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A Standardized, Pragmatic Approach to Knee Ultrasound for Clinical Research in Osteoarthritis: The Johnston County Osteoarthritis Project

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Objective. This study sought to develop and employ a comprehensive and standardized ultrasound (US) protocol and scoring atlas for the evaluation of features relevant to knee osteoarthritis (KOA) in a community-based cohort in the United States, with the goals of demonstrating feasibility, reliability, and validity.

Methods. We utilized data from the fourth follow-up (2016-2018) of the Johnston County OA Project, which includes individuals with (~50%) and without radiographic KOA. All participants underwent standardized knee radiography and completed standard questionnaires including the Knee Injury and Osteoarthritis Outcome Score (KOOS). Bilateral knee US images were obtained by a trained sonographer using a standardized protocol and scored by trained rheumatologists using an atlas developed for this study. A total of 396 knees were each scored by two readers according to the atlas. Associations between US features, radiographic findings (graded by an expert radiologist), and KOOS scores were assessed.

Results. Overall interreader reliability for US scoring was fair to moderate. The strongest correlations between US and radiographic features were seen for osteophytes, and similarly strong correlations were seen between US osteophytes and overall radiographic Kellgren-Lawrence Grade, demonstrating criterion validity. Features of effusion/synovitis and osteophytes were most associated with KOOS pain and impaired function.

Conclusion. US is a feasible, reliable, and valid method to assess features relevant to KOA in clinical and research settings. The protocol and atlas developed in this study can be utilized to evaluate KOA in a standardized fashion in future clinical studies, enabling greater utilization of this valuable modality in osteoarthritis.

INTRODUCTION

Knee osteoarthritis (KOA) is exceedingly common, with radiographic KOA affecting at least 19% of adults aged 45 and older (1); it is more common in women, older individuals (2), and African Americans (3), with predicted substantial increases in the coming years due to aging and obesity trends (4). KOA diagnosis has traditionally been based on a combination of clinical and radiographic features, although there is a known discordance between the two (5); additionally, radiography lacks sensitivity for early detection and to change over time and thus cannot adequately assess soft tissues (such as synovium, tendon/ligament, or meniscus) or signs of inflammation

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[as indicated on ultrasound (US) by synovial hypertrophy/synovitis or effusion]. US provides the ability to image many features relevant to KOA, including bony changes (osteophytes), effusions, synovitis, popliteal cysts, meniscal extrusion, and articular cartilage damage (6,7). Additionally, recent studies have demonstrated reliability when a standardized protocol is utilized (8), although these have not been optimized for use in real-world settings.

Although US can provide comprehensive identification of early changes relevant to OA, it has not been widely utilized, particularly in the United States, due in part to "…challenges not faced by our colleagues outside of the United States" (9). Torralba et al have noted the much earlier and more immersive uptake of US in Europe and other countries as well as the fact that there are differences in the focus of point-of-care US when performed by a rheumatologist in contrast with nonrheumatologists, emphasizing the need for specific guidance (9). However, uptake is likely to increase given that more than 90% of rheumatology fellowship programs are teaching musculoskeletal US (10). Magnetic resonance imaging (MRI) has been much more widely used than US in the characterization of osteoarthritis (OA) for research purposes, and MRI findings, particularly of effusion/synovitis (11–13), have been correlated with knee pain (14). However, MRI is much more expensive and time-consuming compared with US, the optimal sequences needed to image KOA are not yet universally agreed upon or available, and its use is limited in many common clinical situations, including in patients with claustrophobia, larger body habitus, or metal implants.

US allows point-of-care assessment as well as incorporation of dynamic maneuvers to image joints in motion, as well as query multiple joints in a single visit. Because of its higher spatial resolution, US can display fibrillar and structural details of muscles, tendons, and ligaments that MRI cannot detect (15). Additionally, US is highly sensitive and specific for (16–18), and superior to MRI in identifying (19,20), calcium crystal deposition, which is associated with greater inflammation and comorbidities in OA (21–23). A systematic review and meta-analysis of knee US (KUS) evaluation found strong correlations between MRI and US in predominant KOA features, including synovitis, effusion, synovial hypertrophy, cartilage thickness, and popliteal cysts (24). A previous Outcome Measures in Rheumatology (OMERACT) reliability study on US concluded that KOA could be scored reliably with a standardized US protocol, although it was designed as "a reliability study, not a validation exercise" and lacked discussion of some of the features of interest, including calcium crystals and popliteal cysts (8).

In this study, we developed and employed, in a large ongoing community-based cohort study of individuals with and without KOA, a standardized, comprehensive US protocol and scoring atlas for evaluation of US features relevant to KOA that are readily generalizable to other clinical studies in the United States. In addition, we demonstrated the feasibility, reliability, and validity (ie, criterion validity related to radiography and construct validity in relation to pain and function) of this approach.

METHODOLOGY

The Johnston County OA Project

The Johnston County OA Project (JoCo OA) is a population-based prospective cohort study in African American and white men and women who were recruited without regard for OA status, joint pain, or other medical symptoms or conditions. The JoCo OA study was originally designed in 1990 in rural Johnston County, North Carolina, which had experienced, and continues to experience, high rates of poor health outcomes among various sociodemographic subgroups (3). The current analysis included all individuals with consecutive clinic visits on or after November 14, 2017, attending the fourth JoCo OA follow-up visit (2016-2018), excluding only those knees with total joint replacement. All examinations were carried out in the JoCo OA Research Clinic in Smithfield, which has been utilized solely by JoCo OA and related research studies. Various data were collected by trained clinical data collectors including validated self-report questionnaire instruments, blood pressure, weight, height, and waist/hip girths. Standardized radiography and ultrasound were obtained as described below. The parent study, including a modification for ultrasound, was approved by the Institutional Review Board at the University of North Carolina (IRB #92-0583); all participants provided informed consent.

Radiographic imaging

Using the Synaflexer® positioning device that has been shown to be reliable in longitudinal studies (25), fixed flexion posterior-anterior radiographs in weight-bearing were obtained of both knees. All radiographs (XRs) were read for Kellgren-Lawrence grade (KLG) (26), osteophytes, and joint space narrowing (JSN) by an experienced musculoskeletal radiologist (JBR), blinded to other clinical and imaging data and for whom high reliability has been reported [intrarater reliability $\kappa = 0.89$, (27)]. KLG ranged from 0 to 4, whereas osteophytes and JSN were graded on a 0 to 3 scale based on a previously published radiographic atlas (28). Radiographic KOA (rKOA) was defined as KLG ≥ 2. Symptomatic KOA was defined as rKOA with symptoms of pain, aching, or stiffness in the same knee.

US imaging

In order to incorporate US imaging into our existing study workflow, we needed to develop a standardized protocol and ensure its feasibility and reliability. We then adapted prior work to develop a scoring atlas specific to our study. Both processes are detailed below.

US acquisition in JoCo OA. All images were obtained by the JoCo OA radiologic technologist (SSG) according to a landmark-based protocol (Appendix S1, finalized February 2018) that was developed and subsequently revised by the study team via

e-mail, teleconference, and in-person meetings. The technologist (who has 24 years of experience in radiography including 14 years with the JoCo OA) was trained in standardized KUS imaging for this study both in-person and through a formal course. All images were obtained using a Sonosite Edge II-MSK with HFL50x/15-6mHz linear transducer (FUJIFILM SonoSite Inc). Gray scale (GS) images were obtained on the "Gen" setting as frequency and focal points are not adjustable on this machine. Power Doppler (PD) images were obtained with the largest possible region of interest extending from the skin surface to the surface of the femur, with low flow sensitivity and low wall filter, and grain set just above noise. The protocol included instructions to minimize the depth to include only the structure of interest in all views, to center the structure of interest, and to apply minimal probe pressure. The final protocol (see Appendix S1) included six views per knee with standardized positioning: longitudinal and transverse suprapatellar anterior in 30° flexion (29) (subsequently scored for effusion/synovitis and PD), medial and lateral longitudinal in 30° flexion (for osteophytes, meniscal damage, calcium crystal deposition), a maximally flexed suprapatellar transverse view (for cartilage damage and calcium crystal deposition), and a posterior transverse view (for popliteal cysts). Once the images obtained by the technologist were deemed acceptable (eg, appropriate depth, area of interest centered, and evaluable) by all assessors, she obtained US images of both knees in all remaining consecutive individuals in the JoCo OA fourth follow-up. As the US funding occurred after the fourth follow-up had started, this analysis included 203 participants with 396 imaged knees after excluding 10 knees for joint replacement or amputation.

US scoring atlas development. The KUS scoring atlas (Appendix S2) was initially based on prior studies (8,30–33), although none of these alone was sufficient for our purposes; in the end a semiquantitative scoring system and atlas based on these but using images from JoCo OA was developed. The study by Bruyn et al (8) was designed as a reliability study (not an atlas) in which expert rheumatologists obtained the images; we found that some of these (ie, parapatellar recesses) could not be reproducibly obtained by the sonographer because of the lack of landmarks and that the images were hard to compare to those obtained in our study (eg, different machines and settings). In addition, popliteal cysts were not assessed in that study, and there was no differentiation between medial and lateral views for scoring of osteophytes, cartilage, or meniscal damage. We incorporated feature descriptions and scores from this work (8) with that from other groups focused on semiquantitative scoring of specific features—Koski et al (32) for osteophytes, Saarakkala et al (33) for articular cartilage, Bevers et al (30) for popliteal cysts, and Filippou et al for calcium crystal deposition (34)—and from other diseases, eg, Hartung et al (31) who described large joint effusion and synovitis in rheumatoid arthritis, to generate a comprehensive atlas of US features with images from the JoCo OA generated from the above protocol. The atlas was finalized (Appendix S2, September 2018) with input from five rheumatologists (CJB, MJK, JL, JS, AEN) with at least five years of experience with clinical musculoskeletal US and who completed the Ultrasound School of North American Rheumatologists (USSONAR) program.

US reliability and final scoring. Four of the rheumatologists (all but AEN) semiquantitatively scored the images using the atlas via an online scoring survey tool (Qualtrics). For the formal reliability study (completed November 5, 2018), images from 15 participants, selected to represent a range of feature severity (by AEN who did not participate in final scoring), were read by all four scoring rheumatologists (CJB, MJK, JL, JS). Subsequently, all images (bilateral knees) from each participant were assigned randomly to two of the four readers, with each pairing of two readers scoring 33 or 34 of the 203 participants. Thus, each reader scored images from about 100 participants, or 200 knees (completed April 1, 2019). Each pairing of two readers' scores was averaged to reduce overall variability and better reflect the likely true score. The sonographer and the readers were blinded to all other imaging and clinical data.

Clinical assessment and other relevant covariates

All participants also completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire for each knee, including the nine-item pain subscale (35) and the seven-item Physical Function Short form (36) in Likert format (corresponding to none, mild, moderate, severe, extreme) for the amount of knee pain or functional limitation experienced in the last week for various activities. KOOS scores were dichotomized as none (KOOS score = 100) versus any pain or impaired function (KOOS < 100), where 0 = extreme pain or impairment. Other covariates included age, self-reported sex and race, and body mass index (BMI), which was calculated in kg/m^2 at the clinic visit using measured weight in kilograms and height (cm) without shoes.

Statistical analysis

Reliability (n = 15 participants/30 knees). Reliability was assessed using weighted kappa (w kappa) statistics for polytomous US features and simple kappa statistics for dichotomous US features in 15 participants (30 knees) as above. The kappa statistics were independently produced for all possible reader pairs for a total of six different pairs involving the four readers; the median and interquartile range (IQR) of these w kappa or kappa statistics was provided. Kappa statistics can be interpreted as follows: 0 to 0.2 = no agreement; 0.21 to 0.39 = slight agreement; 0.40 to 0.59 = weak/fair agreement; 0.60 to 0.79 = moderate agreement; and 0.8 or greater = strong/substantial agreement (37). The Kendall coefficient of concordance was produced in order to provide an overall rank-based assessment of agreement, ranging from 0 to 1, where polytomous levels were ordinal, assessing the four

raters simultaneously. Finally, percent agreement was produced by dichotomizing all polytomous (nondichotomous) US features (0 vs scores > 0). Each of the six reader pairs (2 × 2) comparisons provided a total (denominator) of 6 × 30 knees = 180 instances of agreement; percent agreement was calculated out of this total.

Overall analyses (n = 203 participants/396 knees). Descriptive statistics at the participant and joint level were computed including mean ± standard deviation (SD) for continuous variables and counts and percentages (%) for categorical variables. Unadjusted Spearman correlations between US features and XR knee features, evaluated by side for both KLG and comparable XR feature, were produced to generate the degree of correlation using ranks. These correlation coefficients can be interpreted as: 0 to 0.3 = negligible; 0.3 to 0.5 = low/weak; 0.5 to 0.7 = moderate; and over 0.7 as strong correlations (38) and are relevant to understand the criterion validity of US for KOA features. Additionally, we used the Cochran-Mantel-Haenszel statistic to test for correlation. Logistic regression with generalized estimating equations to account for within-person correlation between knees was used to estimate the overall association between US features and KOOS subscales, which was relevant to demonstrate the construct validity of US in this setting. In the analysis phase, in order to reduce the number of levels, we collapsed US feature categories from the atlas scoring system into categories for these model-based analyses as determined by an expert rheumatologist considering clinical interpretation as well as the raw score distributions (AEN; see Table 2). For both the pain and function KOOS subscales, scores were collapsed to none (KOOS = 100) or any (KOOS < 100); the log odds of any versus none were modeled as the outcome. Separate models were produced for each of the two KOOS subscale outcomes and each of the 15 US feature main effects. Odds ratios (OR) and 95% confidence intervals (CI) were produced for unadjusted and adjusted (for age, sex, race, BMI, and rKOA) models; two-way interactions between US features and rKOA status were assessed at the 0.10 significance level.

RESULTS

Feasibility

The radiologic technologist, using the standardized protocol, was able to obtain consistently high-quality images for scoring in about 10 to 15 minutes per participant following in-person trainings (6 hours), a 2-day formal continuing medical education course (39), and online/video feedback sessions (1 hour in total). US imaging was therefore able to be incorporated into the research clinic workflow. The rheumatologists were able to read the US images in about 3 to 5 minutes per person (ie, all images for both knees, for all features).

Reliability (n = 15 participants/30 knees)

Reliability was assessed in 15 participants (11 women, 4 men; 11 white, 4 African American) with a mean ± SD age of 76.5 ± 7.7 years (range = 66-93 years) (40). The final overall reliability (Table 1) was deemed to be acceptable by the study

Table 1. Reliability of US features of knee OA for 4 readers and 15 participants (30 knees, right and left combined)

	Reliability Assessments			
	Kappa[a]		Kendall Concordance Coefficient[b]	Percentage Agreement[c]
US Feature	Median	(IQR)		
Gray scale effusion/synovitis	0.44	(0.15)	0.71	50
Gray scale synovitis	0.29	(0.24)	0.62	49
Gray scale effusion	0.35	(0.36)	na	74
Suprapatellar PD	0.50	(0.04)	0.69	69
Osteophytes				
Medial	0.68	(0.16)	0.81	69
Lateral	0.73	(0.08)	0.88	73
Meniscal damage				
Medial	0.29	(0.24)	na	72
Lateral	0.30	(0.02)	na	64
Cartilage damage				
Medial	0.56	(0.21)	0.84	57
Lateral	0.51	(0.14)	0.75	54
Calcium crystal deposition, any view[d]	0.18	(0.38)	na	82
Popliteal cyst	0.35	(0.26)	0.66	58

Abbreviation: IQR = interquartile range, na = not applicable, OA = osteoarthritis, PD = power Doppler, SD = standard deviation, US = ultrasound.
[a] Weighted kappa for multiple levels, simple kappa for binary, assessed for each of six reader pairs and presented as the median (IQR) across these pairs.
[b] Kendall concordance coefficient, 0 to 1, appropriate when multiple levels of scoring (but not for binary scores).
[c] Percentage (%) agreement, for all possible 2 × 2 combinations (six 2 × 2 comparisons and 30 instances =180 total instances).
[d] Calcium crystal deposition was assessed as present or absent in any of three views: suprapatellar transverse, medial, or lateral longitudinal.

team, ranging from slight to moderate (median w kappa, 0.3-0.7) range. The US features for which reliability was highest included synovitis by PD [median w kappa, 0.50; IQR (0.04)], osteophytes (median w kappa, 0.68-0.73), and cartilage damage (median w kappa, 0.51-0.56) when compared with effusion/synovitis by GS [median w kappa, 0.44; IQR (0.15)] and meniscal damage (median kappa, 0.29-0.30). The w kappa for calcium crystal deposition was low at 0.18 (IQR, 0.38), although few cases were present in this small data set; percentage agreement was high at 82%. Agreement as assessed by the Kendall concordance coefficient (range = 0.6-0.9) or percentage agreement (range = 49%-82%) was qualitatively higher than agreement by kappa.

Table 2. Overall knee US features scores[a] for the full sample and by right and left knees

	Ultrasound Feature (range) n = 396		All Knees Right (n = 199)		Side Left (n = 197)	
	n	%	n	%	n	%
Gray scale effusion/synovitis (0-3)						
0	78	19.7	34	17.1	44	22.3
0.5-1.5	263	66.4	135	67.8	128	65
2-3	55	13.9	30	15.1	25	12.7
Gray scale synovitis (0-3)						
0	78	19.7	35	17.6	43	21.8
0.5-1.5	272	68.7	140	70.3	132	67
2-3	46	11.6	24	12	22	11.2
Gray scale effusion (0-1)						
0	111	28.0	53	26.6	58	29.4
0.5-1	285	72.0	146	73.3	139	70.6
Suprapatellar PD (0-3)						
0-0.5	340	85.8	173	86.9	167	84.8
1-2.5	56	14.2	26	13.1	30	15.2
Osteophytes, medial (0-3)						
0	152	38.4	71	35.7	81	41.1
0.5-1.5	172	43.5	84	42.2	88	44.6
2-3	72	18.2	44	22	28	14.2
Osteophytes, lateral (0-3)						
0	141	35.6	69	34.7	72	36.5
0.5-1.5	191	48.3	93	46.8	98	49.8
2-3	64	16.2	37	18.6	27	13.7
Meniscal extrusion, medial (0-1)						
0	242	61.1	118	59.3	124	62.9
0.5-1	154	38.9	81	40.7	73	37.1
Meniscal extrusion, lateral (0-1)						
0	189	47.7	91	45.7	98	49.7
0.5-1	207	52.3	108	54.3	99	50.3
Calcium crystal deposition, any view[b] (0-1)						
0	242	61.1	116	58.3	126	64.0
0.5-1	154	38.9	83	41.7	71	36.0
Cartilage damage, medial (0-3)						
missing	6	1.5	5	2.5	1	0.5
0-0.5	63	15.9	30	15.1	33	16.8
1-1.5	194	49	97	48.7	97	49.3
2-3	133	33.6	67	33.7	66	33.6
Cartilage damage, lateral (0-3)						
missing	6	1.5	5	2.5	1	0.5
0-0.5	115	29.0	52	26.1	63	32
1-1.5	185	46.8	101	50.7	84	42.7
2-3	90	22.8	41	20.6	49	24.9
Popliteal cyst (0-2)						
missing	23	5.8	12	6.0	11	5.6
0	64	16.2	31	15.6	33	16.8
0.5-1	265	66.9	136	68.4	129	65.5
1.5-2	44	11.1	20	8	24	12.2

Abbreviation: JoCo = Johnston County OA Project, OA = osteoarthritis, PD, power Doppler, US = ultrasound.
[a] The US features are the averages of two readers (as described in Methodology: US Acquisition in JoCo OA), which lends itself to some half-grade values and cutoffs.
[b] Calcium crystal deposition was assessed as present or absent in any of three views: suprapatellar transverse, medial, or lateral longitudinal.

Sample characteristics (n = 203 participants/396 knees)

Participants in the full sample had a mean ± SD age of 73 ± 8 years (range = 59-95 years) and mean BMI of 29.4 ± 7 kg/m^2 (range = 17-55 kg/m^2). Sixty-two (30.5%) participants were male, 68 (33.5%) participants were African American, and 82 (40.4%) reported experiencing knee symptoms in at least one knee. At the individual knee level, 213 (53.8%) knees scored less than 100 on the KOOS pain nine-item subscale, and 230 (58.1%) scored less than 100 on the KOOS function seven-item subscale. Additionally, 212 (53.5%) knees had rKOA defined as KLG ≥ 2, and 78 (19.7%) had symptomatic KOA.

Descriptive statistics for US features for all knees are detailed in Table 2. Evidence of effusion/synovitis was found in 318 knees (80.3%), whereas medial and lateral osteophytes were demonstrated in 244 knees (61.6%) and 255 knees (64.4%), respectively. Medial and lateral cartilage damage was found in 374 knees (94.5%) and 357 knees (90.2%), respectively.

US and XR feature correlations

Correlations between US and XR features for right knees are shown in Table 3 (similar patterns were seen for left knees, data not shown). Correlations between US GS effusion/synovitis and KLG were weak but statistically significant; the correlation for GS synovitis was larger in magnitude than that for GS effusion. Suprapatellar PD signal and the presence of popliteal cysts were also significantly correlated with KLG, although to a lesser degree. Medial and lateral osteophytes were moderately correlated with KLG. For features with comparable XR features (eg, osteophytes, JSN), we also made direct comparisons. Medial and lateral osteophytes were moderately correlated with XR osteophytes. Medial meniscal extrusions were also weakly but significantly correlated with both KLG and JSN by XR. Crystal deposition by US was weakly but significantly correlated with both KLG and chondrocalcinosis by XR. Associations between cartilage damage and XR were overall weak and not statistically significant.

Table 3. Spearman correlations[a] between US features and XR features for right knees

KUS Feature (range)	Kellgren-Lawrence Grade (0-4)	Comparable XR Feature[b]
	Spearman correlation CMH *P* value	Spearman correlation CMH *P* value
Gray scale effusion/synovitis (0-3)	**0.30 (0.16, 0.43) <0.0001**	na[c]
Gray scale synovitis (0-3)	**0.29 (0.15, 0.43) <0.0001**	na[c]
Gray scale effusion (0-1)	**0.16 (0.02, 0.30) 0.0257**	na[c]
Suprapatellar PD (0-3)	**0.14 (0.00, 0.28) 0.0347**	na[c]
Osteophytes, medial (0-3)	**0.62 (0.52, 0.71) <0.0001**	**0.58 (0.50, 0.66) <0.0001**
Osteophytes, lateral (0-3)	**0.54 (0.43, 0.64) <0.0001**	**0.57 (0.46, 0.67) <0.0001**
Meniscal extrusion, medial (0-1, compared with XR medial JSN, 0-3)	**0.42 (0.31, 0.54) <0.0001**	**0.36 (0.23, 0.49) <0.0001**
Meniscal extrusion, lateral (0-1, compared with XR lateral JSN, 0-3)	**0.15 (0.01, 0.29)** 0.0798	0.11 (−0.04, 0.25) 0.1818
Calcium crystal deposition, medial (0-1)	0.08 (−0.06, 0.22) 0.1814	**0.24 (0.07, 0.42) <0.0001**
Calcium crystal deposition, lateral (0-1)	**0.21 (0.08, 0.34) 0.0073**	**0.34 (0.18, 0.50) <0.0001**
Calcium crystal deposition, any view[d] (0-1)	**0.23 (0.10, 0.36) 0.0011**	**0.31 (0.16, 0.45) <0.0001**
Cartilage damage, medial (compared with XR medial JSN, both 0-3)	**0.15 (0.01, 0.28) 0.0792**	0.10 (−0.04, 0.23) 0.1369
Cartilage damage, lateral (to XR lateral JSN, both 0-3)	0.13 (−0.00, 0.27) 0.0526	0.13 (−0.01, 0.27) 0.0570
Popliteal cyst (0-2)	**0.25 (0.11, 0.39) 0.0001**	na[c]

Abbreviation: CI = confidence interval, CMH = Cochran-Mantel-Haenszel, JSN = joint space narrowing, na = not available, PD = power Doppler, US = ultrasound, XR = radiographic.
[a] Correlation estimates with 95% CI excluding the null, and 0.05 *P* value level significant statistics for nonzero correlation, are shown in bold.
[b] The feature most comparable to the US feature that was assessed on radiograph (eg, medial osteophytes on US are compared to medial osteophytes on XR, while US cartilage damage and meniscal extrusion are both compared to XR JSN)
[c] na means there is no comparable XR feature.
[d] Calcium crystal deposition was assessed as present or absent in any of three views: suprapatellar transverse, medial or lateral longitudinal.

Associations between US features and KOOS pain

The US features of effusion/synovitis and medial and lateral osteophytes were significantly associated, both in unadjusted models and those adjusted for age, sex, race, BMI, and rKOA, with higher odds of reporting KOOS pain (Table 4). The odds of reporting any KOOS pain were more than doubled in the presence of US effusion/synovitis, more from synovitis than effusion (OR > 3 for synovitis, < 1 for effusion). Mild to moderate medial osteophytes nearly doubled the odds of reported knee pain, whereas more severe osteophytes more than quadrupled the odds. Although both PD and meniscal extrusion increased the odds of any KOOS pain by about 20%, these were not statistically significant. Of note, there was a significant interaction ($P < 0.1$) between medial meniscal extrusion and rKOA such that no significant association was seen in the absence of rKOA [adjusted OR (aOR): 0.71; 95% CI (0.44, 1.15)], but in the presence of rKOA, medial meniscal extrusion increased the odds of KOOS pain by about 70% [aOR: 1.73, 95% CI (1.03, 2.89)]. This was also the case for lateral cartilage damage such that no significant association was seen in the absence of rKOA [1.05 (0.64, 1.72) for mild to moderate cartilage damage and 0.79 (0.37, 1.66) for more severe cartilage damage], but in the presence of rKOA, lateral cartilage damage increased the odds of KOOS pain [2.17 (1.14, 4.14) and 1.88 (0.88, 4.00) for mild to moderate and severe, respectively]. Calcium crystal deposition, cartilage damage, and popliteal cysts were not consistently associated with KOOS pain. No other significant interactions by rKOA status were found.

Associations between US features and KOOS impaired function

The US features of effusion/synovitis, medial and lateral osteophytes, and lateral cartilage damage were also significantly associated with higher odds of reporting impaired function on the KOOS

Table 4. Associations[a] between knee US features and KOOS pain nine-item subscale

US Feature	Score[b]	Knees	None (100)	Mild (<100) to Extreme (0)	Unadjusted: OR (95% CI)	Adjusted: OR (95% CI)[c]
Gray scale effusion/synovitis	0	78	36 (46%)	42 (54%)		
	0.5-1.5	263	130 (49%)	133 (51%)	1.04 (0.68, 1.60)	1.10 (0.68, 1.77)
	2-3	55	17 (31%)	38 (69%)	**2.38 (1.09, 5.19)**	**2.37 (1.04, 5.37)**
Gray scale synovitis	0	78	37 (47%)	41 (53%)		
	0.5-1.5	272	132 (49%)	140 (51%)	1.14 (0.76, 1.71)	1.18 (0.75, 1.86)
	2-3	46	14 (30%)	32 (70%)	**3.15 (1.32, 7.51)**	**3.02 (1.22, 7.49)**
Gray scale effusion	0	111	47 (42%)	64 (58%)		
	0.5-1	285	136 (48%)	149 (52%)	0.91 (0.58, 1.42)	0.93 (0.57, 1.51)
Suprapatellar PD	0-0.5	340	158 (46%)	182 (54%)		
	1-2.5	56	25 (45%)	31 (55%)	1.24 (0.73, 2.11)	1.22 (0.71, 2.07)
Osteophytes, medial	0	152	90 (59%)	62 (41%)		
	0.5-1.5	172	74 (43%)	98 (57%)	**1.85 (1.15, 2.98)**	**1.67 (1.00, 2.79)**
	2-3	72	19 (26%)	53 (74%)	**4.73 (2.29, 9.74)**	**4.07 (1.75, 9.50)**
Osteophytes, lateral	0	141	76 (54%)	65 (46%)		
	0.5-1.5	191	90 (47%)	101 (53%)	1.13 (0.82, 1.56)	0.95 (0.68, 1.33)
	2-3	64	17 (27%)	47 (73%)	**3.02 (1.57, 5.80)**	**2.21 (1.10, 4.43)**
Meniscal extrusion, medial	0	242	119 (49%)	123 (51%)		
	0.5-1	154	64 (42%)	90 (58%)	1.28 (0.89, 1.84)	1.17 (0.80, 1.70)
Meniscal extrusion, lateral	0	189	90 (48%)	99 (52%)		
	0.5-1	207	93 (45%)	114 (55%)	1.14 (0.82, 1.60)	1.07 (0.75, 1.52)
Calcium crystal deposition, any view[d]	0-0.5	369	168 (46%)	201 (54%)		
	1	27	15 (56%)	12 (44%)	0.89 (0.37, 2.18)	0.90 (0.37, 2.20)
Cartilage damage, medial	0-0.5	63	35 (56%)	28 (44%)		
	1-1.5	194	88 (45%)	106 (55%)	1.12 (0.69, 1.82)	0.92 (0.55, 1.54)
	2-3	133	57 (43%)	76 (57%)	1.38 (0.78, 2.43)	1.09 (0.60, 1.99)
Cartilage damage, lateral	0-0.5	115	61 (53%)	54 (47%)		
	1-1.5	185	78 (42%)	107 (58%)	**1.53 (1.08, 2.19)**	1.46 (0.99, 2.15)
	2-3	90	41 (46%)	49 (54%)	1.45 (0.87, 2.40)	1.25 (0.73, 2.16)
Popliteal cyst	0	64	30 (47%)	34 (53%)		
	0.5-1	265	130 (49%)	135 (51%)	0.75 (0.42, 1.34)	0.64 (0.35, 1.18)
	1.5-2	44	14 (32%)	30 (68%)	1.31 (0.62, 2.80)	1.26 (0.58, 2.73)

Abbreviation: CI = confidence interval, KOOS = Knee Injury and Osteoarthritis Outcome Score, OR = odds ratio, PD = power Doppler, US = ultrasound.

[a] Associations with OR (95% CI); associations where the null is not included in the 95% CI are shown in bold.

[b] Scores were dichotomized as none versus any pain, in which 100 represents no pain, and 0 to <100 represents "extreme" to "mild" pain, respectively.

[c] Adjusted for age, sex, race, body mass index, and radiographic knee osteoarthritis.

[d] Calcium crystal deposition was assessed as present or absent in any of three views: suprapatellar transverse, medial or lateral longitudinal.

(Table 5). The presence of effusion/synovitis more than doubled the odds of experiencing impaired function, although this was attenuated after adjustment. Synovitis (OR, ~3) again increased the likelihood of functional impairment more than effusion (OR, ~1). There was a significant interaction ($P < 0.1$) between effusion and rKOA: among knees without rKOA, effusion was positively associated with functional impairment [aOR: 1.48; 95% CI (0.85, 2.56)], but among knees with rKOA, there was a negative association [aOR: 0.68; 95% CI (0.34, 1.39)], although neither association was statistically significant. Likewise, moderate medial osteophytes doubled the odds, whereas severe medial osteophytes more than tripled the odds of reporting impaired function. Compared with medial osteophytes, lateral osteophytes had fewer significant effects on function. Medial meniscal extrusion significantly increased the odds of reporting impaired function by 40%, although this was attenuated after adjustment. Lateral cartilage damage increased the odds of impaired function by 50% to 60%. Medial cartilage damage was not statistically significantly associated with functional impairment. Suprapatellar PD, lateral meniscal extrusion, calcium crystal deposition, and popliteal cysts did not significantly increase the odds of impaired function.

DISCUSSION

In the United States in particular (9), US is not widely used in clinical or research settings for the assessment of features of KOA in part because of a perceived lack of reliability, which is itself related to the lack of standardization of both protocols and scoring methods. Previously published studies on the use of US for KOA have demonstrated variability in US scanning techniques as well as differences in image interpretation based on levels of US experience (24,41) and have emphasized the need for the development of an image atlas to accompany protocols (8). The current study aimed to address some of these issues by developing a standardized, landmark-based US protocol and scoring atlas for various features associated with or relevant to KOA by several expert rheumatologists experienced in musculoskeletal US.

Table 5. Associations[a] between knee US features and KOOS function seven-item subscale

US Feature	Score[b]	Knees	None (100)	Mild (<100) to Extreme (0)	Unadjusted: OR (95% CI)	Adjusted: OR (95% CI)[c]
Gray scale effusion/synovitis	0	78	34 (44%)	44 (56%)		
	0.5-1.5	263	117 (44%)	146 (56%)	1.04 (0.68, 1.58)	1.05 (0.67, 1.66)
	2-3	55	15 (27%)	40 (73%)	**2.21 (1.05, 4.67)**	2.04 (0.99, 4.17)
Gray scale synovitis	0	78	35 (45%)	43 (55%)		
	0.5-1.5	272	119 (44%)	153 (56%)	1.12 (0.75, 1.67)	1.12 (0.73, 1.72)
	2-3	46	12 (26%)	34 (74%)	**2.99 (1.32, 6.76)**	**2.64 (1.23, 5.65)**
Gray scale effusion	0	111	47 (42%)	64 (58%)		
	0.5-1	285	119 (42%)	166 (58%)	1.06 (0.69, 1.62)	1.07 (0.68, 1.68)
Suprapatellar PD	0-0.5	340	146 (43%)	194 (57%)		
	1-2.5	56	20 (36%)	36 (64%)	1.44 (0.82, 2.53)	1.42 (0.80, 2.52)
Osteophytes, medial	0	152	85 (56%)	67 (44%)		
	0.5-1.5	172	63 (37%)	109 (63%)	**2.15 (1.32, 3.51)**	**1.87 (1.13, 3.11)**
	2-3	72	18 (25%)	54 (75%)	**4.07 (2.06, 8.06)**	**3.29 (1.51, 7.17)**
Osteophytes, lateral	0	141	69 (49%)	72 (51%)		
	0.5-1.5	191	81 (42%)	110 (58%)	1.17 (0.84, 1.62)	0.97 (0.69, 1.36)
	2-3	64	16 (25%)	48 (75%)	**2.17 (1.23, 3.83)**	1.46 (0.81, 2.63)
Meniscal extrusion, medial	0	242	111 (46%)	131 (54%)		
	0.5-1	154	55 (36%)	99 (64%)	**1.44 (1.02, 2.05)**	1.29 (0.90, 1.86)
Meniscal extrusion, lateral	0	189	76 (40%)	113 (60%)		
	0.5-1	207	90 (43%)	117 (57%)	0.97 (0.71, 1.34)	0.87 (0.62, 1.22)
Calcium crystal deposition, any view[d]	0-0.5	369	154 (42%)	215 (58%)		
	1	27	12 (44%)	15 (56%)	1.35 (0.57, 3.22)	1.35 (0.58, 3.16)
Cartilage damage, medial	0-0.5	63	34 (54%)	29 (46%)		
	1-1.5	194	82 (42%)	112 (58%)	1.32 (0.82, 2.15)	1.11 (0.68, 1.83)
	2-3	133	47 (35%)	86 (65%)	1.68 (0.95, 2.99)	1.31 (0.72, 2.38)
Cartilage damage, lateral	0-0.5	115	58 (50%)	57 (50%)		
	1-1.5	185	71 (38%)	114 (62%)	**1.61 (1.12, 2.32)**	**1.52 (1.03, 2.23)**
	2-3	90	34 (38%)	56 (62%)	**1.61 (1.01, 2.58)**	1.31 (0.79, 2.15)
Popliteal cyst	0	64	28 (44%)	36 (56%)		
	0.5-1	265	114 (43%)	151 (57%)	0.86 (0.49, 1.50)	0.72 (0.41, 1.29)
	1.5-2	44	15 (34%)	29 (66%)	1.25 (0.58, 2.69)	1.12 (0.52, 2.44)

Abbreviation: CI = confidence interval, KOOS = Knee Injury and Osteoarthritis Outcome Score, OR = odds ratio, PD = power Doppler, US = ultrasound.

[a] Associations with OR (95% CI); associations where the null is not included in the 95% CI are shown in bold.

[b] Scores were dichotomized as none versus any impaired function, in which 100 represents no impaired function, and 0 to <100 represents "extreme" to "mild" impairment in function, respectively.

[c] Adjusted for age, sex, race, body mass index, and radiographic knee osteoarthritis.

[d] Calcium crystal deposition was assessed as present or absent in any of three views: suprapatellar transverse, medial or lateral longitudinal.

Feasibility and reliability of US

The per-participant time for both acquisition of the standard views (10-15 minutes) and for the interpretation of the images (3-5 minutes), as well as the overall training time, supports the feasibility of this approach for clinical research, although adaptations for individual settings and circumstances will likely be needed. The quality of images obtained by the radiologic technologist and the interrater reliability of the scorers in the development of the atlas and evaluation of images from the sample were satisfactory and compared favorably with prior work. We used a landmark-based approach, incorporating methods [such as assessing effusion in the suprapatellar view in 30° of flexion (29)] to maximize sensitivity for detection of pathology.

The reliability was established prior to participant reads in order to ensure reliability of the results gathered in this study. In comparison with the reliability reported in the OMERACT reliability study of KUS (8), our median kappa for effusion/synovitis (0.44) was in range for those reported for synovitis and synovial hypertrophy (0.29-0.52); for effusion, the two studies were essentially identical. Our reliability was slightly lower for meniscal damage (0.3 vs 0.56) but was higher for osteophytes (0.7 vs 0.6) and for cartilage damage (0.5 vs 0.3). A systematic literature review and meta-analysis of US clinimetrics found moderate to substantial reliability [minimum kappa > 0.44; CI (0.15-0.74)] for KOA US overall (24). In this meta-analysis the interrater reliability (pooled semiquantitative kappa mean) was 0.44 for cartilage thickness, 0.63 for synovitis, 0.66 for osteophytes, and 0.75 for meniscal extrusion, with a similar range for binary kappas (24). Although favorable in comparison with the literature, in recognition that our agreement was not perfect, we elected to have two readers read all images and to average their scores, with the goal of reducing variability and better reflecting the likely true score.

Associations with XR (criterion validity)

The strongest correlations between US and XR features in the current analysis were moderate and were seen for US and XR osteophytes and US osteophytes and XR KLG. Correlations for crystal deposition detected by both modalities were also significant, suggesting that US is able to detect calcium crystal deposition at least as well as XR. Medial XR JSN was more closely related to US meniscal extrusion than to US cartilage damage, supporting the idea that medial JSN in KOA may be more strongly related to meniscal extrusion (42,43). In a smaller study of only patients with KOA, the correlation between medial XR JSN and medial cartilage grade on US was 0.71, whereas that for osteophytes was in the 0.7 range, although the protocol and scoring were slightly different and meniscal extrusion was not assessed (44).

Associations with KOOS (construct validity)

Participants whose US demonstrated moderate to severe effusion/synovitis were more likely to report pain and diminished functioning, with the synovitis component rather than the effusion component driving this association. This suggests that earlier intervention specific to knee synovitis may reduce the experience of pain and altered function in KOA patients. Having any medial osteophytes and at least moderate lateral osteophytes was significantly associated with both pain and altered function. These data suggest that the identification of synovitis and osteophytes with US could enable a rheumatologist to evaluate KOA at the point of care, thereby potentially initiating interventions earlier in the disease course. Importantly, these associations persisted with adjustment for the presence of rKOA, and few interactions were seen by rKOA status, suggesting that the US features are providing additional information beyond conventional radiography alone.

The main strength of this study is the development of a comprehensive and standardized protocol and scoring atlas for evaluation of US features relevant to KOA that was subsequently compared with radiography and pain and function in a large cohort, demonstrating both construct and criterion validity of US. Other strengths include collection of US images of nearly 400 knees by a single experienced technologist as well as satisfactory interrater reliability for semiquantitative scoring among four expert rheumatologists, which was comparable to prior studies. The majority of this sample consisted of older women with an age range of 59-95 years, reflecting the parent cohort as well as a typical KOA population. The sample was gathered from the only U.S. population–based cohort with standardized US measures, and it included African American and white men and women and is therefore more representative of a general population than are studies that use clinical samples.

Limitations of our analysis include its cross-sectional design, which allowed us only to describe associations at this time. We are unable to assess causality between US features and pain and function outcomes until longitudinal data are obtained in future work. Additionally, although we have adjusted for factors that are related to pain and function or that can explain the associations between US features and pain and function, we were not able to adjust for the multitude of all of these factors in this study. Further studies are needed to evaluate the responsiveness to change and predictive validity of the scoring atlas in a longitudinal manner. In particular, we plan on evaluating whether baseline KOA US features predict radiographic or symptomatic KOA at follow-up.

In conclusion, we have shown that US is a feasible, reliable, and valid (compared with both radiography and patient-reported outcomes reflecting pain and function) method to assess a variety of features relevant to KOA in clinical and research settings (specifically in the United States where US is not widely used for the

assessment of OA). The protocol, semiquantitative scoring system, and atlas developed in this study can be used to improve standardization of US assessments in other clinical studies, with the goal of increasing overall utilization of this promising modality in OA clinical care and research.

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AUTHOR CONTRIBUTIONS

Conception and design. Alvarez, Schwartz, Bakewell, Kohler, Lin, Samuels, Nelson.
Acquisition of the data. Savage-Guin, Renner, Nelson.
Analysis and interpretation of the data. Yerich, Alvarez, Schwartz, Renner, Bakewell, Kohler, Lin, Samuels, Nelson.

Drs. Yerich, Alvarez, and Nelson drafted the article. All authors critically revised the article for important intellectual content and gave final approval of the article. Dr. Nelson takes responsibility for the integrity of the work as a whole, from inception to finished article.

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