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Development and validation of a pediatric internationally agreed ultrasound knee synovitis protocol (PIUS-knee) by the PReS imaging working party

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Abstract

Objectives To identify an optimal pediatric musculoskeletal ultrasound (MSUS) protocol for the detection of knee arthritis in patients with juvenile idiopathic arthritis (JIA) including a comparison with existing protocols. Secondary aims were to correlate MSUS-identified B-Mode (BM) and Power Doppler-Mode (PD) synovitis with clinical findings.

Methods Consecutive JIA patients with confirmed knee arthritis after clinical examination underwent a thorough MSUS study protocol which included views identified and consented by the Pediatric Rheumatology european Society (PReS) Imaging Working Party for the detection of synovitis. In total eight views including measurement of the suprapatellar recess were included. Scoring of synovitis followed the pediatric OMERACT criteria (BM and PD severity grading 0 to 3). Interobserver reliability of BM and PD was tested before study begin. Previously published MSUS protocols for knee synovitis were also identified from the literature and their scan protocols compared to identify differences in sensitivity for synovitis according to the number and specific type of views included. Finally, a clinically applicable MSUS protocol for knee synovitis could be proposed.

Results In 114 patients with clinically active knee inflammation, BM positivity (grading ≥ 1) was most frequently detected in the suprapatellar longitudinal and transverse scans performed in any positioning (frequency 97–99% in suprapatellar longitudinal in 30° or neutral respectively). PD positivity was however higher in these views performed in 30° flexion compared to neutral. Intrasynovial PD positivity (grading ≥ 1) was most frequently detected in the lateral parapatellar (69%, sensitivity 0.68, specificity 0.98), medial parapatellar (frequency 67%, sensitivity 0.67, specificity 1.0), the longitudinal lateral (68%, sensitivity 0.67, specificity 0.98) and suprapatellar transverse in 30° (frequency 64%, sensitivity 0.64, specificity 1.0). A combination of five views was the most sensitive for BM and PD synovitis. The suprapatellar recess size was analyzed by age and gender. For each group, the recess was wider in knees with arthritis than without ($p < 0.001$). Interobserver reliability of BM and PD positivity showed 85% agreement, with kappa 0.74 (very good). Three published studies with knee synovitis MSUS protocols were identified, which included a range of 1–3 views. Evaluation of the sensitivity of positive PD findings of each of these protocols reached

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a range of 53–83%; the highest sensitivity (91%) was achieved with the 5 views as identified by this study. These five views were therefore combined to form the Pediatric Internationally agreed Ultrasound (PIUS) knee protocol.

Conclusion BM and PD positivity reliably correlated with the identification of pathological findings in knees of patients with JIA. From an internationally agreed protocol of eight images, a combination of five showed the greatest sensitivity for synovitis. This protocol, termed 'PIUS-Knee' performed well when compared to existing protocols.

Key messages

• Synovitis detected using B-Mode and Doppler-Mode Musculoskeletal Ultrasound (MSUS) correlated strongly with clinical examination findings.

• A combination of five specific MSUS views achieved the most sensitive B-Mode and Doppler-Mode protocol for knee synovitis.

• This optimized knee examination ultrasound protocol termed PIUS-Knee (Pediatric Internationally Agreed Ultrasound) has high sensitivity for detecting intrasynovial hypervascularity.

Keywords Juvenile idiopathic arthritis, Knee synovitis, Ultrasound protocol, Intrasynovial hypervascularization

Introduction

Pediatric musculoskeletal ultrasound (MSUS) can play a large role in the interpretation of unclear clinical findings and has been tested in protocols both as an alternative and as an adjunct to clinical practice [1, 2]. However, multiple techniques and protocols exist [3–7]. Specific advantages of MSUS are the discrimination of tenosynovitis from arthritis, e.g. in the ankle region [8], the differentiation of active from residual findings or identification of differential diagnoses [9–14]. However, few studies describe the development of MSUS examination protocols used in juvenile idiopathic arthritis (JIA) and there remains a lack of internationally agreed protocols with standardized planes and positioning which affects the sensitivity for effusion or synovial hypervascularization [4, 15, 16]. Existing imaging protocols for the knee joint include a range of views based on the superior, medial and lateral knee compartments, performed in partial flexion or neutral position. Posterior and infrapatellar views are additionally required in routine knee MSUS examination to assess for popliteal cysts and infrapatellar pathologies as bursitis or enthesitis which are common in JIA. Therefore, the development of a sensitive but also practical protocol has been limited by the breadth of imaging positions and views possible.

Newer techniques, sensitive Doppler software and the inclusion of alternative planes as standard have encouraged international consensus groups to improve and define pediatric specific examination protocols [5, 7, 13, 17–23]. A semi-quantitative ultrasound score for the evaluation of B-Mode (BM) and conventional power Doppler (PD) published by the Outcome Measures in Rheumatology (OMERACT) Working Group has aided the evaluation of imaging protocols [24].

The PReS imaging working party initiated this study to develop the most sensitive knee joint specific MSUS protocol with feasible clinical use to advance an internationally unified approach. Therefore, the specific aims of this study were to identify an optimal pediatric MSUS protocol for the detection of knee synovitis in patients with JIA by evaluating validated semi-quantitative MSUS measures of synovitis using BM and PD in multiple scan views. Secondly, BM and PD measures of synovitis were evaluated with the aim of determining the most sensitive views to achieve a short but high sensitivity protocol for synovitis.

Methods

Patients aged ≤ 18 with JIA diagnosed according to the ILAR criteria and with clinically diagnosed active inflammation of at least one knee joint were eligible for the study. By eligible patients, both knees were scanned, including those without clinical arthritis as a control group for comparison. Clinical arthritis of the knee was defined as the presence of a palpable joint effusion and limited range of motion (LOM) or pain on clinical examination. All patients received a standard complete clinical examination of all large peripheral joints and a standard physical examination to exclude co-existing diagnoses e.g. infection. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were determined as routine laboratory investigations. Disease activity was recorded using the validated JADAS-10 score.

Patients who fulfilled the inclusion criteria and had confirmed arthritis of at least one knee with arthritis after clinical examination, were eligible for recruitment. Exclusion criteria included active infection, presence of other autoimmune diseases, injuries, other musculoskeletal disorders and weight above 90 percentile.

Written patient (when aged > 6 years) and parental consent was obtained before study inclusion. Patients were consecutively recruited between 2019 and 2023 in each participating center (total nine) until the required 'n' (102 knees) for statistical analysis was reached. Ethical approval was obtained from the ethic commissions of the University of Giessen and the Ärztekammer Westfalen-Lippe, Germany. MSUS examiners were pediatric rheumatology specialists (≥ 5 years' experience in MSUS) and also members of the imaging groups of the PReS (Pediatric Rheumatology european Society) and/or the GKJR (German Pediatric Rheumatology Society). MSUS examiners performed the scans and grading of BM and PD.

Ultrasound assessment

All participants underwent MSUS examination of both knees following the study protocol which was internationally agreed and tested in an investigator face-to-face meeting in January 2019 in Munich, which included the practical application of the study protocol. Eight different standard views incorporating different positions were included as follows:

- The longitudinal suprapatellar scan (in neutral position with muscle tension and in 30° flexion).
- The transverse suprapatellar scan (in neutral position with muscle tension and in 30° flexion).
- Both transverse parapatellar scans (lateral and medial).
- Both longitudinal scans (lateral and medial, encompassing the meniscus region).

The suprapatellar recess (in longitudinal and transverse, in 30° and neutral position) was also measured in each examination. The examination of all views was performed with a linear transducer (minimal BM frequency 12 MHZ) and the most sensitive setting for PD in each center, adapted to minimize artifacts. Investigators used their own ultrasound devices as per routine clinical use.

Analysis of ultrasound findings

For each scan in the protocol, the highest possible BM and PD finding was documented. BM findings indicate effusion and synovial hypertrophy, and are quantified by the internationally agreed synovitis score of the Pediatric OMERACT group (grade 0 = no effusion, grade I = mild effusion and/or synovial hypertrophy, grade II = effusion and/or synovial hypertrophy leading to convex shaped recess, grade III = large effusion and/or synovial hypertrophy). BM positivity refers to any BM grading of ≥ 1. PD findings were also graded by the internationally consented synovitis score by the Pediatric OMERACT group (grade 0 = no intrasynovial Doppler signal, grade 1 = few individual dots of synovial Doppler signals, grade 2 = confluent Doppler signals, but representing less than 30% of the visible synovial tissue and grade 3 = confluent Doppler signals in more than 30% of the visible synovial tissue) [25].

The recess size (maximal height in mm) measured in the suprapatellar longitudinal view (maximal anterior-posterior diameter) and transverse view (maximal anterior-posterior diameter perpendicular to the femur) were recorded for all examinations.

An interobserver US reliability test for the BM and PD positivity was performed using 20 still images with different degrees of synovitis with BM and PD grades of 0–3 evaluated by ten MSUS examiners.

Finally, the results of the MSUS BM and PD findings in the JIA group were compared to the results of those in the healthy knee control group. Clinical examination was taken as the gold standard in the determination of arthritis. The most sensitive and practical combination of views for BM and PD were collated into the PReS Imaging Working group agreed "PIUS" protocol which was compared numerically to existing protocols for the MSUS evaluation of knee arthritis by application of their protocol for detecting intrasynovial hypervascularization within our patient group and the resulting sensitivity.

Statistical analysis

Descriptive statistics were used to summarize the clinical, laboratory and sonography data collected as follows: frequency and percentage for categorical variables; mean, median, standard deviation, minimum and maximum values for continuously distributed variables. The Chi-square test or Fischer's exact test and Student's t-test or Mann-Whitney U test were used to compare the proportions and variables between groups. A p value of < 0.05 was considered as statistically significant.

For the evaluation of diagnostic accuracy for categorical variables, the sensitivity, specificity, predictive values, likelihood ratios, accuracy and diagnostic odds ratio were evaluated with a 95% confidence interval for BM and PD scores for each view plane. For the statistical analysis of BM and PD as 2-variable categorical variables, the effusion and synovitis grading of ≥ 1 was defined as positive and 0 negative. A receiver-operating characteristic (ROC) curve was used to determine the cut-off values with the best sensitivity and specificity for the MSUS detection of arthritis. The predictive ability of MSUS was also evaluated using likelihood ratios. For the area under the ROC curve (AUC), discrimination ability was evaluated according to the following categories: 0.90-1 = excellent, 0.80–0.90 = good, 0.70–0.80 = moderate, 0.60–0.70 = poor, and 0.50–0.60 = unsuccessful. The

optimal cutoff points for predicting pathologic effusion were based on the highest Youden index.

Reliability for the interobserver analysis agreement BM and PD positivity was determined using Fleiss Kappa. A kappa score of < 0.2 is considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81-1.00 excellent. All statistical analyses were performed using the IBM SPSS software version 25 and MedicReS Good Biostatistical Consultancy Standards (www.e-picos.com, NY, New York software and MedCalc statistics).

Results

Patients

114 patients (80 female, 70%) aged 11.0 (mean, SD ± 4.3) years with JIA diagnosed according to the ILAR criteria and current active inflammation of at least one knee joint as determined by clinical examination ('clinical arthritis') were included. 92 patients (81%) had oligoarticular arthritis, 18 (16%) had polyarticular arthritis. The JADAS-10 score median (min-max) was 11.3 (3.0–30.0) for all JIA patients. The demographic, disease and clinical characteristics of the patients are shown in Table 1. Clinical arthritis was present in 137 knees in 114 patients; 23/114 patients had bilateral knee arthritis. 66 clinically healthy knees from the 114 patients formed the control group and were subjected to the same study ultrasound protocol as knees with clinical arthritis. Patients with unilateral arthritis had statistically significant lower JADAS10 scores (mean 10.5 ± 3.6 SD vs. 12.6 ± 5.4) and lower number of total active joints (1.5 ± 1.4 SD vs. 2.9 ± 4.6) compared to the whole patient cohort, but did not otherwise differ. MSUS examinations were performed by 11 different examiners and 72/137 (52%) knee ultrasound examinations were performed by an examiner blinded to the clinical findings.

Table 1 Demographic and clinical characteristics of patients with knee arthritis

Patients with knee arthritis	*n* = 114 (%)
Gender	
Female	80 (70.2)
Male	34 (29.8)
Mean age ± SD/ median (min-max)	11.0 ± 4.3 / 11.6 (1–18)
Category of JIA	
Oligoarticular JIA	92 (80.7)
Polyarticular JIA	18 (15.8)
Enthesitis related arthritis	2 (1.8)
Psoriatic arthritis	2 (1.8)
Previous Intraarticular steroid application of the knee joint(-s)	72/114 (63.1)
Unilateral	42/114 (36.8)
Bilateral	30/114 (26.3)
ANA positivity	97/112 (86.6)
HLAB-27 positivity	11/94 (11.7)
RF positivity	3/109 (2.8)
Anti-CCP positivity	3/63 (4.8)
Clinical signs of arthritis	
Palpable joint effusion	107/110 (97.3)
LOM	75/102 (73.5)
Pain	83/111 (74.8)
Swelling	108/112 (96.4)
Current medication use	81/113 (71.7)
Biologicals	6/113 (5.3)
Methotrexate	36/113 (32)
Systemic steroid	6/113 (5.3)
Other medications	61/113 (54)
Current eye involvement	13/113 (11.5)
	Mean ± SD / median (min-max)
Parameters of disease activity	
JADAS10 score	12.6 ± 5.4 / 11.3 (3.0–30.0)
Number of active joints	2.9 ± 4.6 / 2.0 (1–45.0)
VAS activity of patient	4.6 ± 2.2 / 5.0 (0–9.0)
VAS activity of physician	4.9 ± 1.9 / 3 (1.0–10.0)
Erythrocyte sedimentation ratio (mm/h)	19.0 ± 18.7 / 11.5 (1.0–84.0)
C-reactive Protein (mg/dL)	1.3 ± 2.7 / 0.3 (0-23.7)

Abbreviations: *ANA* anti-nuclear antibody, *CCP* Anti-cyclic citrullinated peptide, *JIA* juvenile idiopathic arthritis, *LOM* limted range of motion, *min-max* minimum-maximum, *RF* rheumatoid factor, *SD* standard deviation, *VAS* visual analogue scale

Ultrasound findings: effusion and synovial hypertrophy

MSUS identified effusion and/or synovial hypertrophy (BM positivity) in at least one of the imaging views in all patients with clinical arthritis. Comparing single images, BM positivity was most frequently detected in the suprapatellar scans, with at least 95% of knees showing positivity depending on the specific view (Table 2). The level of positivity of the BM score of each individual image varied within the protocol (Supplement Table 1), with the highest BM grade (score 3) also being most often found in one of the four suprapatellar images (longitudinal or transverse in flexion or neutral). Low grade (maximum grade 1) BM positivity was also detected in 8/66 control knees in at least one of the suprapatellar views. In 5 of these 8 cases, all other views had a BM grade of 0. In the other 3 cases, 2 cases had BM Grade 1 positivity also in the lateral and medial parapatellar views and control knee additionally had BM Grade 1 positivity in the medial and lateral longitudinal views.

The sensitivity and specificity with 95% confidence intervals for each individual view for the detection of synovitis in knees with and without clinical synovitis are shown in Supplement Table 2, for both the evaluation of BM and PD. The sensitivity of the suprapatellar scans

Table 2 Positivity of B-Mode and Power-Doppler-Mode in Arthritis and Control Groups

Arthritis group (*n* = 137 knee joints)			**Control group (*n* = 66 knee joints)**		
B-Mode findings					
Region	Positive *n* (%)	Negative *n* (%)	Positive *n* (%)	Negative *n* (%)	*P**
30°					
Longitudinal	133 (97.1)	4 (2.9)	4 (6.1)	62 (93.9)	< 0.001
Transverse	131 (95.6)	6 (4.4)	4 (6.1)	62 (93.9)	< 0.001
0°					
Longitudinal	135 (98.5)	2 (1.5)	2 (3.0)	64 (97.0)	< 0.001
Transverse	134 (97.8)	3 (2.2)	3 (4.5)	63 (95.5)	< 0.001
Long. Lateral	118 (86.1)	19 (13.9)	2 (3.0)	64 (97.0)	< 0.001
Long. Medial	106 (77.4)	31 (22.6)	1 (1.5)	65 (98.5)	< 0.001
PP-lateral	122 (89.1)	15 (10.9)	2 (3.0)	64 (97.0)	< 0.001
PP-medial	121 (88.3)	16 (11.7)	2 (3.0)	64 (97.0)	< 0.001
Power-Doppler Mode findings					
30°					
Longitudinal	72 (52.6)	65 (47.4)	0 (0)	66 (100)	< 0.001
Transverse	88 (64.2)	49 (35.8)	0 (0)	66 (100)	< 0.001
0°					
Longitudinal	59 (43.4)	77 (56.6)	0 (0)	66 (100)	< 0.001
Transverse	75 (54.7)	62 (45.3)	0 (0)	66 (100)	< 0.001
Long. Lateral	93 (67.9)	44 (32.1)	1 (1.5)	65 (98.5)	< 0.001
Long. Medial	69 (50.4)	68 (49.6)	0 (0)	66 (100)	< 0.001
PP-lateral	94 (68.6)	43 (31.4)	1 (1.5)	65 (98.5)	< 0.001
PP-medial	92 (67.2)	45 (32.8)	0 (0)	66 (100)	< 0.001

Abbreviations: L*ong* Longitundinal

*Fisher's Exact Test

combined was 100%, specificity 87.8%, positive predictive value (PPV) 94.4% and the negative predictive value (NPV) 100%.

The positioning of the patient in 30° flexion or neutral for the suprapatellar longitudinal or transverse views was not associated with a statistically significant difference in the BM positivity. However PD positivity was more frequent and more sensitive in 30° flexion in the transverse scan compared to in neutral.

Ultrasound findings: intrasynovial hypervascularisation

Intrasynovial hypervascularization (PD positivity) could be identified in at least one view of the scan protocol in 124/137 knees (102/114 patients) with clinical arthritis (Table 2). The sensitivity (level of positivity of PD score) of each individual imaging view within the protocol varied, as with the evaluation of BM (Supplement Table 1). The highest grade of PD positivity (grade 3) was most frequently found in the lateral parapatellar ($n=20/137$, 15%) and lateral longitudinal scans ($n=15/137$, 11%). An example of synovitis in the lateral longitudinal image in a knee with clinical and MSUS arthritis, with BM and PD positivity is shown in Fig. 1. Additionally, the probe positioning and corresponding MRI image is shown.

PD positivity of any grade was most frequently found in the medial ($n=92/137$, 67% of knees) and lateral parapatellar scans ($n=94/137$, 69%), the longitudinal lateral ($n=93/137$, 68%) and the transverse suprapatellar scan in 30° flexion (88/137, 64%) in knees with clinical arthritis (Table 2). As these four views indicated the highest likelihood of identifying PD positivity, we evaluated the potential for these four imaging views to be used as screening planes for the examination protocol. PD positivity in at least one of the four views had a sensitivity of 98.4%, specificity of 89%, positive predictive value (PPV) of 99.1% and negative predictive value (NPV) of 81.2% for the identification of knee with clinical arthritis. Low grade PD positivity (PD=1) was identified in one clinically healthy control knee at the longitudinal lateral and parapatellar longitudinal images.

Ultrasound findings: suprapatellar recess size

Recess size was analyzed in subgroups according to the age and gender of patients, to achieve age and sex-matched healthy controls. The recess size was statistically significantly larger in knees with clinical arthritis compared to controls in both the suprapatellar longitudinal and transverse scans regardless of the age and gender (Table 3). ROC analysis was used to determine

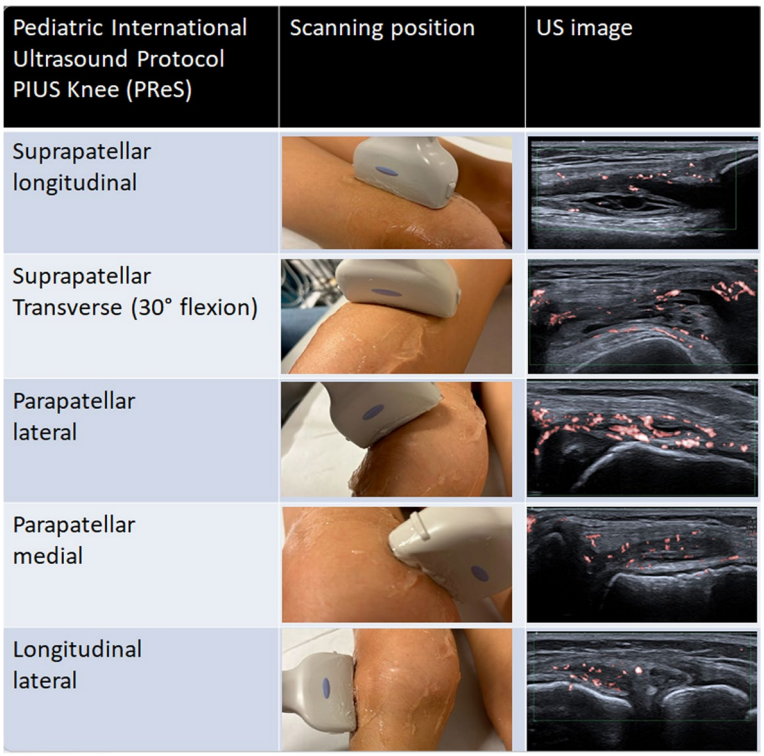

Fig. 1 The new PReS„PIUS protocol" for the sensitive detection of intrasynovial hypervascularization in the pediatric knee joint includes five views for the optimal detection of arthritis, as shown

Table 3 Comparison of the suprapatellar recess size as measured by ultrasound in patients with and without clinical arthritis

Suprapatellar Recess size **Mean ± SD** **Median (Min-Max)**				*P* Value
Knees with clinical arthritis		Knees without clinical arthritis		
1–3 years Boys (*n* = 0) Girls (*n* = 11)	n/a 9.9 (6.7–10.7) 3.9–12.0	1–3 years Boys (*n* = 0) Girls (*n* = 3)	n/a 1.3 (0.7-[§]) 0.7–1.5	< 0.001
4–6 years Boys (*n* = 4) Girls (*n* = 14)	5.8 (2.5–7.1) 1.5–7.6 7.9 (4.6–9.3) 3.6–10.2	4–6 years Boys (*n* = 1) Girls (*n* = 7)	-[§] 1.0 (0.7–1.4) 0.1–2.2	0.004
7–9 years Boys (*n* = 10) Girls (*n* = 12)	6.2 (3.5–10.2) 2.1–12.0 9.3 (8.6–11.5) 7.0-13.4	7–9 years Boys (*n* = 5) Girls (*n* = 2)	1.3 (1.0-1.5) 1.0-1.8 1.0 (0.9-[§]) 0.9–1.2	< 0.001
10–12 years Boys (*n* = 7) Girls (*n* = 28)	7.6 (4.9–23.6) 4.3–69.0 7.8 (5.7–9.5) 1.9–13.9	10–12 years Boys (*n* = 3) Girls (*n* = 20)	1.9 (1.2-[§]) 1.2–4.3 1.5 (1.0-1.9) 0.6–2.6	< 0.001
13–15 years Boys (*n* = 12) Girls (*n* = 21)	11.2 (9.2–16) 4.0-18.3 7.2 (5.6–8.9) 3.6–13.1	13–15 years Boys (*n* = 5) Girls (*n* = 10)	1.2 (0.5–2.4) 0-3.4 1.7 (1.1–2.5) 0-3.4	< 0.001
16–18 years Boys (*n* = 8) Girls (*n* = 10)	9.7 (7.3–10.7) 5.6–16.8 6.6 (4.7–11.6) 3.7–17.5	16–18 years Boys (*n* = 6) Girls (*n* = 4)	0.8 (0-1.6) 0-1.8 1.1 (0.8–1.3) 0.7–1.4	< 0.001

min-max minimum-maximum, *SD* standard deviation

[§] incalculable

cut-offs for recess size in both these scan views. The cut-off of 3.5 mm and 3.0 mm for the suprapatellar longitudinal and transverse views respectively for the identification of arthritis resulted in an area under the curve of at least 95%, regardless of whether performed in 0 or 30° flexion. The sensitivity was at least 86% and specificity at least 95%, depending on whether the scan was performed in neutral or 30° flexion and if the transverse or longitudinal view suprapatellar was performed (Supplement Table 3).

Evaluation of a combined knee ultrasound protocol

Five of the eight images could be combined to establish a short but clinically sensitive protocol for the identification of arthritis. This combination included the suprapatellar longitudinal scan and the transverse suprapatellar scan in 30° flexion, the medial and lateral parapatellar scans and the lateral longitudinal scan (Fig. 2). These five images extracted from the study protocol together achieved a combined sensitivity of 91% for the identification of Doppler synovitis.

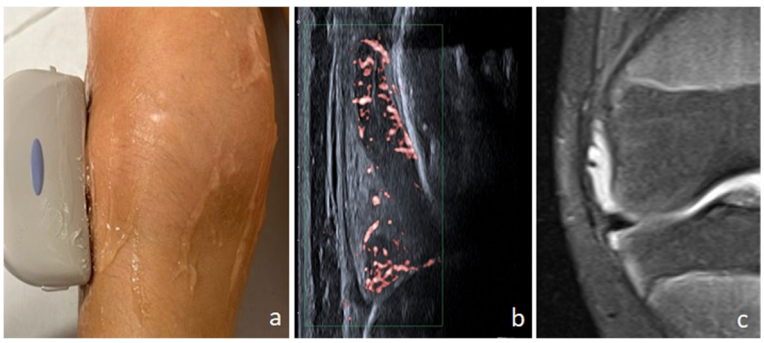

Fig. 2 Images illustrate the longitudinal lateral view scanning position (**a**) and corresponding ultrasound image (**b**) in comparison to the MRI image of the corresponding plane (**c**)

Evaluation of the external protocols identified is summarized in Table 4. The application of the identified alternative scan protocols to this dataset revealed a sensitivity for the identification of hypervascularization ranging from 53 to 85%. Higher sensitivity was achieved with protocols which included more views. Therefore, the five-image protocol established for synovitis in this study achieved a higher sensitivity for the detection of synovitis compared to the alternative protocols reviewed.

Interobserver test

The interobserver-test for the evaluation of BM and PD positivity showed substantial agreement (kappa 0.848, $p < 0.001$, CI 95% 0.765–0.930) between the investigators.

Discussion

The knee is the most commonly affected site in JIA and has therefore been a focus for the investigation of MSUS studies of normative and pathological findings over the last 15 years [4, 26–30]. Increasing standardization, technical developments and newer Doppler techniques have encouraged the optimization of examination protocols to reliably diagnose knee arthritis [17, 31]. A large German study by the GKJR reported age related normal findings of pediatric knee joints using MSUS in 2016 which formed the basis of characterizing pathological findings [29]. More recently, studies have reported significant differences between normal and pathological findings in MSUS, although MSUS results which conflict with clinical findings are also reported [2, 5, 9, 32, 33].

Individual views were more likely to show BM than PD positivity. However, BM alone is insufficient for the determination of the presence of synovitis. Contralateral knees without clinical synovitis were used as a control group as they were easily available, and clinically significantly differed from the knees with clinical arthritis. Subclinical synovitis could still potentially be present and potentially detectable by ultrasound. However, it was not the aim of this study to evaluate the sensitivity of the MSUS protocol for the detection of relevant subclinical synovitis, though this could be a focus of future studies. In this study, eight control knee joints which had no LOM, palpable joint effusion or pain present had BM positivity. The aforementioned GKJR study indicated healthy children can have low grade but positive BM findings and larger suprapatellar recess size without co-existing pathology [29]. However, no intrasynovial hypervascularization is expected in healthy children [27, 34, 35].

The suprapatellar recess size could distinguish non-arthritic and pathological knee joint effusions well in this study (sensitivity > 86%, specificity > 95% depending on positioning) and a cut-off of 3.5 mm (longitudinal suprapatellar) or 3.0 mm (transverse suprapatellar) had a high AUC for determining a pathological joint effusion. However, our patients were pre-selected for having a JIA diagnosis, and recess width remains unspecific as it is affected in multiple pathologies including traumatic or hemorrhagic causes.

The inclusion of multiple sensitive views for BM and evaluation of intrasynovial hypervascularization using PD are therefore important additional criteria for the specific detection of pathology. However, whilst PD increasingly influences the interpretation of inflammation in joints [4, 27, 34, 35], it's use and sensitivity in protocols has been so far variable and with low sensitivity [5–7]. In this study, intrasynovial hypervascularization was most frequently found in the medial parapatellar, lateral parapatellar, longitudinal lateral and the transverse suprapatellar scan in 30° flexion. These views capture more superficial lying synovial vessels in comparison to those involving the longitudinal suprapatellar plane, allowing easier detection by the ultrasound probe. Evaluation of PD in these views therefore aided a more specific discrimination of active inflammation from non-arthritic findings.

Table 4 Comparison of the sensitivity of the PReS study ultrasound protocol and different ultrasound protocols in our arthritis group

Combinations	Combination I (6)	Combination II (5)	Combination III (7)	Combination IV (unpublished PReS data)	Combination V (PIUS protocol as suggested in this study)
Regions	Suprapatellar scan (longitudinal)	Suprapatellar scan (longitudinal 30°)	Suprapatellar scan (longitudinal 30°)	Suprapatellar scan (longitudinal 30°)	Suprapatellar scan (longitudinal 30°)
	------	Medial parapatellar scan	------	Medial parapatellar scan	Medial parapatellar scan
	------	Lateral parapatellar scan	Lateral parapatellar scan	Lateral parapatellar scan	Lateral parapatellar scan
	------	-----	------	Lateral longitudinal scan	Lateral longitudinal scan
	------	------	------	------	Suprapatellar scan (transversal 30°)
B-Mode plus PD-Mode positivity	52.6%	82.5%	76.6%	85.4%	90.5%

Intrasynovial PD positivity was found only in one knee joint without clinical arthritis. Reviewing the finding, this image showed a small feeding vessel, rather than active inflammation. Published OMERACT data which reports vascularization in healthy knees has determined feeding vessels should not considered as a sign of inflammation. In contrast, 13 knees with BM positivity and clinical arthritis had no detectable PD positivity. These findings could represent a subset of patients with secondary clinical findings and a residual effusion rather than active inflammation.

This was the first study comparing the neutral position and 30 degree flexion position in pediatric MSUS suprapatellar scan examination. The sensitivity was slightly but not significantly higher with the neutral position for the suprapatellar longitudinal scan for BM positivity, but both positions showed a high specificity. However, PD positivity was more sensitive in the 30° flexion position when performing the transverse suprapatellar view. Whilst these results are encouraging for the identification of arthritis, the suprapatellar scan together with the recess height alone is insufficient to reliably discriminate active arthritis from non-arthritic findings.

Whilst MSUS protocols for examining standard regions in patients with JIA exist, specific protocols for individual joints are limited, though the knee has been the most intensively researched. Often protocols have focused on shorter protocols for ease of use in the clinical setting [6, 7]. However, this carries the risk of missing intrasynovial hypervascularization in some patients. Both these published protocols incorporated the longitudinal suprapatellar scans, whilst Sande et al. additionally included the lateral parapatellar scan for synovitis. When the alternative protocols were used on this data set, it resulted in a minimum sensitivity of only 53% and maximum sensitivity of 83% [5]. Using the five-image protocol as defined here, a sensitivity of 91% for BM and PD positivity in knees with clinical synovitis was reached with only an average 5–7 min scan time required for both knees.

Conclusion

In summary, our study was able to show that a protocol of five-images can safely identify synovitis and discriminate between clinically defined healthy and arthritis knees in patients with JIA. The five-image protocol incorporating BM and PD measures, termed the Pediatric International knee US or 'PIUS' Protocol, performed well compared to existing protocols and remains short enough for routine use in the clinic. An optimized MSUS knee protocol that can reliably detect inflammation is fundamental to allow dependable use in the treat-to-target approach, for example, for longitudinal monitoring of disease activity including the identification of subclinical inflammation or for the quantification of improvement after therapeutic interventions. Whilst the ability of MSUS to achieve these aims is not yet proven, studies are ongoing to address such questions [36].

Abbreviations

AUC	Area under the curve
BM	B-Mode
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
GKJR	German Pediatric Rheumatology Society
JADAS-10	juvenile arthritis disease activity score, 10-point
JIA	juvenile idiopathic arthritis
LOM	limited range of motion
MSUS	musculoskeletal ultrasound
NPV	negative predictive value
OMERACT	Outcome Measures in Rheumatology
PD	Power Doppler-Mode
PIUS-knee	Pediatric International agreed Ultrasound Knee synovitis protocol
PPV	positive predictive value
PReS	Pediatric Rheumatology european Society
ROC	receiver-operating characteristic
SD	Standard deviation

Supplementary Information

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Supplementary Material 1

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Authors' contributions
DW, RT, MKL, LF, RB, MH and SSM conceived and planned the study. All authors recruited patients and performed ultrasound examinations. DW, HAD, FG, RT, MKL, RB, MH analyzed and interpreted the patient data. DW, FG, HAD, SV, SS, LF, FD, BS and SMM were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Data availability
This manuscript has additional data available as a supplement file.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the ethic commissions of the University of Giessen and the Ärztekammer Westfalen-Lippe, Germany. Written patient (when aged > 6 years) and parental consent was obtained before study inclusion.

Consent for publication
Consent for publication of images was obtained from patients and their legal guardians.

Competing interests
The corresponding and last author is an associate editor for the Journal Pediatric Rheumatology.

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