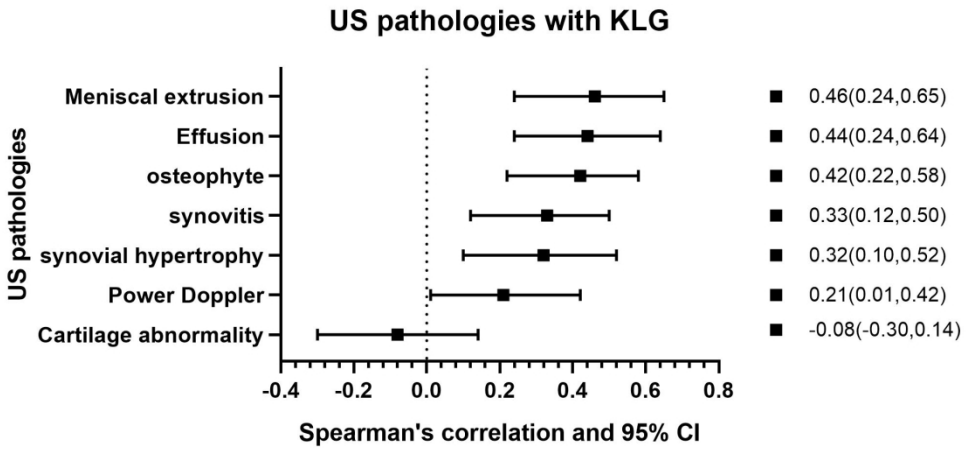

Figure 1. The association of OMERACT ultrasound OA scores with KLG on radiograph

173x84mm (300 x 300 DPI)

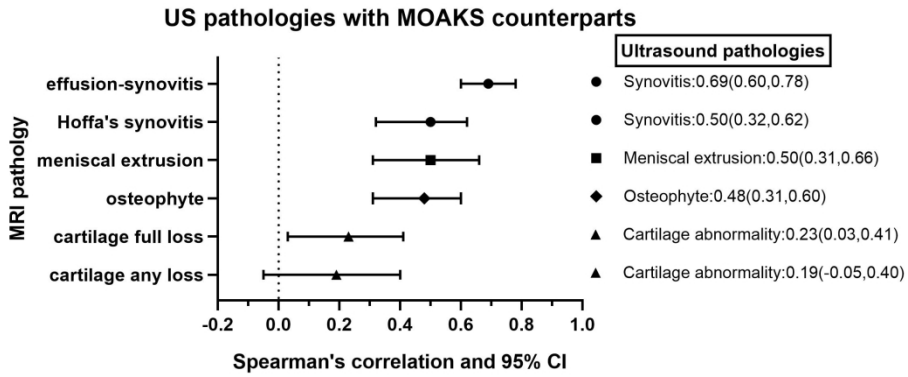

Figure 2. The association of OMERACT ultrasound OA scores with MOAKS on magnetic resonance imaging

208x97mm (300 x 300 DPI)

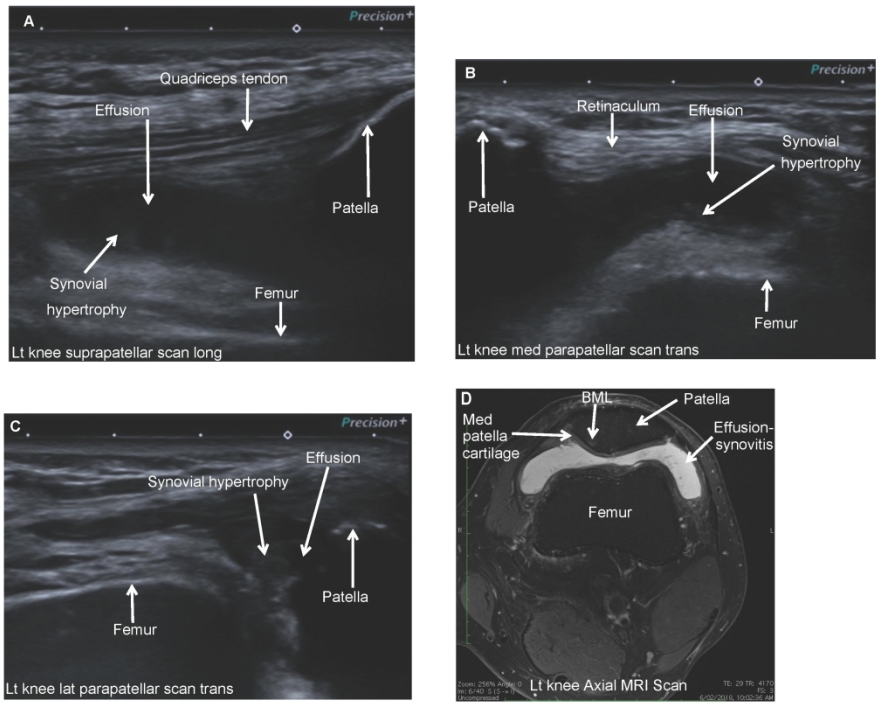

Figure 3. The demonstration of ultrasound and MRI synovitis from three synovial recesses of the knee in the same patient

279x215mm (300 x 300 DPI)

Table 1. Intra-rater and inter-rater reliability of OMERACT ultrasound scores in knee OA

Ultrasound pathologies	Intra-rater reliability (Kappa/ Weighted Kappa)	Percent agreement	Inter-rater reliability	Percent agreement
Synovitis (Supra-patella)	0.81(0.58 to 1.00)#	80	0.55 (0.36 to 0.75)	55
Synovitis (Medial parapatella)	0.63(0.22 to 1.00)#	70		
Synovitis (Lateral Parapatella)	0.75(0.43 to 1.00)#	80		
Effusion	1.00	100		
Synovial hypertrophy	0.80(0.44,1.00)	90		
PD (Supra-patella)	0.80(0.44,1.00)	90	0.62(0.15 to 0.87)	90
Med Osteophyte grade	0.67(0.32 to 1.00)#	80	0.88(0.72to 1.00)	90
Lateral osteophyte grade	0.74(0.40 to 1.00)#	80		
Medial Meniscal Extrusion grade	0.74(0.26 to 1.00)#	90	0.55(0.25 to 0.84)	70
Medial Cartilage grade	0.64(0.04 to 1.00)#	70		
Lateral cartilage grade	0.7540.51 to 0.99)#	70		

# indicates weighted kapp; OA=Osteoarthritis

Table 2. Baseline clinical, radiographic, ultrasound and MRI data of study participants

	Number (%)	Mean (SD)/Median (Range)
Population	89	
Age, years		61.5±6.9
Female	48(53.9)	
BMI		27.5±6.4
Disease duration, years		8.9±9.4
NRS pain		5.8±1.5
KOOS Symptom		49.5±16.4
KOOS Pain		51.3±14.5
Radiological scores		
Kellgren and Lawrence grade		3(2-3)
II	36(40.4)	
III	53(59.6)	
Ultrasound OMERACT Scores		
Synovitis grade		2(0-3)
0	4(4.5)	
I	18(20.2)	
II	33(37.1)	
III	34(38.2)	
Effusion (+)	53(59.6)	
Synovial Hypertrophy (+)	42(47.2)	
PD (+)	42(47.2)	
Cartilage grade		2(0-3)
0	4(4.5)	
I	21(23.6)	
II	41~~28~~(46.1~~31.5~~)	
III	23~~31~~(25.8~~34.8~~)	
Osteophyte grade		2(1-3)
0	0	
I	11(12.4)	
II	41(46.1)	

III	37(41.6)	
Meniscal Extrusion grade		2(1-2)
0	0	
I	23(25.8)	
II	66(4.2)	
MRI MOAKS Scores		
Effusion-synovitis grade		2(0-3)
0	6(6.7)	
I	24(27)	
II	26(29.2)	
III	33(37.1)	
Hoffa's synovitis grade		1(0-3)
0	5(5.6)	
I	40(44.9)	
II	32(36)	
III	12(13.5)	
Cartilage Any Loss grade		3(2-3)
0	0	
I	0	
II	12(13.5)	
III	77(86.5)	
Cartilage Full Loss grade		2(0-3)
0	2(2.2)	
I	15(16.9)	
II	37(41.6)	
III	35(39.3)	
Osteophyte grade		3(1-3)
0	0	
I	1(1.1)	
II	8(9)	
III	80(89.9)	
Meniscal Extrusion grade		3(0-3)

0	3(3.4)
I	10(11.2)
II	31(34.8)
III	45(50.6)

~~BML= Bone Marrow Lesion(s);~~ KOOS= Knee Injury and Osteoarthritis Outcome Score; MRI= Magnetic Resonance Imaging; MOAKS= MRI Osteoarthritis Knee Score; NRS =Numerical Rating Scale; OMERACT= Outcome Measure in Rheumatology; PD= Power Doppler

Table 3. The association of OMERACT ultrasound KOA scores with NRS pain, KOOS symptoms and KOOS pain

Ultrasound pathologies	Grading score	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)
		NRS		KOOS Symptoms		KOOS pain	
Synovitis	0-3	0.06 (-0.30,0.41)	0.23 (-0.17,0.62)	-1.22 (-2.66,0.22)	**-7.00 (-11.09,-2.90)**	-1.12 (-4.64,2.40)	-3.00 (-6.85,0.87)
Synovial hypertrophy	0-1	0.49 (-0.12,1.10)	**0.92 (0.25,1.58)**	-4.47 (-11.39,2.44)	**-10.81 (-18.10,-3.51)**	-0.29 (-1.37,0.79)	-6.82 (-13.53,-0.12)
Effusion	0-1	0.16 (-0.47,0.78)	0.50 (-0.23,1.23)	-4.19 (-11.23,2.85)	**-10.74 (-18.54,-2.94)**	-1.84 (-8.08,4.40)	-5.29 (-12.49,1.90)
Power Doppler	0-1	**0.54 (0.11,0.96)**	**0.73 (0.11,1.35)**	**-6.12 (-10.93,-1.31)**	**-12.66 (-19.20,-6.12)**	**-4.73 (-9.01,-0.45)**	**-8.39 (-14.47,-2.30)**
Meniscal extrusion	0-2	**0.71 (0.02,1.40)**	**1.01 (0.22,1.80)**	-5.42 (-13.29,2.46)	**-9.88 (-18.60,-1.10)**	**-8.11 (-14.90,-1.31)**	**-10.84 (-18.57,-3.10)**
Osteophyte	0-3	0.21 (-0.25,0.67)	0.25 (-0.28,0.77)	**-6.46 (-11.45,-1.48)**	**-7.79 (-13.35,-2.24)**	-3.58 (-8.07,0.91)	-0.28 (-7.96,2.37)
Cartilage thickness	0-3	-0.11 (-0.48,0.27)	-0.22 (-0.61,0.18)	2.30 (-1.93,6.53)	2.27 (-2.11,6.64)	3.10 (-0.59,6.80)	3.52 (-0.35,7.38)

CI=Confidence Interval; KOA= Knee Osteoarthritis; KOOS= Knee Injury and Osteoarthritis Outcome Score; NRS =Numerical Rating Scale; OMERACT= Outcome Measure in Rheumatology; PD= Power Doppler
Significant results with p value <0.05 are denoted in bold. Adjustment included age, gender, BMI, duration of disease and radiographic Kellgren and Lawrence grade