Pediatric Rheumatology

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Development and validation of a Pediatric Internationally agreed UltraSound Hip synovitis protocol (PIUS-hip), by the PReS imaging working party

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Abstract

Background Whilst musculoskeletal ultrasound (MSUS) normal values for examination of the hip joint have been established for healthy children, equivalent values for patients with juvenile idiopathic arthritis (JIA), as well as internationally validated MSUS protocols for the optimal evaluation of synovitis are lacking. This study aimed to develop and validate the most sensitive MSUS protocol for the detection of hip synovitis in JIA.

Methods In consecutive JIA patients with ≥ 1 clinically affected hip joint, affected and unaffected hips underwent MSUS. Disease, demographic and clinical findings were recorded. Synovitis was graded using the pediatric OMERACT score for B-Mode (BM) and power-Doppler Mode (PD) in the longitudinal and transverse scans and the sensitivity and specificity was analyzed. Additionally anterior recess size (bone to capsula distance), capsula thickness and femoral head cartilage thickness (transverse view) were measured. Published data provided further control data for anterior recess size (children without JIA). Interobserver reliability of BM and PD was tested using Fleiss-Kappa.

Results 60 patients were enrolled who had 76 hips with and 32 without clinical arthritis. BM was positive (grade ≥ 1) in 74/76 of hips with clinical arthritis (97%, sensitivity 0.97 (0.93–1.0), specificity 0.85 (0.74–0.97) versus 2/32 (6%) in hips without arthritis. PD positivity frequency was 6 (8%) in hips with arthritis versus 0 in hips without. Anterior recess size (mean ± SD) was significantly wider in patients with clinical arthritis (9.9 ± 2.5 vs 5.5 ± 1.3, *p*-value 0.001). Use of the cut-off of ≥ 7.2 mm resulted in an area under the curve of at least 95%, with a sensitivity of 86% and specificity of 94%. Articular capsula and femoral head cartilage thickness did not differ between patients with and without arthritis. Recess size was comparable in the internal and external control groups (n = 449). Interobserver reliability of BM and PD positivity showed excellent agreement (kappa = 0.85).

Conclusions The Pediatric internationally agreed UltraSound hip synovitis protocol (PIUS-hip) could be limited to one longitudinal scan including B-Mode scoring plus measurement of anterior recess size for maximal sensitivity and specificity for synovitis.

Keywords Juvenile idiopathic arthritis, Hip synovitis, Ultrasound

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Key message

Internationally validated Musculoskeletal Ultrasound (MSUS) protocols for the optimal evaluation of hip synovitis are lacking, although hip synovitis can be frequent and damaging in patients with Juvenile Idiopathic Arthritis (JIA).

B-mode was the most informative ultrasound modality for grading the extent of hip joint involvement in JIA whilst Doppler findings were rarely detected.

The longitudinal anterior scan view along the femoral head and neck using B-Mode with the inclusion of semiquantitative BM grading and quantitative measurement of the anterior recess size were included in the final PIUS-hip protocol.

Background

Ultrasound examination techniques and protocols are increasingly used for the detection of synovitis in juvenile idiopathic arthritis (JIA). Several initiatives have led to relevant achievements in the standardization of pediatric musculoskeletal ultrasound (MSUS) including acquisition protocols, though internationally consented standardized scan protocols are still lacking for children.[1,2] The sensitivity and specificity of MSUS for the detection of joint effusion and/or synovial hypertrophy with potential pathological vascularization vary with the joint area explored and on the scan planes adopted [3, 4]. Additionally, newer scanning techniques such as the implementation of microvascular Doppler methods or higher frequency transducers and the accrual of standardized measurements, e.g. recess size, can support the development of new international consensus protocols for the examination of key joints such as the hip in children with JIA. The 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 and development of a pediatric specific score [1, 5]. However, there is still uncertainty of using the Doppler Mode to score synovitis of the hip joint as no study has to date confirmed the clinical utility of PD for this purpose. Additionally, the experience of the authors in clinical practice has shown that the detection of Doppler signals is a rare finding in the hip region in JIA patients, though this also has not been yet been addressed in existing literature. Therefore, scanning and scoring protocols require adaptation for each specific joint.

The PIUS project (Pediatric Internationally consented UltraSound protocols) of the PreS (Pediatric Rheumatology european Society) imaging working party aims to develop homogeneous MSUS examination protocols for all pediatric joints. The PIUS-knee joint protocol has been recently published and addressed international consensus for a standardized scan for the most frequently affected joint in JIA [3]. However, 15–50% of patients with JIA could have hip joint involvement [6, 7] which carries a significant risk of complications with potential destruction of the hip joint requiring surgery if inadequately treated [8]. However, to date few studies have developed MSUS examination protocols and included the hip joint in children. Whilst some study groups have started this process of adapting semi-quantitative scores into joint specific scoring protocols, the number of JIA patients included, particularly with hip joint involvement, remains very low [2, 9].

The shape and structure of the anterior capsula in ultrasound plays an important role in the evaluation of hip joint synovitis. The capsula articularis, or joint capsule, is a sack-like structure composed of a posterior and anterior (external) layer, consisting of dense fibrous tissue [10]. Normal values of the anterior recess, or bone-to capsula distance measured in the longitudinal view have been published and show age and sex differences [11–13]. Zuber et al. measured the synovial joint space (SJS) from the femoral neck to joint capsule, and where possible, the distance from the femoral neck to external joint capsule [13]. Almost 25 years ago one study aimed to compare the anterior joint capsula of the normal hip in children with transient synovitis. This study has shown increased widening of the anterior recess by effusion but there was no MSUS evidence for additional capsula swelling [14].

This study was therefore supported by the PReS imaging working party to develop the most sensitive hip joint specific MSUS protocol with feasible clinical use to advance an internationally unified approach. The specific goals of the study were to identify an optimal pediatric MSUS protocol for the detection of hip synovitis in patients with JIA with use of the semi-quantitative BM and PD pediatric OMERACT score and to determine the potentially relevant measures of recess size and cartilage thickness.

Methods

Patient inclusion

Patients aged ≤ 18 with JIA diagnosed according to the ILAR criteria and with clinically diagnosed arthritis of at least one hip joint were eligible for the study. Demographic data including date of birth, age at time of study and gender were additionally documented. Clinical arthritis of the hip was defined as the presence of a limited range of motion (LOM) and pain on clinical examination. All patients received a standard complete clinical musculoskeletal examination of the joints and a standard physical examination to exclude co-existing diagnoses e.g. infection. C-reactive protein (CRP), erythrocyte

sedimentation rate (ESR) and disease activity (JADAS-10 score, range 0–40) were performed as routine and documented. Patients who fulfilled the inclusion criteria and had confirmed arthritis of at least one hip after clinical examination, were eligible for recruitment. Exclusion criteria included active infection, presence of other autoimmune diseases, injuries, other musculoskeletal disorders and weight above the 90th percentile. Written patient assent (when aged > 6 years) and parental consent were obtained before study inclusion. Patients were consecutively recruited between 2019 and 2023 in each of the nine participating centers until the required 'n' (97 hips) for statistical analysis was reached. The hip joints of the same JIA patients without current clinical signs of active arthritis were analyzed as a comparison group. A third group of subjects from a previously published cohort of healthy children without any chronic disease or inflammatory diagnosis was also included as a control group [11].

Ethical approval was obtained from the ethic commissions of the University of Giessen and the Ärztekammer Westfalen-Lippe, Germany. Investigators performing the MSUS examinations and grading/measurements were pediatric rheumatology specialists (≥ 5 years' experience in MSUS) and members of the PReS and/or the GKJR (German Pediatric Rheumatology Society) imaging groups.

Ultrasound assessment

The study protocol was internationally agreed and tested by expert ultrasonographers from four different European countries in an investigator face-to-face meeting in January 2019 in Munich, Germany. The hip joint was imaged using an anterior recess approach with the femur in slight external rotation in the longitudinal plane parallel to the femoral neck. This positioning has been long accepted as being optimal for the demarcation of the articular structures of the hip joint with ultrasonography and an example is shown in Fig. 1.[9, 12] BM and PD grading were assessed in this longitudinal view and documented. BM ultrasound is a grayscale imaging technique that uses varying shades of gray to represent the amplitude of returning echoes, creating a two-dimensional image. PD is an ultrasound technique that focuses on detecting the presence of blood flow, particularly in areas with low blood flow velocity, by analyzing the amplitude of the Doppler signal. Measurements of the hip anterior recess size (maximum distance bone surface on the femoral neck to outer border of the anterior capsula, mm) and the anterior and posterior articular capsula thickness (mm) were also documented (Fig. 2). In the transverse scan, as shown in Fig. 3, the femoral head cartilage thickness on an ideal line perpendicular to the probe footprint

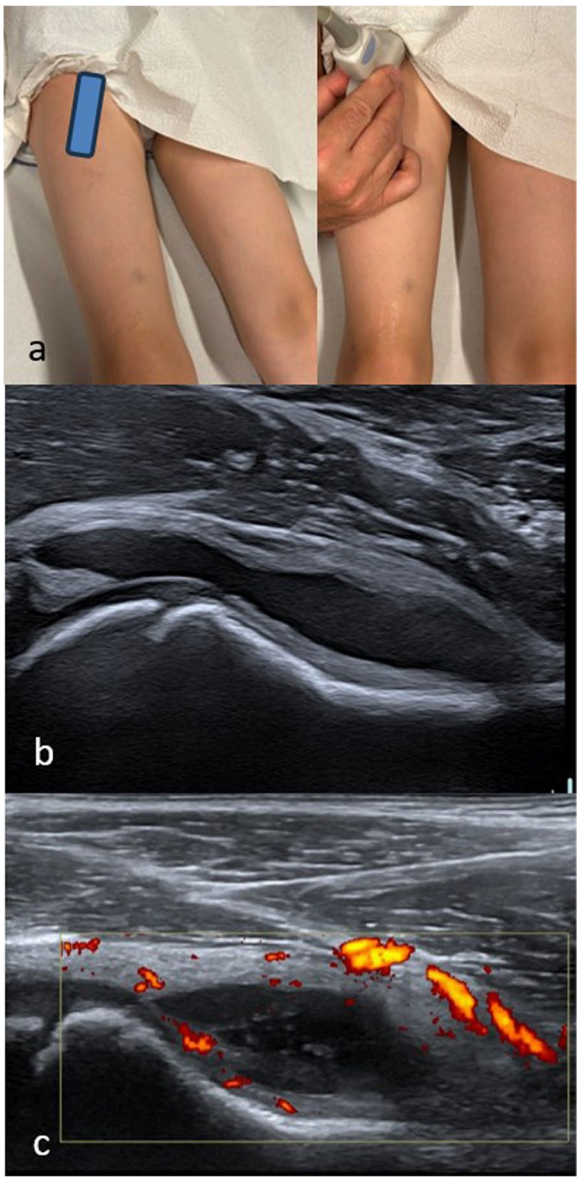

Fig. 1 Ultrasound probe placement and example B-Mode and Power-Doppler appearance in the anterior longitudinal view of the hip joint. The optimal placement of the US probe for evaluation of the anterior longitudinal view is shown (**a**), hip joint effusion with significant distension of the joint capsula (B-Mode Grade 3) is shown (**b**) and multiple PD signals outside of the joint capsule indicating physiological blood vessels or within the synovial membrane are shown (**c**)

was measured (mm). All participants underwent MSUS examination of at least one, or where possible, both hips following the study protocol. A linear transducer (minimal BM frequency 6 MHZ) and the most sensitive setting for PD in each center, adapted to the demarcation of artifacts was used. Investigators used their own ultrasound devices as per routine clinical use.

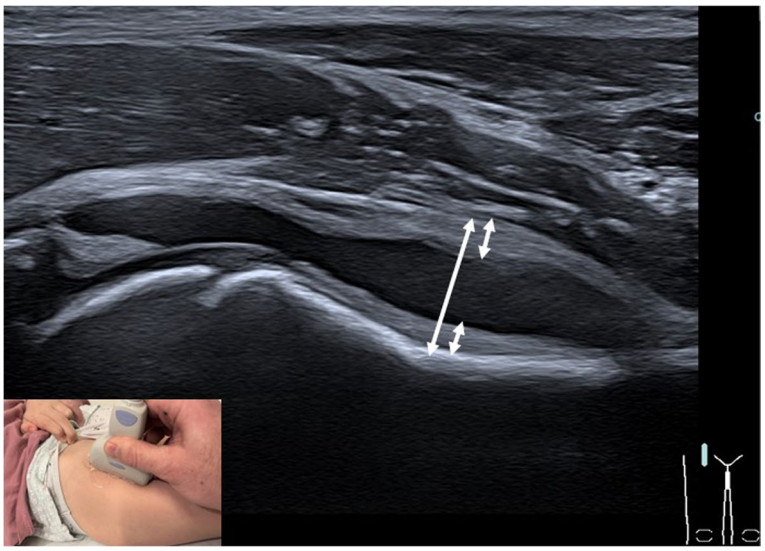

Fig. 2 Ultrasound measurement of the anterior recess size, anterior and posterior capsula thickness. Example of anterior recess size, including the anterior and posterior capsula thickness in the anterior longitudinal view

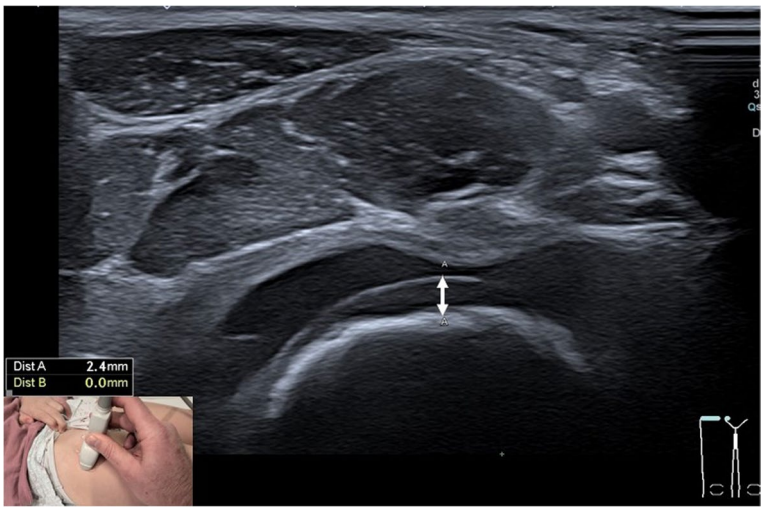

Fig. 3 Ultrasound measurement of the femoral cartilage thickness performed in the transverse view. Example of the femoral head as seen in the transverse view. The double-headed arrow indicates femoral cartilage thickness

An interobserver MSUS reliability test for the BM and PD positivity was performed using ultrasound images of 20 JIA patients with different degrees of hip synovitis evaluated by ten MSUS examiners at the start of the study.

For the evaluation of synovitis, the semi-quantitative Pediatric OMERACT group score for BM and PD findings was used as described by Rossi et al.[5] Effusion and synovial hypertrophy are graded using BM with a grade of 0 representing no effusion, grade I indicates a mild effusion and/or synovial hypertrophy, grade II indicates a more significant effusion and/or synovial hypertrophy leading to a convex shaped recess and the highest grade III, which represents a large effusion and/or synovial hypertrophy extending to over the femoral head. BM positivity refers to any BM grading of ≥ 1. Similarly, PD was graded 0 if no intrasynovial Doppler signal was present, grade 1 when a few individual dots of synovial Doppler signals are detectable, grade 2 with the presence of confluent Doppler signals but representing less than 30% of the visible synovial tissue and grade 3 when confluent Doppler signals in more than 30% of the visible synovial tissue are present.

Statistical analysis

Clinical, laboratory and ultrasound data were summarized with descriptive statistics, with the frequency and percentage indicated for categorical variables and the mean, median, standard deviation, minimum and maximum values for reporting 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, according to the normal or not-normal distribution of values. A p-value of < 0.05 was considered to be statistically significant.

Sensitivity, specificity, predictive values, likelihood ratios, accuracy and diagnostic odds ratio were evaluated with a 95% confidence interval for BM and PD scores for the evaluation of their diagnostic accuracy. For the analysis of BM and PD as 2-variable categorical variables, the grading of ≥ 1 was defined as positive, and zero as negative. Analyses were also performed for articular capsula and femoral head cartilage thickness. Receiver-operating characteristic (ROC) curve analysis determined the cut-off values with high 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 of the inter-observer analysis agreement for BM and PD positivity was determined using Fleiss Kappa and a score of < 0.2 was 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

60 patients (28 female, 47%) aged 12.0 (mean, SD ± 4.4) years with JIA diagnosed according to the ILAR criteria and current active inflammation of at least one hip joint, determined by clinical examination ('clinical arthritis'), were included. 27 (45%) patients had polyarticular arthritis and 19 (32%) had oligoarthritis. Disease activity (JADAS-10) for all JIA patients was a median score 15 (min. 5.0, max. 32.6). Table 1 summarizes the demographic, disease and clinical characteristics of the included patients. Clinical arthritis was present in 76 hips in 60 patients; in 12/60 patients only the affected hip with clinical arthritis was included. 32 clinically healthy hips from the 60 patients formed the JIA comparison group. MSUS examinations were performed for these patients by a total of 11 different examiners in four different centers. Data from the additional control group was available from 449 healthy children without any known musculoskeletal or inflammatory disease

Table 1 Demographic and clinical characteristics of patients with hip arthritis

Patient, total n (%)	**60 (100)**
Female (%)	28 (46.7)
Male (%)	32 (46.7)
Hips scanned, total n (%)	108 (100)
With clinical arthritis, n (%)	76 (70)
Without clinical arthritis, n (%)	32 (30)
Mean age ± SD/median (min–max)	11.9 ± 4.4/12.0 (2–19)
Category of JIA, n (%)	19 (31.7)
Oligoarticular JIA	27 (45.0)
Polyarticular JIA	8 (13.3)
Enthesitis related arthritis	2 (3.3)
Psoriatic arthritis	3 (5.0)
Systemic JIA	1 (1.7)
Undifferentiated JIA	
Previous Intraarticular steroid application	26/56 (46.4)
Unilateral	11/55 (20.0)
Bilateral	8/55 (14.5)
ANA positivity	42/58 (72.4)
HLAB27 positivity	10/55 (18.2)
RF positivity	2/59 (3.4)
Anti-CCP positivity	3/48 (6.3)
Symptoms of arthritis:	
Loss of function	48/58 (82.8)
History of pain	48/59 (81.4)
History of swelling	1/59 (1.7)
Current medication use	45/60 (75.0)
Biologicals	18/60 (30.0)
Methotrexate	19/60 (31.7)
Systemic steroid	7/60 (11.7)
Other medications	32/60 (53.3)
Current eye involvement	1/60 (1.7)
	Mean ± SD/median (minimum–maximum)
Parameters of disease activity, age ± SD/median (min–max)	
JADAS10 score	14.6 ± 6.9/13.0 (5.0–32.6)
Number of active joints	4.3 ± 3.3/3.0 (1.0–12.0)
VAS activity, patient	4.8 ± 2.3/5.0 (0–9.0)
VAS activity, physician	4.9 ± 2.3/5.0 (1.0–10.0)
Erythrocyte sedimentation ratio (mm/h)	21.4 ± 19.0/14.0 (2.0–74.0)
C-reactive Protein (mg/dL)	1.1 ± 1.5/0.5 (0–6.2)

diagnosis, with their characteristics published in full in the publication from Trauzeddel and colleagues [11].

Ultrasound findings: BM and PD

In the longitudinal view of the anterior recess in the clinical arthritis group, 74/76 hips had BM grades from 1 to 3 and two hips from two patients had grade 0. In the non-clinical arthritis group, 30/32 hips had BM grade 0 whilst the two remaining hips had grade 1 BM. BM positivity (grading ≥ 1) was therefore detected in 97% of scanned hips with a sensitivity 0.97 (0.93–1.0) and specificity 0.85 (0.74–0.97) compared to in 6% of scanned hips (sensitivity and specificity not calculable) without arthritis. PD grade 0 was found in 70/76 of the clinical arthritis hips, grade 1 found in 2/76, grade 2 in 3/76 and grade 3 in 1/76. In hips without arthritis, PD grade 0 was found in 32/32 joints. The frequency of PD positivity (grading ≥ 1) was therefore 6 (8%) in the arthritis group versus 0 (0%) in hips without arthritis. Findings are summarized in full in Supplement 1 and an example of BM and PD grading is given in Fig. 1.

Ultrasound findings: anterior hip recess size

In the whole group analysis, the anterior recess size in patients with clinical arthritis was 9.9 ± 2.5 versus 5.5 ± 1.3 mm (mean ± SD) in hips without clinical arthritis ($p = 0.001$) (Table 2, Fig. 2). In the subgroup analysis performed according to age and gender (Table 3), the anterior recess size in hips with clinical arthritis was higher for all age groups compared to unaffected hips of the same patients ($p = 0.001$) as well as the additional external control group of healthy controls ($p < 0.001$). Recess size was comparable in the internal and additional healthy children control group ($p = 0.94$). ROC analysis

Table 2 Anterior recess size, anterior and posterior capsula thickness and femoral head cartilage measurement in hip joints with and without clinical arthritis

	Clinical arthritis group ($n = 76$)	Without clinical arthritis group (n = 32)	p
	Mean ± SD Median (Min–Max)		
Anterior recess size (distance bone to capsula), longitudinal view	9.9 ± 2.5 9.8 (5.2–17.1)	5.5 ± 1.3 5.8 (1.2–8.0)	**0.001**
Anterior capsula thickness (size in mm)	2.9 ± 1.1 3.1 (0–5.8)	2.4 ± 1.0 2.4 (0–4.4)	0.845
Posterior capsula thickness (size in mm)	1.9 ± 1.1 1.7 (0–5.5)	1.2 ± 0.9 1.0 (0–3.3)	0.380
Femoral head cartilage thickness (in mm)	2.2 ± 1.3 2.0 (0.5–8.0)	1.8 ± 0.8 1.7 (0.5–3.5)	**0.031**

Table 3 Anterior recess size in hip joints with and without clinical arthritis categorised by age

Hips with clinical arthritis[1]		Hips without clinical arthritis[2]			Healthy control hips[3]			
Age Groups (n)	Mean ± SD Median (Min–Max)	Age Groups (n)	Mean ± SD Median (Min–Max)	P Value[1 vs 2]	Age Groups (n)	Mean ± SD Median (Min–Max)	*P* Value[2 vs 3]	*P* Value[1 vs 3]
1–3 years (n = 5)	7.8 ± 1.4 8.5 (5.8–9.3)	*1–3 years* [§] (n = 1)	[§]	[§]	*1–3 years* 4.2 ± 0.9 (n = 56) 4.2(2.3–6.6)	*	**< 0.001**
4–6 years (n = 8)	7.3 ± 1.2 7.7 (5.2–9.0)	*4–6 years* 5.2 ± 1.4 (n = 3) 5.2 (3.8–6.6)	0.033		*4–6 years* 5.1 ± 0.7 (n = 73) 5.1 (3.4–7.2)	0.850	**0.001**
7–9 years (n = 10)	9.4 ± 2.5 9.0 (5.8–14.9)	*7–9 years* 6.3 ± 0.6 (n = 3) 6.1 (5.8–7.0)	0.028		*7–9 years* 5.4 ± 1.0 (n = 93) 5.4 (3.6–8.4)	0.187	**< 0.001**
10–12 years (n = 23)	10.0 ± 1.5 9.9 (6.4–13.5)	*10–12 years* 5.5 ± 1.0 (n = 11) 5.5 (4.4–8.0)	< 0.001		*10–12 years* 5.9 ± 1.1 (n = 90) 5.9 (3.5–10.9)	0.270	**< 0.001**
13–15 years (n = 13)	11.3 ± 3.5 11.1 (6.5–17.1)	*13–15 years* 4.9 ± 1.4 (n = 4) 5.1 (3.4–6.2)	0.004		*13–15 years* 6.3 ± 1.3 (n = 88) 6.2 (4.1–9.9)	0.045	**< 0.001**
16–18 years (n = 17)	10.9 ± 2.3 10.9 (6.3–15.2)	*16–18 years* 5.5 ± 1.7 (n = 10) 6.0 (1.2–7.2)	< 0.001		*16–18 years* 6.2 ± 1.1 (n = 49) 6.1 (3.7–9.2)	0.148	**< 0.001**
Total *(n = 76)*	9.9 ± 2.5 9.8 (5.2–17.1)	*Total* 5.4 ± 1.3 *(n = 32)* 5.6 (1.2–8.0)	0.001		*Total* 5.6 ± 1.2 *(n = 449)* 5.4 (2.3–10.9)	0.938	**< 0.001**

Abbreviations: min–max = minimum–maximum, SD = standard deviation. [§]incalculable, vs: versus

was used to determine a cut-off for the anterior recess size associated with synovitis. Use of the cut-off of ≥ 7.2 mm resulted in an area under the curve of at least 95%, with a sensitivity of 86% and specificity of 94% (Supplement 2).

Ultrasound findings: hip capsula thickness

The anterior capsula thickness, measurement method shown in Fig. 2, was 2.9 ± 1.1 vs 2.4 ± 1.0 mm and posterior capsula 1.9 ± 1.1 vs 1.2 ± 0.9 mm in hips with versus without clinical arthritis did not differ between the groups in the whole-group (Table 2) or subgroup analysis (Supplement 3).

Ultrasound findings: femoral head cartilage thickness

In the whole group analysis, the femoral head cartilage thickness in patients with clinical arthritis was 2.2 ± 1.3 (mean ± SD) versus 1.8 ± 0.8 mm (p-value 0.031) in hips without clinical arthritis (Table 2), measured as shown in Fig. 3. In the subgroup analysis (Supplement 4), performed according to age and gender, the femoral head cartilage thickness in hips with clinical arthritis, was numerically higher in the 7–9 and 13–15 years age groups compared to those without arthritis (3.0 ± 1.7 vs 2.2 ± 0.1 mm and 2.3 ± 1.9 vs 1.3 ± 0.2 mm, respectively). The difference was however not statistically significant in any subgroup.

Evaluation of a combined hip ultrasound protocol

A combination of presence of BM positivity in the anterior recess as well as increased anterior recess size of ≥ 7.2 mm had a sensitivity and specificity of 86.8% and 100% respectively, which was summarized as the PIUS-hip protocol, as shown in Fig. 4. Addition of PD positivity, measurement of articular capsula thickness or femoral head cartilage thickness in the transverse view did not improve the sensitivity.

Interobserver test

The interobserver-test for the evaluation of BM and PD positivity showed excellent agreement (kappa 0.85, $p < 0.001$, CI 95% 0.765–0.930) amongst the investigators.

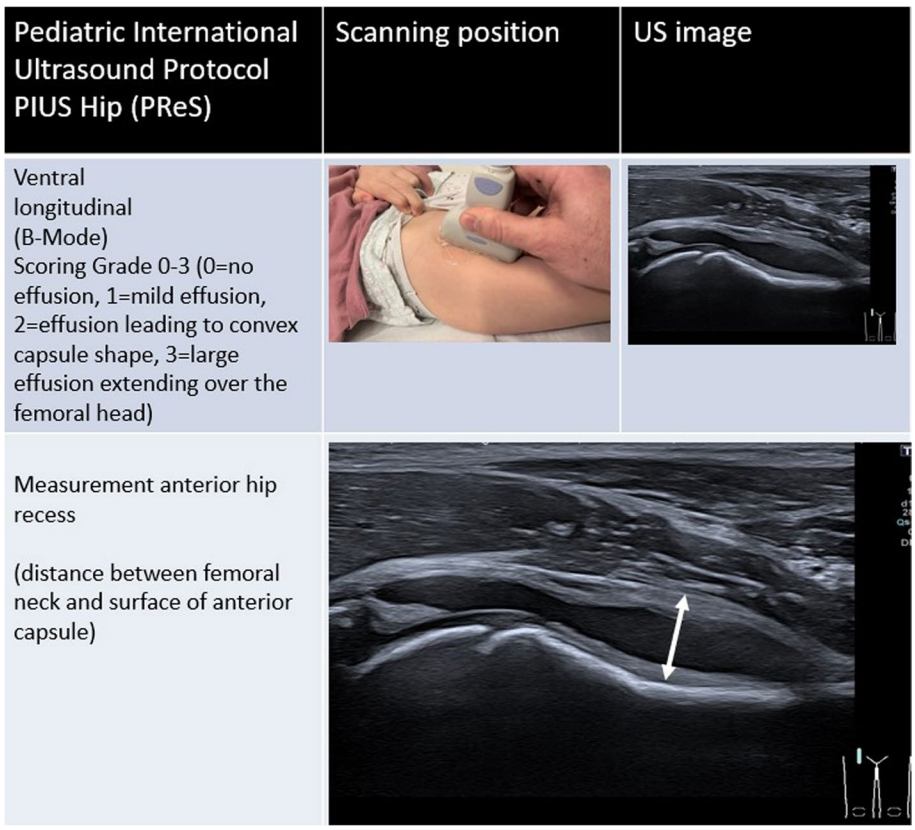

Fig. 4 Overview of the PIUS-Hip Ultrasound Protocol for Synovitis. The anterior longitudinal view, with ultrasound probe position, corresponding example of B-Mode image is shown, along with the pediatric OMERACT grading criteria for B-Mode findings. The measurement of the anterior hip recess is also shown, also performed in the anterior longitudinal view, which forms the second necessary image to fulfil the PIUS-protocol

Discussion

An internationally agreed protocol for the MSUS detection of hip synovitis in children with JIA was developed and tested. The protocol showed good sensitivity and specificity, with good inter-operator reliability. Hip joint involvement in patients with JIA can be frequent (15–50%) and disabling [6, 7, 15]. Insufficient recognition leads to chronic synovitis which can be characterized by pain, stiffness and progressive joint destruction and in the worst-case lead to a requirement for joint replacement surgery [7, 16, 17]. MRI is regarded as the gold standard imaging technique for identification of hip arthritis and the associated findings, due to the depth of the joint, which does not allow the detection of swelling or warmth on clinical examination, as in other joints [18]. Despite this, the clinical assessment of the hip remains a cornerstone. Nistala et al. showed a sensitivity of 25.7% and specificity of 91% for the clinical detection of arthritis when compared to the MRI findings in a cohort of 34 JIA patients with established disease [19]. Ostrowska et al. report a sensitivity of 25% and specificity of 100% of MRI in discriminating between patients with suspected hip disease who later had a confirmed or disapproved JIA diagnosis [20]. Nonetheless, MRI examination requires sedation in the less cooperative children. Furthermore, it is expensive and may not be widely accessible. Therefore, the use of simple and reliable protocols for examination using non-invasive, child-friendly, relatively inexpensive repeatable imaging technique such as MSUS can be of major benefit for clinicians both in clinical care and in research. Indeed, MSUS provides a quick and easily accessible method of differential diagnosis in clinical practice which can be routinely employed. Additional applications include monitoring of arthritis under treatment and the involvement of enthesis and tendons [21]. MSUS is also increasingly being recognised to be equivalent to MRI in some situations, e.g. the evaluation of shoulder and ankle tendon abnormalities, Baker's cyst and wrist ganglion cysts [22] and is superior to clinical examination for the evaluation of synovitis in peripheral joints [23]. Abnormal MSUS findings associated with clinical synovitis was shown by Silva et al. who performed ultrasound of 184 hip joints in patients with JIA with and without hip-related symptoms [24]. The study additionally showed ultrasound changes in 31.5% (29/92) of patients, which was termed subclinical arthritis.

This study showed that BM positivity in the longitudinal view was highly sensitive for the evaluation of synovitis in the anterior recess. In contrast, PD had a very low sensitivity in this region and was therefore not included in the final PIUS-Hip protocol. PD negativity is in line with the hypothesis that the very low intrasynovial blood flow in the depth cannot be sufficiently represented by Doppler technique, even with the newer scanning devices. This limitation of the Doppler modality was also acknowledged in a recent paper from this working group, on the development of a PIUS-Knee protocol. Similarly, PD-positivity had higher sensitivity in more superficial views of the knee joint, including the medial (0.67, 0.59–0.75) and lateral (0.69, 0.60–0.76) parapatellar scans and longitudinal lateral (0.67, 0.60–0.75) views compared to the deeper suprapatellar longitudinal view (0.43, 0.35–0.51) [3].

BM showed to be a very reliable technology to discriminate normal and pathological JIA findings in hip joints. Two clinically affected JIA hips had negative BM findings in all views. These clinical findings were therefore suspected to be due to extra-articular causes, such as muscle strain or soft tissue involvement. Two clinically unaffected JIA hips had a grade I positive semiquantitative B-Mode finding, possibly representing a residual or early ultrasound finding. The semiquantitative joint specific scoring showed an excellent sensitivity and specificity (Supplement 1). Sensitivity of BM grading was marginally higher than the anterior recess size cut-off use in BM, though that had a marginally higher specificity. Therefore, a combination of the semiquantitative BM grading and the quantitative anterior recess measurement would comprise the optimal protocol.

Ultrasound derived anterior recess size has already been deemed a relevant aspect of the hip joint examination [18, 25], whilst a positive correlation with reduced range of movement of the hip joint has also been described [26]. Silva et al. used a cut-off of < 6 mm to define normal, also defined by Frosch et al. and Fedrizzi et al., and found 29% of the measurements were abnormal, though correlations with symptoms or clinical signs were not described [24]. Fedrizzi et al. showed that 50% of their JIA patient sample, also not defined as having clinical pathology of the hip, had an anterior recess size > 6 mm as well as other signs of synovitis in ultrasound including increased echogenicity and distension of the joint capsula [18]. In this study, a cut-off of 7.2 mm was established. Measurements from a previously published independent control cohort of healthy hip joints in children without any arthritis were included in the data analysis in order to avoid the limitation of only including patients with JIA and their hips without clinical arthritis as controls. Indeed, analysis showed no statistically significant differences between the internal (JIA patients, arthritis or healthy hips) and external (no JIA, both hips included) analysis of anterior recess size, indicating that no cases of subclinical JIA arthritis had an impact on the study results. A limitation recognised by the authors is the lack of patients in the youngest age group aged 1–3 years, with the included number increasing with age. This

reflects the relative lack of coxarthritis in young patients with JIA.

An anterior transverse view was added to the protocol presented here to visualize the femoral head and to measure the cartilage thickness. In a study published by Spannow and colleagues the cartilage thickness in the knee region was significantly lower in JIA patients in comparison to healthy controls [27]. Although a significant difference in femoral head cartilage thickness between the JIA patients with and without clinical hip arthritis could be seen (Table 2), this difference was not maintained in the age-specific subgroup analyses (Supplement 4). Therefore, the inclusion of the transverse view to measure the cartilage thickness is not mandatory in a routine protocol for evaluating hip synovitis.

Furthermore, this study was able to show the anterior and posterior capsula thickness in hips did not differ between JIA patients with or without hip synovitis, which reflected the findings from the study by Robben et al., which was however performed in patients with transient hip synovitis [14]. Therefore the routine measurement of capsula thickness for the evaluation of hip synovitis is not recommended. Zuber et al. described normal values for the hip joint capsule in 816 hip MSUS examinations in children referred to the rheumatology clinic who subsequently had no musculoskeletal disease diagnosed, showed a relationship to height rather than age, but no difference between the genders. However, the anterior and posterior capsula thickness was not specifically discriminated [12].

Conclusions

In this study, the most sensitive MSUS examination protocol with excellent interrater reliability for synovitis was established after analysis of the individual MSUS parameters for the evaluation of joint effusion, synovial hypertrophy and capsula shape and termed the "PIUS-hip protocol" (Pediatric Internationally agreed UltraSound hip synovitis). This protocol consists of the single anterior longitudinal view with measurement of the bone to outer capsula distance/anterior recess size with cut-off set at $\geq$7.2 mm and the evaluation of BM grading using the OMERACT-established 0–4 semi-quantitative score for the highest sensitivity and specificity for synovitis. Compared to other joints, the finding of PD positivity was rare in MSUS of the hip joint in JIA and was therefore not recommended as a marker of hip affection.

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
MSUS	Musculoskeletal ultrasound
OMERACT	Outcome Measures in Rheumatology
PD	Power Doppler-Mode
PIUS-hip	Pediatric Internationally agreed Ultrasound hip 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
No datasets were generated or analysed during the current study.

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
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