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ORIGINAL ARTICLE

Is Ultrasound a Validated Imaging Tool for the Diagnosis and Management of Synovitis in Juvenile Idiopathic Arthritis? A Systematic Literature Review

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Objective. **Ultrasound (US) has been shown to be a sensitive tool for evaluating synovitis in rheumatoid arthritis. However, the validity of US has not yet been established in juvenile idiopathic arthritis (JIA). The purpose of this study was to assess the validity of US for detecting synovitis for both diagnosis and followup in JIA.**

Methods. **A systematic literature search in Embase and PubMed was performed before February 25, 2011. Selection criteria included original articles on children, JIA, US, Doppler, synovitis, and management published in the English language. Data were extracted from the articles meeting the inclusion criteria, particularly those focused on the US definition of synovitis, scoring systems used, and metric properties studied. The type and number of joints tested, study design, and quality of the studies were assessed.**

Results. **Twenty studies were identified using US to assess synovitis in JIA. The knee was the joint most commonly studied in these articles. There was heterogeneity regarding the US definition and quantification of synovitis. Synovitis was commonly assessed by using gray scale and only a few studies included the Doppler technique. Construct validity was reported in 80% of articles, including the clinical examination as the main comparator. US demonstrated higher sensitivity in detecting synovitis as compared to clinical examination. Few studies reported US reliability and responsiveness in JIA.**

Conclusion. **US is a valuable tool for detecting synovitis in JIA, and demonstrated higher sensitivity in assessing synovitis as compared to clinical examination. However, further studies are needed for evaluating the reliability and responsiveness to assess synovitis changes over time.**

INTRODUCTION

The term juvenile idiopathic arthritis (JIA) encompasses a group of clinically heterogeneous arthritides that begin before the age of 16 years, are of unknown causes, and persist for more than 6 weeks (1). It is characterized by an inflammatory process of the synovium and periarticular tissue associated with neovascularization. The extent of this inflammation leads to joint damage and growth abnormalities in these children. The primary goal in the management of JIA is getting an early and extensive diagnosis of inflammatory activity in order to avoid physical disability in adult age.

As in adults, the gold standard for detecting joint inflammation (i.e., synovitis) has traditionally been the clinical assessment of swollen joints by physicians. However, clinical evaluation of joint swelling and pain in children has proven to be difficult and not entirely reliable, both in diagnosis and followup (2). The availability of new effective therapies for JIA has increased the need to look for valid and feasible imaging tools for monitoring changes in disease activity. Among the new imaging modalities, ultrasound (US) appears to be a very promising tool. In fact, US has extensively demonstrated higher sensitivity for detecting synovitis as compared to clinical examination (2–10). US is a noninvasive, nonionizing, and child-friendly technique that allows for dynamic evaluation of

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Significance & Innovations

- Despite the increasing use of ultrasound (US) for evaluating juvenile idiopathic arthritis (JIA) in the clinical setting, the real validity of US in the diagnosis and followup of JIA is not yet available.
- The definition of synovitis has shown heterogeneity across studies. A US definition of synovitis in pediatric patients is a crucial prerequisite for the development of a valid agreed-upon synovitis scoring method suitable for assessing synovitis in the followup of JIA.
- US has shown higher sensitivity than clinical examination in detecting synovitis. It could have important implications for patient classification in the JIA categories and, therefore, for the management of the disease. Lastly, regarding reliability and responsiveness to treatment, additional studies are required for demonstrating the utility of US as an outcome tool in JIA.

several joints. Moreover, as compared to magnetic resonance imaging (MRI), sedation is not required for scanning in younger children. US can evaluate synovitis at the anatomic and vascular levels. The gray-scale setting enables visualization of synovial hypertrophy (SH) and effusion, whereas the power Doppler (PD) settings allow for visualization of the movement of blood flow, therefore detecting changes in the microvascular blood flow in synovitis. PDUS allows the evaluation of synovial hyperemia and discrimination between active and inactive joint disease. However, the assessment of US findings in growing children is challenging, as physiologic findings may be misinterpreted as pathologic. The US anatomy of a joint in childhood changes during development of the skeleton, resulting in variations on the US image of a child's joint from anechoic, the unossified immature skeleton, to a hyperechoic structure. This is the reason for the lack of well-established US definitions of pathologic features in children with JIA to date. To use US as a valid modality for the assessment of synovitis, the Outcome Measures in Rheumatology (OMERACT) filter states that an outcome measure must be accurate, feasible, and discriminatory (11). The validity of a test is its ability to accurately reveal what it is supposed to. This is a critical issue because US is used by pediatric rheumatologists for the diagnosis of JIA. Despite the widespread use in pediatric patients, the true validity of this technique in the management of JIA is not known, especially with regard to its metric properties.

Therefore, the purpose of this article was to systematically assess the published literature for evidence of the validity of US in the assessment of synovitis in JIA.

MATERIALS AND METHODS

Study selection, data sources, and search strategy. Inclusion criteria were articles reporting any result for the detection and followup of synovitis by US in juvenile rheumatoid arthritis (RA). The article search was performed in the PubMed and Embase databases by a single investigator (MA). The following medical subject heading (MeSH) terms were used in PubMed: (Ultrasonography) AND (Synovitis OR Juvenile Rheumatoid Arthritis) AND (Diagnosis OR Follow-up OR Studies Medication Therapy Management OR Disease Management) with limits (language = English, humans only, children between 1 month and 18 years of age from January 1st 1966 to February 25th 2011). In Embase, the search was performed using the following keywords: (Juvenile Rheumatoid Arthritis) AND (Echography OR Doppler) AND (Arthritis OR Synovitis OR Bursitis) AND (Diagnosis OR Follow-up OR Studies Medication Therapy Management OR Disease Management) with limits (language = English, humans only, children between 1 month and 18 years of age from January 1st 1966 to February 25th 2011). For both searches, the keywords referred to MeSH terms or, if not available, to keywords present in the title/abstract. A manual search of references was also performed. Reviews, editorials, letters, and abstracts of scientific congresses were excluded. Studies on synovitis with a mixed patient population (i.e., adult and children) were not included. The selection process was initially based on the title and abstract of the article, and then on full texts. In the present review, we also decided to include in the search terms the old terminology of "juvenile rheumatoid arthritis" (for the American College of Rheumatology) and "juvenile chronic arthritis" (for the European League Against Rheumatism) in order to cover all subtypes of arthritis included under those previous terms.

The data from each selected study were extracted by 2 authors (SJ-J, PC) using a predetermined form that was designed for a previous musculoskeletal US review (12). The items selected were information on study design, the type and number of joints examined, the definition of US synovitis, if present, the global description of the US technique, the US mode used (i.e., gray scale alone, color or PD alone, or a combination of both), and the scoring systems used in the scanned joint: 1) binary (yes/no) for the presence of SH or effusion or PD alone, 2) semiquantitative, or 3) quantitative (millimeters for gray scale or colored pixel count in the region of interest [ROI]). Information about the construct and criterion validity, intraobserver and interobserver reliability, and discriminant validity of US was also recorded. For the purpose of this review, criterion validity was considered when US was compared with a gold standard (either direct macroscopic or microscopic visualization of the synovitis). Construct validity was considered when US was compared with other modalities known to measure synovitis (i.e., other imaging techniques, clinical examination, and laboratory tests). The reliability of US was also assessed. The intraobserver (within the operator) and interobserver (between operators) reliability were considered for image acquisition and reading. The discriminant validity of US (i.e., responsiveness) was considered when US was able to detect changes over time. Additionally, clinical data such as subtype of juvenile arthritis (i.e., monarthritis, oligoarthritis, polyarthritis, systemic, enthesitis-related arthritis, and psoriatic arthritis) were collected.

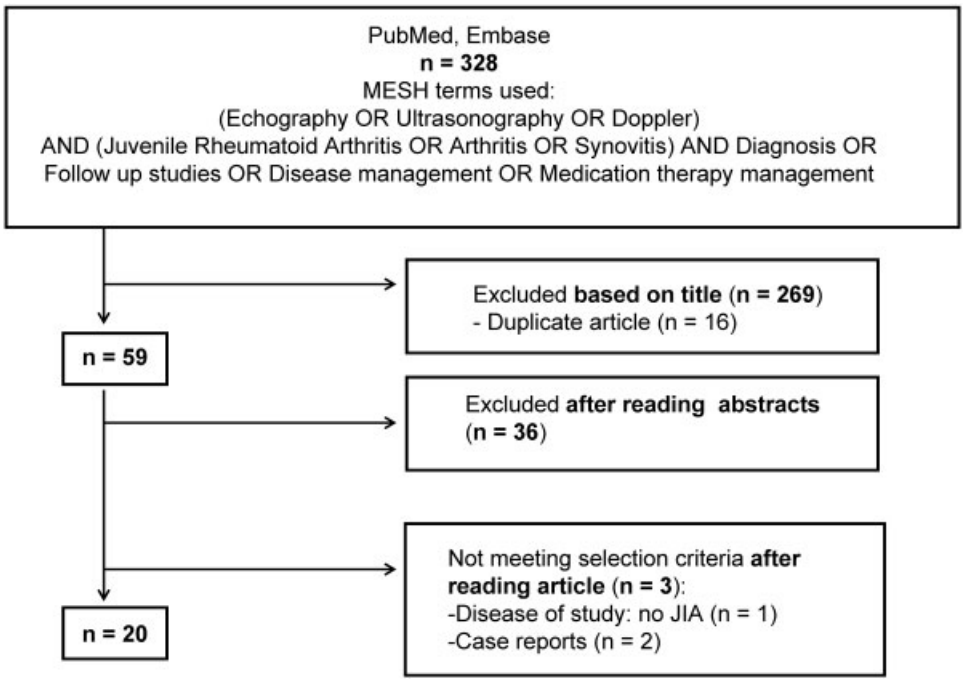


Figure 1. Flow chart of the systematic review process. MESH = medical subject headings; JIA = juvenile idiopathic arthritis.

The assessment of the evidence of US as an outcome tool in the literature was based on the independent evaluation of different aspects of the validity (i.e., criterion validity, construct validity, reliability, and discriminant validity). The methodology used in each included study was collected. The quality of the studies was assessed using a set of 6 predefined criteria specially developed for the objective of this review and evaluated in a binary mode (yes/no). These criteria were developed based on a similar quality assessment tool previously used (13). The predefined criteria were the following: 1) Was the recruitment of patients well defined in the methods section? 2) Was there a description of normal US anatomy of childhood joints? 3) Was there a description of the US scanning technique (settings used, type of machine, and protocol of scanning)? 4) Was there a description of the blinding attempted for observers? 5) Was there a description of US synovitis and the scoring system mentioned? and 6) Was the comparator adequately explained (baseline and/or followup) and the results presented in their entirety? Quality was reported on a scale of 0–6, with higher results indicating higher quality.

Statistical analysis. The various statistical tests used for evaluating the different types of validity in these studies were collected (i.e., Spearman's rank correlation, kappa statistic, *t*-test, chi-square test, and the Kruskal-Wallis test). Significant statistical value was considered according to the reference values included in each study. However, the analyzed studies were performed by using small sample sizes and open-label or observational studies, and the heterogeneity of the joint evaluated did not permit us to compare the results. Therefore, the data from the included studies were analyzed only descriptively. Categorical data were expressed as frequencies and continuous variables were given as the mean ± SD or median (range), depending on the distribution.

RESULTS

Figure 1 shows the flow chart of the systematic review process. Of 328 initially eligible studies, 23 articles were selected for analysis after reading the abstract (2–10,14–27). Three selected articles were not included: 2 because they were a series with a small number of cases (20,27), and the third one because the study population included adolescents and adults with a heterogeneous group of diseases different from JIA (26).

Characteristics of the studies. The characteristics of the studies are shown in Table 1. Most of the included studies featured a prospective cohort design. The sample size ranged between 10 and 53 patients (mean 32 patients). Oligoarthritis (arthritis involving ≤4 joints) was the subtype most commonly included in the studies (18 [90%] of 20). The knee was the most commonly examined joint (12 [60%] of 20), whereas the wrist and small joints of the hand (3 [15%] of 20) were the most uncommon joints investigated. Only 45% of studies (9 of 20) included a healthy control group; the sample size ranged between 5 and 30 controls (mean 14 controls). None of those studies provided a definition of the components of the joint scanned in the control group. Moreover, some authors proposed using the asymptomatic joint as a control to detect synovitis, bilaterally examining the joint and measuring the difference between the symptomatic and asymptomatic joint as the distance between the bone cor-

Table 1. Description of the 20 studies reporting ultrasound validity in the assessment of synovitis in juvenile arthritis*

Author, year (ref.)	Study design	No.	Arthritis subtype (no.)	Joint region assessed	Control, no.	Comparator	Sensitivity to change	Quality score (range 0–6)
Cellerini et al, 1999 (2)	L	49	O	Knee	No	CE	Yes	3
Doria et al, 2001 (4)	C-S	22	O (5), P (7), S (10)	Knee	5	Enhanced Doppler	No	5
Eich et al, 1994 (5)	L	10	O (8), P (1), S (1)	Knee, hip	No	MRI, CR	Yes	2
El-Miedany et al, 2001 (6)	C-S	38	O (27), P (8), S (2)	Knee	10	CE, ESR, CR, MRI	No	3
Fedrizzi et al, 1997 (7)	L	53	O (26), P (18), S (9)	Hip	10	CE, CR	No	2
Friedman and Gruber, 2002 (8)	C-S	24	O	Hip	24	CE	No	1
Frosch et al, 2003 (9)	L	28	O, P	Knee, hip	10	CE, ESR, CRP	Yes	2
Haslam et al, 2010 (10)	C-S	17	O	E, W, IP, MCP, knee, A, toes	No	CE	No	2
Kakati et al, 2007 (14)	L	30	O	Knee	No	CE	Yes	2
Karmazyn et al, 2007 (15)	C-S	20	O, P, S	MCP	12	CE	No	5
Laurell et al, 2011 (21)	L	30	O (19), P (11)	Ankle	No	CE	Yes	4
Magni-Manzoni et al, 2009 (16)	C-S	32	O (20), P (7), ERA (4)	E, W, IP, MCP, knee, A, toes	No	CE, ESR, CRP; PhGA VAS; PGA VAS; C-HAQ	No	4
Neidel et al, 2002 (17)	C-S	50	O (18), P (24), S (6)	Hip	No	CE, CR, MRI	Yes	2
Pascoli et al, 2010 (18)	C-S	42	O (17), P (21), S (1), ERA (1)	Ankle	No	CE	No	3
Rooney et al, 2009 (19)	PC	34	O (13), P (19), S (1), PsA (1)	Ankle	No	CE	No	3
Shahin et al, 2001 (22)	PC	30	O (5), P (13), S (12)	Knee	15	CE, ESR, CRP, CR	Yes	4
Shahin et al, 2002 (23)	PC	19	P (10), S (9)	Knee	No	IL, TNFα, CE, ESR, CRP, CR	No	2
Shanmugavel et al, 2008 (24)	PC	30	O	Knee	10	CE	Yes	2
Sureda et al, 1994 (3)	PC	36	O (27), P (7), S (2)	Knee	30	CE	Yes	3
Tynjäla et al, 2004 (25)	R	32	NS	Hip, A, tarsal	No	CE, CRP, MRI	No	2

* L = longitudinal; O = oligoarthritis; CE = clinical examination; C-S = cross-sectional; P = polyarticular; S = systemic; MRI = magnetic resonance imaging; CR = conventional radiography; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; E = elbow; W = wrist; IP = interphalangeal joint; MCP = metacarpophalangeal joint; A = ankle; ERA = enthesitis-related arthritis; PhGA = physician's assessment of global disease activity; VAS = visual analog scale; PGA = patient's or parent's global disease activity; C-HAQ = Childhood Health Assessment Questionnaire; PC = prospective cohort; PsA = psoriatic arthritis; IL = interleukin (IL-2, IL-6, IL-10); TNFα = tumor necrosis factor α; R = retrospective; NS = not specified.

tex and the capsule of the studied joint by using electronic calipers. Following this assumption, some studies established the reference value of mean ± SD 0.5 ± 0.05 cm for the anterior capsule distance of the asymptomatic hip joint in order to suggest the presence of synovitis (7,8).

The definition of US synovitis was documented in 13 (65%) of the selected studies. Almost all of the studies included clinical examination as a comparator for assessing construct validity, and 6 studies included laboratory markers as well. MRI was used as a comparator in 25% of the studies (4 of 20) and radiograph in 30% of the studies (6 of 20). Three studies reported the US reliability in detecting synovitis. Eight studies reported US as an assessment tool for monitoring arthritis in children.

US synovitis definition and synovitis scoring. Table 2 shows the definition of synovitis, the US component evaluated in the scoring system, and synovitis scoring. The US definition of synovitis, including SH, effusion, and Doppler signal, was provided in more than half of the studies (Figure 1), but it was not specified in 5 studies (8,15,22–24). Five studies stated that they followed OMERACT definitions (28). The US appearance of SH was mainly described as hypoechoic areas or as thickening of the synovial membrane with poorly defined contours at the

Table 2. Description of the studies reporting the definition of US synovitis, the US components evaluated, and synovitis scoring systems*

Author, year (ref.)	Synovitis definition	Gray-scale SH	Gray-scale effusion	Doppler signal	Scoring system	Scoring system: binary	Scoring system: semiquantitative	Scoring system: quantitative
Cellerini et al, 1999 (2)	Yes	Yes	Yes	No	Yes	No	No	Yes
Doria et al, 2001 (4)	Yes	Yes	Yes	Yes†	Yes	No	No	Yes‡
Eich et al, 1994 (5)	Yes	Yes	Yes	No	No	No	No	No
El-Miedany et al, 2001 (6)	Yes	Yes	Yes	No	Yes	No	No	Yes
Fedrizzi et al, 1997 (7)	Yes	No	No	No	Yes	No	No	Yes
Friedman and Gruber, 2002 (8)	No	No	Yes	No	Yes	No	No	Yes
Frosch et al, 2003 (9)	Yes	Yes	Yes	No	Yes	No	No	Yes
Haslam et al, 2010 (10)	Yes§	Yes	Yes	No	Yes	No	Yes	No
Kakati et al, 2007 (14)	Yes	Yes	Yes	No	Yes	No	No	Yes
Karmazyn et al, 2007 (15)	No	No	No	Yes¶	Yes	No	Yes¶	No
Laurell et al, 2011 (21)	Yes§	Yes	Yes	Yes¶	Yes	No	Yes¶	No
Magni-Manzoni et al, 2009 (16)	Yes§	Yes	Yes	Yes¶	Yes	No	Yes¶	No
Neidel et al, 2002 (17)	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Pascoli et al, 2010 (18)	Yes§	Yes	Yes	No	Yes	No	Yes	No
Rooney et al, 2009 (19)	Yes§	NS	NS	No	No	No	No	No
Shahin et al, 2001 (22)	No	Yes	Yes	Yes‡	Yes	No	No	Yes‡
Shahin et al, 2002 (23)	No	Yes	Yes	Yes‡	Yes	No	No	Yes‡
Shanmugavel et al, 2008 (24)	No	Yes	Yes	Yes#	Yes	No	No	Yes#
Sureda et al, 1994 (3)	Yes	Yes	Yes	No	Yes	No	No	Yes
Tynjäla et al, 2004 (25)	Yes	Yes	Yes	No	Yes	No	No	Yes

* US = ultrasound; SH = synovial hypertrophy; NS = not specified (or unclear).
† Unenhanced Doppler and enhanced Doppler.
‡ Resistive index.
§ Synovitis definition according to the Outcome Measures in Rheumatology 7 consensus statement.
¶ Pannus vascularity evaluated on a 4-point semiquantitative scale.
# Measurement of pixel area or colored pixel count in the region of interest.

level of the suprapatellar bursa. Effusion was described as intraarticular anechoic fluid. Doppler signal was described in 7 studies, 5 studies using PD (16,21–24) and 2 studies using color Doppler (4,15). Doppler signal, when defined, was generally considered with the presence of 1 or more vessel signals in the intraarticular area. Contrast-enhanced color Doppler US was used in 1 study (4) (Figure 2).

The scoring systems used demonstrated great variability, being dichotomous, ordinal, or continuous. Five studies that reported the grade of synovitis on gray-scale US images used similar semiquantitative scores (4-point grade: 0 = absent, 1 = mild, 2 = medium, and 3 = severe). Seven studies on the knee joint used a quantitative scoring system on gray-scale US that included the synovial thick-

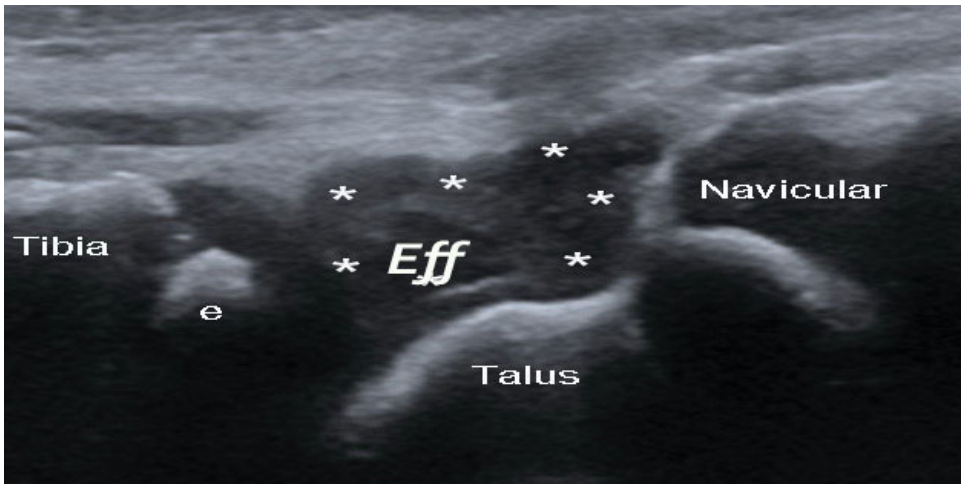


Figure 2. Ultrasound image of the ankle joint (anterior recess, longitudinal dorsal scan) showing the ultrasound components of synovitis. e = epiphysis; * = synovial hypertrophy; Eff = effusion.

Table 3. Results of construct validity and reliability of synovitis detection by US*

Author, year (ref.)	N	NJCE	NJUS	Construct validity	Statistic	Results†	Reliability
Cellerini et al, 1999 (2)	49	148	148	Yes	Spearman's coefficient	Significant correlation between CE and US (r = 0.45, $P <$ 0.01)	No
Doria et al, 2001 (4)	22	31	31	No	Kruskal-Wallis test	Contrast-enhanced Doppler distinguishes between active and inactive groups	No
Eich et al, 1994 (5)	10	15	15	Yes	Descriptive	US was as sensitive as MRI in demonstrating SH and effusion	No
El-Miedany et al, 2001 (6)	38	NS	NS	Yes	Descriptive	MRI was more sensitive in distinguishing between SH/effusion	No
Fedrizzi et al, 1997 (7)	53	33	44	Yes	Kruskal-Wallis test	US was more sensitive than CR in detecting synovitis	No
Friedman and Gruber, 2002 (8)	24	48	48	Yes	*t*-test	Positive correlation between CE and US	No
Frosch et al, 2003 (9)	28	159	145	Yes	Kruskal-Wallis	Strong correlations between CE and effusion (but not with SH) in the knee joint No correlations in the hip joint	No
Haslam et al, 2010 (10)	17	680	680	Yes	Sensitivity, specificity	CE was most accurate for detection of synovitis when compared with US Sensitivity from 0.5–1 Specificity from 0.9–1	No
Kakati et al, 2007 (14)	30	46	46	Yes	Spearman's coefficient	Correlation between US and CE (r = 0.62, $P < 0.01$)	Yes
Karmazyn et al, 2007 (15)	20	200	200	Yes	Chi-square test Kappa	US abnormalities and CE scores were significantly associated ($P < 0.01$) Interobserver agreement between US and CE was poor (κ = 0.1) and between US and CR was fair (κ = 0.4)	No
Laurell et al, 2011 (21)	30	40	40	No	Descriptive *t*-test	This is a descriptive interventional study and was not designed to compare results from CE and US assessments	No
Magni-Manzoni et al, 2009 (16)	32	52	52	Yes	Spearman's coefficient Kappa	Moderate to poor correlations between US parameters and CE (r = 0.66, r = 0.3, and r = 0.31) Interobserver agreement between US and CE was moderate (κ = 0.4 for SJC and SH/effusion) and fair (κ = 0.3 for SJC and PD signal)	Yes
Neidel et al, 2002 (17)	50	67		No	Descriptive	Associations were not studied	No
Pascoli et al, 2010 (18)	42	61	61	Yes	Kappa	Poor agreement between CE and US (κ = 0.2–0.3)	Yes
Rooney et al, 2009 (19)	34	0	49	Yes	Descriptive	Possible associations were not studied	No
Shahin et al, 2001 (22)	30	NS	NS	Yes	Spearman's coefficient	Significant correlations between effusion and SJC, between loculation of effusion and knee score (r = +0.3, $P < 0.05$), and between the degree of vascularity by PD and the knee score by CE (r = +0.5, $P < 0.05$)	No
Shahin et al, 2002 (23)	19	NS	NS	Yes	Spearman's coefficient	Significant correlations between serum levels of IL-6 and the degree of PD (r = +0.6, $P < 0.01$) and between serum levels of IL-2 receptor and SH in JIA (r = +0.6, $P < 0.01$)	No
Shanmugavel et al, 2008 (24)	30	60	60	Yes	Pearson's correlation	Statistically significant positive correlations between CE and PD (r = 0.65 at baseline, r = 0.36 at the end of 6 months)	No
Sureda et al, 1994 (3)	36	72	72	Yes	ANOVA	Significant differences between control subjects and JIA groups (active and inactive) for both effusion and SH ($P < 0.001$)	No
Tynjälä et al, 2004 (25)	32	42	42	No	ANOVA	Possible associations were not studied	No

* The statistic used to study possible associations between ultrasound (US) findings and comparator is shown. NJCE = number of joints clinically evaluated according to protocol; NJUS = number of joints assessed by US according to protocol; CE = clinical examination; r = Spearman's correlation coefficient; MRI = magnetic resonance imaging; SH = synovial hypertrophy; NS = not specified (or unclear); CR = conventional radiography; SJC = swollen joint count; PD = power Doppler; IL-6 = interleukin-6; JIA = juvenile idiopathic arthritis; ANOVA = analysis of variance.
† Results show the statistical value when it was documented in the article.

ness for scoring synovitis (i.e., the largest anteroposterior diameter of SH at the suprapatellar recess measured in millimeters) (2–4,6,8,9,14). One of those 7 studies included a semiquantitative scale based on a quantitative

Table 4. Results of discriminant validity (responsiveness) of US for detection of synovitis changes*

Author, year (ref.)	No.†	Joint assessed	Time‡	Treatment evaluated (no. of patients that received treatment)	Results of treatment
Cellerini et al, 1999 (2)	13	Knee	1–15 months	IA CS (7), NCI (2)	Improvement: CE (9/13 patients), US findings (9/13 patients)
Eich et al, 1994 (5)	10	Knee, hip	1–30 days	IA CS (10)	Improvement: pain (10/10 patients), effusion and/or SH (8/10 patients)
Fedrizzi et al, 1997 (7)	9	Hip	28 months	NCI	US abnormalities: increased (3/9 patients), unchanged (4/9 patients), normal (2/9 patients)
Frosch et al, 2003 (9)	28	28	3 months	NCI	US examination showed arthritic changes (50% of hips, 81% of knees) in the absence of clinically active arthritis
Kakati et al, 2007 (14)	30	Knee	6 months	Naproxen (30)	US abnormalities: increased (1/46 joints), no change (28/46 joints), improved (22/46 joints)
Laurell et al, 2011 (21)	30	Ankle	4 weeks	IA CS	Talocrural joint SH: normalized in 55% (17/31 joints), regressed in 32% (10/31 joints) Quantitative evaluation of MST of the talocrural joint showed a statistically significant decrease ($P < 0.001$; other data not shown)
Shahin et al, 2001 (22)	14	Knee	1 week	IM CS (5), IA CS (3), NCI (6)	Improvement in CE was associated with US findings: decreased SH and effusion in 93% of knees and decreased PD signal in 78% of knees Difference in knee score of all followups correlated significantly with the difference in US findings: SH and PD signal ($r = +0.8$, $P < 0.05$)
Shanmugavel et al, 2008 (24)	30	Knee	6 months	Naproxen (30)	Statistically significant positive correlations between total clinical score and PD score in the knee joint ($r = 0.65$ at baseline, $r = 0.36$ at the end of 6 months)
Sureda et al, 1994 (3)	18	Knee	1 year	NCI	Clinical improvement was associated with disappearance of effusion (50% of knees) and decrease of SH (37% of knees)

* US = ultrasound; IA = intraarticular; CS = corticosteroid; NCI = no CS injection (treatment according to routine care); CE = clinical examination; SH = synovial hypertrophy; MST = mean synovial thickness; IM = intramuscular; PD = power Doppler; r = Spearman's correlation coefficient.
† Number of patients included in the followup.
‡ Range of time in the followup study.

assessment of SH (mild = <5 mm, medium = 5–10 mm, and severe = >10 mm) (2). In PD mode, quantitative scoring was used in 4 studies that included the pixel count in the ROI and/or resistive index (4,22–24). Three studies that assessed the grade of synovial hyperemia used different 4-point semiquantitative scores (15,16,21).

Technical aspects of US machines and image acquisition. Several different machine brands were used. Machine settings were described in 6 articles (4,15,18,22–24). Some description of transducer and joint position for examination was provided in most of the studies (18 [90%] of 20). However, information about the probe position and image acquisition was less well described. Frequency of the linear transducer used was variable (from 5–15 MHz).

US validity in the assessment of synovitis. Tables 3 and 4 show the metric properties of the articles according to the OMERACT filter, including statistics and results.

Criterion validity. None of the articles evaluated the criterion validity.

Construct validity. Construct validity was the most common aspect of US validity reported, which included clinical examination and laboratory markers as comparators in 12 and 6 studies, respectively. Overall, US showed higher sensitivity for detecting synovitis as compared to clinical examination (Table 3). However, when US was taken as the standard against which clinical examination was compared, the sensitivity of clinical examination in some joints (i.e., the ankle, wrist, and midfoot) was higher than US examination (10). In the latter, however, the authors recognized that there were limitations in the interpretation of results. Contrast-enhanced color Doppler US was proposed for comparing active and inactive arthritis in 1 study that demonstrated improvement in the detection of subclinical inflammation, although this was examined exclusively at the knee joint (4). Only 4 studies compared US-detected synovitis and MRI. One study showed US to be as sensitive as MRI in detecting synovitis (5). In another study, MRI examination following gadolinium was superior to US (6) and comparison information was not clear in the remaining evaluated studies (17,25).

Reliability. Reliability was reported in 3 studies; 2 of the studies reported involved the interobserver reliability of reading static recorded images (14,16). One study reported the interobserver reliability of the image acquisition (18). Overall, the interobserver US reliability analysis showed there was good agreement between the 2 sonographers ($\kappa = >0.8$).

Discriminant validity of US. Nine studies examined the ability of US to detect changes over time (Table 4). The description of the results of these studies, the number of patients followed up, the joint region assessed by US, and the followup time and treatment were provided in variable detail. Information about US changes after therapy was mostly descriptive. Nevertheless, there were 2 studies documenting US changes more objectively. One study has demonstrated significant positive correlations between effusion and the swollen joint count and the clinical knee score when the differences in these variables from baseline to followup visit were analyzed (22). The second study reported quantitative evaluation of the synovial thickness of the ankle joint in patients with JIA, which was evaluated before and 4 weeks after steroid injection, showing a statistically significant decrease (21). Overall, the patients showed improvement in both clinical and US findings after therapy. Intraarticular corticosteroid injection was the treatment most often documented.

Quality of publications. The recruitment of patients was well defined in the methods section of 12 studies. None of the studies provided a description of normal anatomy scanned in the control group. A detailed description of the US scanning technique was not common in the articles selected. Sonographers were blinded to the results of clinical examination in only 4 studies. The definition of the imaging appearance of synovitis was provided in more than half of the studies. More than half of the selected studies reached a quality score of 2 or 3.

DISCUSSION

Despite the increasing application of pediatric US in routine care, the present systematic review has demonstrated that there is a lack of data for evaluating US as a validated tool for the assessment of synovitis in JIA, particularly in reliability and discriminant validity.

It has already been recognized in the literature that the oligoarthritis subtype is the most common childhood arthritis and the knee joint is commonly involved (29). The present review has highlighted the heterogeneity of the definition of synovitis and the synovitis scoring methods used for children. Unlike in adults, US definitions of the components of synovitis have not yet been proposed in children. The OMERACT definitions for RA have been included in recent studies of childhood arthritis (10,16,18,19). However, their applicability to pediatric patients may require consideration. Due to the paucity of literature on US anatomy in healthy children, it does not surprise us that there were few studies comparing healthy and pathologic joints (30,31). However, a clear understanding of normal US anatomy of joints is needed in order to interpret US findings in JIA (Figure 2).

The scoring systems utilized were not always detailed, although quantitative methods on gray-scale images seem to be more homogeneous. In this point, the potential variability of the position of the probe during scanning may make it difficult to compare results between studies. Hardly any data exist on the evaluation of synovial hyperemia by Doppler US in JIA. Different systems for assessing Doppler flow were also documented, but the semiquantitative method is more frequently employed in clinical practice. Despite the observed heterogeneity of data and the low number of studies, the superiority of US over clinical examination in the detection of synovitis appears in all analyzed studies and therefore can also be assumed in the pediatric evaluation. However, the scarcity of reliability studies is a problem for completely assuming the added value of US over clinical examination. Although only a few studies included the US monitoring of patients with JIA as the main objective of the study, the analyzed data suggest that US can be a useful tool for the assessment and the monitoring of joint involvement in JIA.

However, the quality assessment showed that most of the articles did not reach a sufficient score. In general, the number of articles on metric properties of US in adult RA is higher than in JIA. In addition, most of the articles on pediatric patients were descriptive. These facts can explain the lower quality of articles on pediatric patients when compared with those performed in adults.

We believe that a number of important questions should be answered in future works in order to reduce variation in the results. In particular, it is important to clearly define normal US anatomy of the childhood joint according to age. In addition, the normal location of the growing skeleton's supply vessels should be considered when studies using the Doppler technique are performed. Second, a US definition of synovitis in childhood should be proposed in order to obtain an agreed-upon synovitis scoring method that is suitable for assessing synovitis in the followup of children. This could be relevant for aiding in clinical decision making, as detection of US synovitis with Doppler reflects ongoing active disease. At the same time, it is necessary to reach a consensus on a standardized way of measuring synovitis, as well as standardization of the scanning technique for each joint in the pediatric population. In conclusion, this review showed the utility of US for detecting synovitis in JIA and its superiority to clinical examination. However, additional studies are required in order to demonstrate US reliability and responsiveness in JIA and to validate this imaging technique as an outcome tool in JIA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. D'Agostino had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Collado, Naredo, D'Agostino.
Acquisition of data. Collado, Jousse-Joulin, Alcalde.
Analysis and interpretation of data. Collado, Naredo, D'Agostino.

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