Flares of Disease in Children with Clinically Inactive Juvenile Idiopathic Arthritis Were Not Correlated with Ultrasound Findings

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ABSTRACT. ***Objective.*** The validity of our current definitions for clinically inactive disease (CID) in juvenile idiopathic arthritis (JIA) based on physical examination is challenged by the development of advanced musculoskeletal imaging tools. We aimed to prospectively determine the prevalence of abnormal ultrasound (US) findings in children with CID in JIA and their clinical significance.

Methods. Children aged ≥ 4 years with CID and a history of arthritis from a single tertiary center were approached over 1 year. Standard US of knees, tibiotalar joints, subtalar joints, and wrists were performed at baseline and at a followup visit. US images were scored by 2 pediatric musculoskeletal radiologists.

Results. Forty children with CID were enrolled and followed clinically. The median duration of inactive disease was 1 year. The most common International League of Associations for Rheumatology JIA categories were extended oligoarticular JIA (30%) and rheumatoid factor–negative polyarthritis (38%). At baseline, among a total of 289 joints scanned, 24 joints (8%) had at least 1 abnormal finding in 18 (45%) of 40 subjects. When evaluated at the individual joint level against flares identified during followup exams, these baseline US findings had a sensitivity of 15% and a positive predictive value of 12%. The predictive performance of the second US was even less.

Conclusion. Our study demonstrates that nearly half of children with CID had abnormal US findings in 1 of 8 commonly affected joints. These findings did not correlate with subsequent clinical flares in up to 2 years of followup. (J Rheumatol First Release April 1 2018; doi:10.3899/jrheum.170681)

Key Indexing Terms:
MUSCULOSKELETAL ULTRASOUND
CLINICALLY INACTIVE DISEASE
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Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic illness and the most common cause of acquired childhood disability. Current treatments have improved overall outcomes in children with JIA. Many children are able to achieve clinically inactive disease (CID), defined as the following: no joints with active arthritis; no fever, rash, serositis, active uveitis, splenomegaly, or generalized lymphadenopathy attributable to JIA; normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); physician's global assessment (PGA) of disease activity of the best score possible as defined by Wallace, *et al*[1], and the revised definition including < 15 min of morning stiffness and a PGA of 0[2]. However, when children with CID were evaluated with magnetic resonance imaging (MRI), 45% were found to have subclinical arthritis[3]. This finding questions the validity of our current definitions for CID and remission. Do children with JIA in these clinical disease states truly have no active arthritis? It is well established that compared to clinical examinations, imaging modalities such as MRI and ultrasound (US) have greater sensitivity to detect active arthritis in children with JIA[3,4]. However, the longterm

significance of these findings in the absence of clinical symptoms and a normal joint examination are not known.

US has emerged as a sensitive, reliable, and child-friendly bedside imaging examination to assist rheumatologists in assessing inflammation of joints and tendons, as well as guiding therapeutic intraarticular and tendon sheath injections[4,5,6,7,8]. Collado, *et al* systematically reviewed published US studies in children with JIA and concluded that US is a valuable tool for detecting synovitis in JIA with excellent construct validity and higher sensitivity to detect synovitis, when compared to clinical examination alone[9].

Three previous cross-sectional studies demonstrated detection of synovitis by US in asymptomatic joints of children[7,8,10]. However, none of these studies offered longitudinal followup of clinical status or US findings to determine the significance of the sonographic abnormalities identified initially. We aimed to prospectively determine not only the prevalence of abnormal US findings in JIA children with CID but also to determine their clinical significance regarding the physical examination and later flares of arthritis. Do abnormal US findings in children with CID predict a clinical flare of disease?

While our study was in progress, Magni-Manzoni, *et al*[11] reported the prevalence of abnormal US findings in children with CID of ≥ 3 months with 2 years of clinical followup. Among the 39 patients enrolled, 87% had ≥ 1 abnormal US finding including synovial hyperplasia, joint effusion, power Doppler (PD) signal abnormality, and tenosynovitis. Abnormal US findings were present in 7% of all joints scanned. During the 2-year followup period, 24 patients (61.5%) had sustained inactive disease, whereas 15 patients (38.5%) experienced a clinical flare of synovitis. However, only 40% of the flared joints during followup had US abnormalities at baseline, suggesting a low predictive value of future arthritis flare. Further, this study identified abnormal US findings in 36% of healthy children.

MATERIALS AND METHODS

Reported here is a 2-year prospective observational study with US evaluation of the wrists, knees, ankles, and subtalar joints at study entry and at a subsequent visit in children with JIA and CID. Associated clinical data including laboratory results and disease activity measures were collected for 24 months following the baseline visit. This research project was approved by the Institutional Review Board at Seattle Children's Hospital (approval #14089). Written consent was obtained for participation and publication of data.

Patient characteristics. Children with clinically inactive JIA between August 2012 and August 2013 were enrolled at the Division of Rheumatology Clinic at Seattle Children's Hospital. Patients included in our study met the following criteria: (1) International League of Associations for Rheumatology (ILAR) JIA categories of persistent oligoarthritis, extended oligoarthritis, enthesitis-related arthritis, or polyarticular [rheumatoid factor (RF)+ and RF–] JIA; (2) clinically inactive disease (defined as no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, normal ESR or CRP, PGA disease activity of 0, and < 15 min of morning stiffness)[2]; (3) previously active arthritis (defined as a joint with swelling not as a result of bony enlargement or, if no swelling is present, limitation of motion accompanied by either pain on motion and/or tenderness by the American College of Rheumatology guidelines) in 1 of the targeted joints (wrist, tibiotalar joint, subtalar joint, or knee); and (4) age ≥ 4 years, to increase probability of patient compliance with the US examination.

Clinical measurements. At each visit, the following were recorded: rheumatologic joint examination for 72 joints by the treating physician prior to US examination, PGA (scale 0–10), and laboratory tests including ESR when available. Baseline laboratory test results including antinuclear antibody (ANA), RF, anticyclic citrullinated peptide, and HLA-B27 were also recorded, as well as Childhood Health Assessment Questionnaire (CHAQ)[12], patient/parent-reported global assessment of overall health (between 0 and 10), and assessment of arthritis activity. The US result was not shared with the treating physician.

Followup visits were made based on clinical needs every 3–6 months for patients with polyarticular course or who were receiving systemic medications and every 3–12 months for patients with persistent oligoarticular course based on clinical needs. JIA flare for purposes of our study was defined as the return of clinical synovitis in any joint as per the American College of Rheumatology definition of synovitis. Treatment was not prescribed through the study and was managed per primary rheumatologist, separate from study inclusion.

US imaging acquisition. Standard longitudinal views of the knees were collected at baseline and during a followup visit within 3 to 16 months: longitudinal suprapatellar flexed 20–30°, tibiotalar joints (anterior longitudinal) in plantar flexing position, subtalar joints (lateral longitudinal) in neutral position, and wrists (dorsal longitudinal) in neutral position without compression. The views were taken by 1 pediatric rheumatologist (NER) with Ultrasound School of North American Rheumatologists (USSONAR) certification and 2 years of experience. USSONAR is a society of rheumatologists and other health professionals in North America that promotes the use of musculoskeletal US in patients with rheumatic diseases and trains rheumatologists to be proficient in obtaining standard US images of joints. A USSONAR reference guide was used to ensure the accurate collection of standardized images for all joints (except subtalar joint[13]). Also, published guidelines provided by Outcome Measures in Rheumatology[14,15] have been followed. On average, it took 20–30 min to acquire images for each subject. Only 1 view of the joint was collected, which was the standard for publication at the time of our study. Dynamic assessment and image collection from perpendicular planes were not done. Matching joint examinations were performed on the same day before US images were obtained. The Sonosite M-Turbo US machine (FUJIFILM Sonosite Inc.) with a linear array 13–6 MHz probe was used for image acquisition. PD signal was adjusted to enhance Doppler sensitivity by setting the pulse repetition frequency to 0.6 KHz (wall filter function was not available) and adjusting the gain to a level just below random noise. Room temperature was consistent at 70°F for all patients, because temperature may affect PD findings. The sonographer was blinded to clinical status, laboratory results, and prior treatment. The US findings were not revealed to patient participants nor to the treating physicians. Real-time interpretation of these images was not performed.

US reading. A small set of US images from previous patients was reviewed by 2 radiologists (RSI and MT) and a rheumatologist (NER) for calibration purpose prior to independent reading. When bone and tendon landmarks were not well visualized, images were excluded. US images were scored independently by 2 pediatric musculoskeletal radiologists (RSI and MT). Joint effusion was defined as anechoic material within the joint space or within the suprapatellar bursa (knee) that displaced a fat pad in the radiocarpal (wrist) joint, tibiotalar joint, and subtalar joint, as shown in Figure 1. Caution was taken to distinguish effusion from cartilage that shared same echogenicity but with a smooth contour and without an interface sign (a hyperechoic interface created between joint fluid and the hyaline cartilage)[16]. In young children, as reported by Roth, *et al*[17], cartilage surface can be detected as a hyperechoic line next to the soft tissue in a normal joint. Presence or absence of joint effusion was recorded. Synovial thickening was

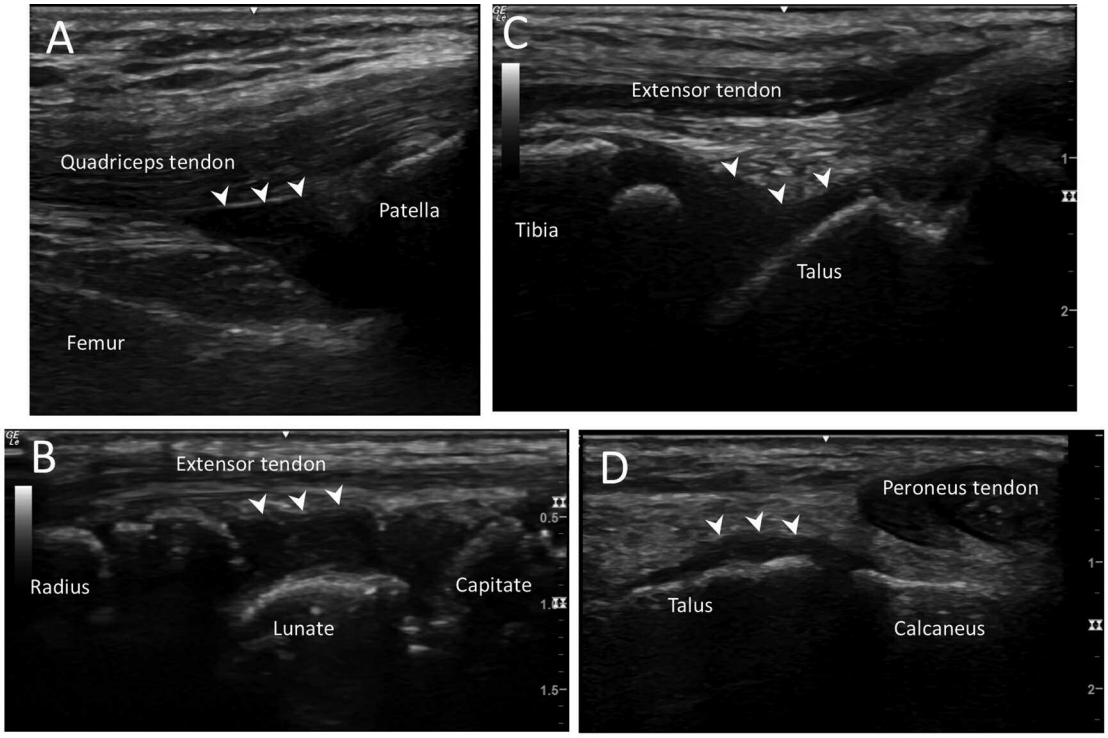

Figure 1. Representative ultrasound images illustrating joint effusion in (A) knee, (B) wrist, (C) tibiotalar, and (D) subtalar joints. Arrowheads indicate joint effusion.

defined as hypoechoic material within the joint space. Illustrations of the synovial thickening are shown in Supplementary Figure 1 (available with the online version of this article). Hyperemia was defined as blood flow within the joint capsule as indicated by PD signal[17]. Tenosynovitis was defined as anechoic or hypoechoic tissue within the tendon sheath and circumscribing the tendon. However, evaluation of tendons was limited because of the absence of transverse views in all joints. Doppler signal and tenosynovitis were reported as presence or absence. Though a grading system was reported by Bartoli, *et al*[18], because of our small sample size, we expected decreased statistical power by further grading and thus decided to record only in a binary approach. Independent reading was used to determine interreader variability. Images with poor quality, as judged by the interpreting radiologists, were discarded. After independent reading, a consensus reading was convened, and final results were used for further analysis.

Statistics. Data were entered into the Research Electronic Data Capture (REDCap) database[19]. Patient characteristics were summarized using descriptive statistics. Categorical data were expressed using frequencies. Continuous data were expressed as median with interquartile range. To evaluate interreader agreement, Cohen κ, the most commonly used interrater metric, was calculated for each sonographic finding (synovial thickening, joint effusion, PD). Overall percent agreement was also calculated, but it is less informative because the vast majority of joints had no abnormal findings.

To evaluate US utility in predicting flares among the study population, all flare reports from all followup visits were tallied and tabulated versus US findings at the individual joint level. Sensitivity, positive predictive value (PPV), and OR were calculated for each joint type (knee/wrist/tibiotalar/subtalar), as well as for the entire set of joints as a whole. As a sensitivity analysis, these calculations were repeated while ignoring abnormal PD findings. All analyses were performed in R versions 3.3 and 3.4 (R Foundation for Statistical Computing).

RESULTS

Baseline demographic characteristics. There were 183 children with JIA who were screened. Forty-six patients were enrolled in the study and had clinical and US evaluations at baseline. Five patients were found to have > 15 min of morning stiffness and were excluded from study analysis. One patient did not have a clinical followup visit and was excluded. Baseline data of 40 patients meeting CID criteria with PGA of 0 are summarized in Table 1. The median age at enrollment was 10.7 years and the median duration of disease was 5.5 years. The median duration of inactive disease was 1 year. Eighty-two percent of subjects were girls. Patients had clinical followup at a median of 22 months.

The most common ILAR JIA categories were extended oligoarticular JIA (n = 12, 30%) and RF– polyarthritis (n = 15, 38%). Almost half of the patients were ANA-positive. The median CHAQ score was 0 and the parent global assessment of overall health was 0, with parental report of arthritis activity of 0. The majority of patients (78%) were treated with disease-modifying antirheumatic drugs (DMARD) and/or biologics at the time of enrollment, indicating moderate to severe disease burden in this patient cohort.

Baseline US findings. At baseline US evaluation (289 joints scanned), 24 joints (8%) had ≥ 1 abnormal finding in 18 (45%) of 40 subjects (Table 2). Among the joints scanned, the subtalar joints had the highest rate of abnormal

Table 1. Baseline characteristics (n = 40). Values are median (IQR) or n (%).

Characteristics	Values
Age at enrollment, yrs	10.7 (8.9–12.5)
Disease duration at enrollment, yrs	5.5 (2.4–8.4)
Duration of inactive disease, yrs	1 (0.5–1.8)
Duration between last joint injection and enrollment (n = 32), yrs	2.3 (1.5–5.9)
Duration between last flare and enrollment, yrs	1.3 (0.2–5.5)
Female	33 (82)
Race	
White	33 (83)
African American	1 (3)
Asian	1 (3)
Native American	1 (3)
Pacific Islander	0 (0)
Other	4 (10)
ILAR category	
Persistent oligoarticular	10 (25)
Extended oligoarticular	12 (30)
RF– polyarthritis	15 (38)
RF+ polyarthritis	1 (3)
Enthesitis-related arthritis	2 (5)
Laboratory findings	
ANA+	19 (48)
RF+	1 (3)
CCP+	2 (5)
HLA-B27+	5 (13)
Erythrocyte sedimentation rate (n = 7; normal 0–20), mm/h	6 (4–18)
Parent/patient measures	
Parent's global assessment of overall health, range 0–10	0 (0–1)
Parent's assessment of arthritis activity, range 0–10	1 (0–1)
CHAQ	0 (0–0)
PGA	0 (0–0)
Treatment at study entry	
No therapy	5 (13)
NSAID only	4 (10)
DMARD only	15 (38)
Biologic only	6 (15)
DMARD and biologic	10 (25)

IQR: interquartile range; ILAR: International League of Associations for Rheumatology; ANA: antinuclear antibody; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; CHAQ: Childhood Health Assessment Questionnaire; PGA: physician's global assessment; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug.

sonographic findings (25%), while other joints had 6–15% abnormal findings, based on the radiologists' consensus interpretation. PD signals were the most common abnormal imaging findings (7.2% of all scanned joints), followed by effusion (3.1%) and synovial thickening (2.4%). No tenosynovitis was identified in any of these patients at baseline. After removing PD data, there were 14 abnormal findings from 9 patients (23%) at baseline. Detailed US findings from each subject are reported in Supplementary Table 1 (available with the online version of this article). Representative US images of joint effusion in each targeted joint and other changes are shown in Figure 1 and Figure 2.

Correlation between US findings during CID and future clinical flares. Eighteen patients (45%) had JIA flares during followup, within 3–24 months of baseline visit (median 12, IQR 6-17). Among these patients, the following joints were flared: 20 knee joints, 2 wrist joints, 4 tibiotalar joints, and 1 subtalar joint. Among those flared joints, baseline US identified abnormal signals only in 2 knees, 1 tibiotalar joint, and 1 subtalar joint, for a combined sensitivity of 15%. Further, baseline US found 29 false-positive signals in joints that never flared during followup, yielding a PPV of 12%. Excluding Doppler signals, PPV somewhat improves to 27%, but sensitivity is only 11% (Table 3). OR of JIA flares between patients with abnormal and normal US findings were not significant in all joints. Detailed information of joint flare is included in Supplementary Table 2 (available with the online version of this article).

Of the 33 patients who had a second US while still in CID, 13 subsequently had flares within 3–19 months (median 10, IQR 6-13). Subsequent US predictive performance was even worse than baseline US: 11% sensitivity (2/19) with or without Doppler signals, and 6% PPV (7% without Doppler signals).

Interreader variability of US scoring. Independent interpretations of US images by 2 musculoskeletal radiologists were compared for agreement analysis. For this analysis, 73 sets of images from baseline and followup visits (8 joints in each set) were pooled. The agreement of the readings was excellent for effusion (99% agreement, Cohen κ 0.84, 95% CI 0.72–0.96), and was poor for PD (92% agreement, Cohen κ 0.33, 95% CI 0.10–0.55) and synovial thickening (96% agreement, Cohen κ 0.29, 95% CI 0.08–0.50; Table 4).

Table 2. Abnormal US findings at baseline visits in patients with CID (n = 40). Some images with unsatisfactory quality were excluded from the final reading. Values are number of abnormal joints/total studied joints.

Joints	Synovial Thickening	Joint Effusion	PD Signal	Tenosynovitis
Wrists	1/80	0/80	11/78	0/80
Knees	0/80	4/80	1/76	0/80
Tibiotalar	0/73	0/73	5/68	0/73
Subtalar	6/56	5/56	3/54	0/56

US: ultrasound; CID: clinically inactive disease; PD: power Doppler.

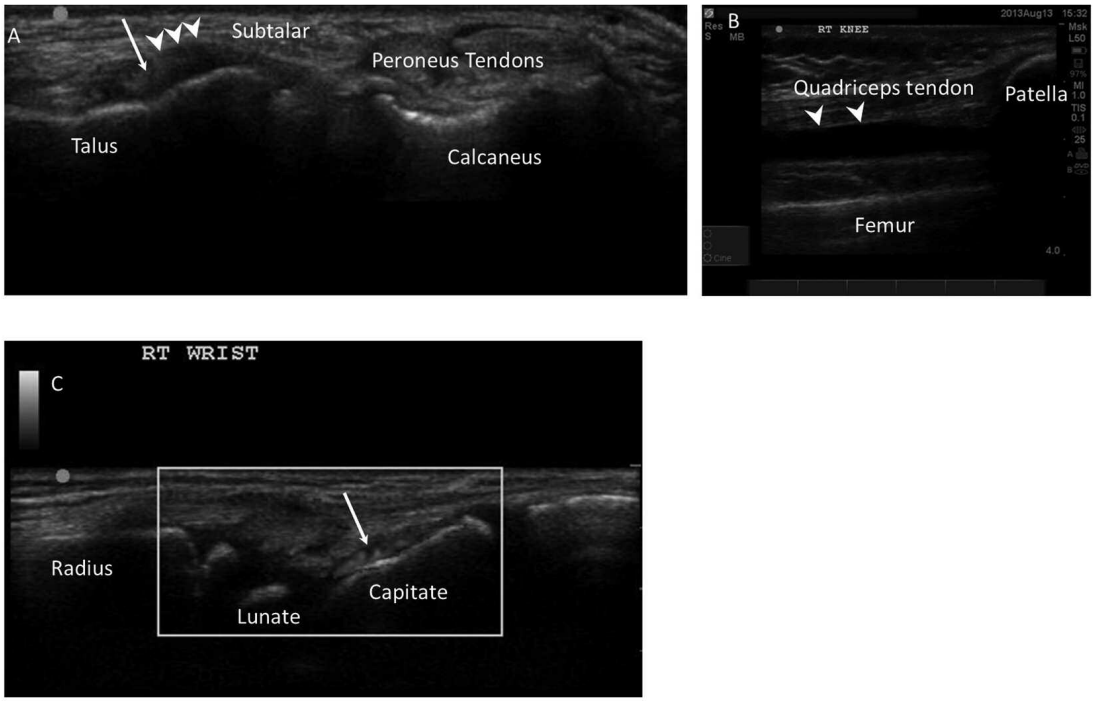

Figure 2. Representative ultrasound images with abnormal findings. A. Lateral longitudinal view of the subtalar joint shows joint effusion (arrowheads) and synovial thickening (arrow). B. Anterior longitudinal view of suprapatellar bursa of the knee joint shows joint effusion (arrowheads). C. Dorsal longitudinal view of the wrist showed positive power Doppler signals (arrow).

Table 3. Sensitivity and positive predictive value of baseline US findings in JIA children with CID.

Joints	Baseline US				Sensitivity	PPV	OR (95% CI)
	Normal		Abnormal				
	No flare	Flare	No flare	Flare			
Wrist	67	2	11	0	0	0	0 (0–34.5)
Knee	56	18	4	2	0.10	0.33	1.5 (0.1–11.9)
Tibiotalar	65	3	4	1	0.25	0.20	5.2 (0.1–85.9)
Subtalar	47	0	10	1	1.00	0.09	Infinite (0.1–infinity)

US: ultrasound; JIA: juvenile idiopathic arthritis; CID: clinically inactive disease; PPV: positive predictive value.

Table 4. Agreement between independent radiologists' readings of US in patients with CID.

Variables	Total No. Scanned (Abnormal)	Scans Agreed, n (%)	Cohen κ (95% CI)
Joint effusion	524 (19)	517 (99)	0.84 (0.72–0.96)
PD	507 (13)	466 (92)	0.33 (0.10–0.55)
Synovial thickening	528 (5)	506 (96)	0.29 (0.08–0.50)

US: ultrasound; CID: clinically inactive disease; PD: power Doppler.

DISCUSSION

Our study describes the common prevalence, yet poor predictive value, of abnormal US findings in JIA patients with CID. In at least 1 of the 8 scanned joints at the time of enrollment, 45% had abnormal US findings. This was consistent with previous studies showing that joint effusion, synovial thickening, and PD abnormalities may be commonly present in children with clinically inactive JIA[4,11,20].

In our study, similar to others, the presence of abnormal US findings did not correlate with a subsequent arthritis flare during clinical followup. There were not enough patients with specific abnormalities to determine whether particular US findings correlated more closely with future disease flare than others. This observation suggests that some US findings were transient and may not be reliable indicators of persistent joint inflammation.

The normal range of pediatric musculoskeletal US findings was recently established for hips[21], knees[22], wrists, tibiotalar joints, and second metacarpophalangeal (MCP) joints[23]. These definitions will help determine the age-appropriate US findings for each scanned joint and aid in the inter-

pretation of findings in children with JIA. PD signal in articular cartilage may be found in normal children because of vascular supply, so interpretation of this finding in children with JIA must be done with caution. Extensive data collection including dynamic assessment and multiple standardized views will be necessary for future US studies in children.

Though synovium is not detectable by US in healthy children, as concluded by an expert panel in Roth, *et al*[17], its presence in children with inactive disease of JIA may be different. For example, in some children with inactive disease of JIA, it is conceivable that the synovium may be normal in thickness (and therefore normal on greyscale US imaging), but demonstrate mild hyperemia detected on PD. Given the sensitivity of PD to minimal hyperemia, it is not unreasonable, based on the available literature, that there may not always be a 1:1 correlation between synovial thickening and PD signal. Clarifying this relationship is a ripe opportunity for future research. Nevertheless, our definition may overestimate the presence of PD compared to the previous definition.

A significant association has been reported between the PD score at baseline and structural progression over 12 months in asymptomatic MCP joints in adults with rheumatoid arthritis[24]. However, subsequent followup did not show correlation of arthritis flare with US-detected synovitis[11]. Our study did not show correlation between PD and disease flare, but this patient group was relatively small; only 7.2% of scanned joints had abnormal PD signal at baseline.

Compared to the patient population in Magni-Manzoni, *et al*[11], our study had fewer patients with persistent oligoarticular JIA (24% vs 46%) and a higher rate of treatment with DMARD and/or biologics (78% vs 41%). Despite the greater disease burden in our patients, we found similar rates of abnormal US findings among scanned joints with inactive disease and did not observe a correlation between these abnormal findings and subsequent clinical arthritis flares.

Among the different joints scanned in JIA patients with CID, the wrists and tibiotalar joints rarely had US findings of joint effusion or synovial thickening. These suggest an equivalent value of physical joint examination with US, as previously suggested by Magni-Manzoni, *et al*[6]. However, knee and subtalar joints had disproportionately higher abnormal US findings that were not detected by clinical examination. Particularly, effusions in these 2 joints may be identified by US but not appreciated clinically.

The interreader reliability in these patients with CID was low for PD and synovial thickening but high for joint effusion. This could be due to relatively small overall prevalence of abnormal findings and the limitation of accurate detection of minimal disease. To our knowledge, there are no published articles for comparison of US interreader reliability from JIA patients with CID.

Our study had several limitations. First, our study did not include a group of age-matched healthy control patients to assess the prevalence of each US variable in normal children. Second, not all patients were kept on the same treatment regimen throughout the observation period. Third, joint examination was performed at various timepoints among individuals. Fourth, only the 8 most commonly affected joints in JIA were evaluated by US. Fifth, our study was based on a still image of 1 plane, which may overestimate abnormalities. Further, our study did not compare US findings to MRI, and targeted imaging was not performed to determine whether abnormal US findings predicted later joint damage.

Our study demonstrated that 45% of children with clinically inactive JIA may have abnormal US findings in at least 1 of 8 commonly affected joints. These findings did not correlate with subsequent clinical flares in up to 2 years of followup. Imaging findings seen at baseline did not persist during subsequent US examinations. At this time, the significance of US findings from still images regarding ongoing active disease in patients thought to be clinically inactive is unknown. Larger longitudinal studies of repeated well-defined US examinations correlated with clinical findings are needed to establish the sensitivity, specificity, significance, and predictive value of specific abnormal US findings in JIA children with CID.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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