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Invited Review

Ultrasound in pediatric rheumatology: Highlighting the differences with adults

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Abstract

Musculoskeletal ultrasound (MSUS) is a powerful tool of major importance in rheumatology. MSUS is ideally suited for the evaluation of pediatric patients because it is a safe technique with a high patient acceptability, it does not require sedation, and it is excellent for exploring multiple joints. It is also the most operator-dependent imaging modality, and assessing joints in patients with juvenile idiopathic arthritis (JIA) is particularly challenging due to the unique features of the growing skeleton. Years ago, MSUS was already extensively used to manage rheumatoid arthritis (RA), which allowed pediatric rheumatologists to apply the knowledge generated in adult studies. It was a good starting point to study the joints of healthy children and JIA patients. Luckily, there is increasing evidence regarding the possibilities of MSUS in the management of JIA patients, with recent definitions for synovitis, descriptions of the sonographic features of joints in healthy children, and a better understanding of the role of subclinical synovitis. This review highlights the differences in normality and in pathological findings between children and adults assessed by MSUS. Specifically, this provides a summary of the current information on characteristics, scores, and definitions that are frequently different between JIA and RA patients. Despite the existence of several unresolved questions in the field, the value that MSUS adds to clinical examination in JIA has already been demonstrated, and we believe that MSUS may be included in the near future in treatment to target strategies.

Keywords: Juvenile idiopathic arthritis, ultrasound, synovitis, cartilage thickening, bone erosion, subclinical synovitis

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Introduction

In recent decades, musculoskeletal ultrasound (MSUS) has been postulated as a tool of increasing interest in the diagnosis and monitorization of patients with rheumatic diseases. Although its implementation in pediatric rheumatology is more recent, different guidelines and definitions have been made to standardize its use. The Outcome Measures in Rheumatology Clinical Trials (OMERACTs) pediatric ultrasound task force has published on topics ranging from the definition of MSUS images in healthy children to the definition of pathological findings. This is of particular importance since the growing skeleton has structural differences when compared with the adult skeleton. Some physiological findings in children, including Doppler signal within the joint, might be misinterpreted as pathological. We elaborate on those differences in the present review. Also, we are aware that in many places, pediatric rheumatologists are not readily available and adult rheumatologists may need to step in for the follow-up of patients with juvenile idiopathic arthritis (JIA). For that reason, we considered relevant to discuss the unique peculiarities that differentiate the role and definitions of MSUS in JIA from those in rheumatoid arthritis (RA).

Characteristics that make MSUS a technique of special interest in children

Ultrasound is an imaging tool particularly appropriate to explore pediatric population for several reasons[1]:

- It is noninvasive and it does not generate pain or discomfort to the patient.
- It is portable, quick-access, and easy to perform.
- Unlike other imaging tests, MSUS does not require patient sedation or the need to remain in the same position for extended periods of time.
- It is a low-cost test.
- Multiple joints can be scanned in the same procedure, reducing the need for complementary explorations.
- It is a highly accepted method by the patient and their families.

Table 1. Summary of the nine EULAR/PReS points to consider for the use of imaging to diagnose and manage JIA in different clinical situations; for each point, the level of evidence and the grade of recommendation are listed.

	Points to Consider in Different Clinical Situations	Level of Evidence	Grade of Recommendation
	When making a diagnosis of JIA		
1	At JIA diagnosis, US and MRI are superior to clinical examination in the evaluation of joint inflammation and should be considered for more accurate detection of the extension of joint involvement	3b	C
2	CR, US, or MRI can be used to improve the certainty of JIA when there is a clinical diagnostic doubt	3b	C
	When detecting damage		
3	CR can be used to detect structural damage, and MRI or US may be used to detect damage at an earlier time point	3b	C
	When imaging specific joints		
4	When assessing certain joints, such as the TMJ and axial involvement, the use of MRI may be of particular benefit over routine clinical evaluation	3b	C
	When predicting outcome		
5	Imaging (CR, US, or MRI) may be considered for use as a prognostic indicator of further joint damage	4	C
	When monitoring inflammation		
6	In JIA, US and MRI can be useful in monitoring disease activity given their sensitivity over clinical examination and good responsiveness (imaging modality used may be joint dependent)	3b	C
	When monitoring damage		
7	Periodic evaluation of joint damage should be considered, and the imaging modality used may be joint dependent	3b	C
	When guiding local treatment		
8	US can be used for accurate placement of intra-articular injections	3b	C
	When assessing remission		
9	US and MRI can detect inflammation when clinically inactive disease is present; this may have implications for monitoring	3b	C

The level of evidence and grade of recommendation are based on the Oxford Center for Evidence-Based Medicine system referenced in Ref. 3. Level of evidence scale, 1a–5; grade of recommendation scale; A–D.
CR, conventional radiography; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance imaging; TMJ, temporomandibular joint; US, ultrasound.
Adapted from Colebatch-Bourn et al.[3]

Main Points

- Musculoskeletal ultrasound (MSUS) is an imaging technique that can be used to diagnose, monitor, and control the response to treatment in pediatric inflammatory rheumatic diseases, especially in juvenile idiopathic arthritis (JIA).
- MSUS operators need to receive specific training to properly recognize and interpret the changing anatomical and physiological characteristics of growing children.
- Different MSUS aspects still need to be standardized (for example, positions to scan each joint, and interpretation of MSUS findings depending on the age of the patient).
- MSUS has demonstrated to add value to clinical examination in JIA, but many subjects remain still controversial (for instance, the prognostic value of subclinical synovitis in detecting risk of flare and damage, and the number of joints that should be periodically explored).
- Prospective large-scale studies will be required to define the role of MSUS in treat-to-target strategies in JIA.

On the other hand, there are some disadvantages of the use of MSUS in children:

- It is a highly operator-dependent technique.
- There is not a comprehensive set of standards for interpreting pediatric MSUS findings.
- Not all joints (e.g., sacroiliac joint or temporomandibular joint) are accessible with ultrasound.

General indications of MSUS in pediatric rheumatology

Ultrasound is used in pediatric rheumatology for musculoskeletal evaluation of inflammatory rheumatic diseases, predominantly for JIA. MSUS has a higher sensitivity than physical examination for diagnosis and assessment of arthritis and its extent. There also is a possibility for the early detection of structural lesions, such as erosions or loss of cartilage thickness. Finally, given its increased sensitivity, MSUS could be used for monitoring disease and treatment response in JIA.[1,2] In 2015, the European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) group task force published a consensus-based points to consider in order to help define standards of care for appropriate use of imaging in the diagnosis and management of JIA (Table 1).[3]

Other indications of MSUS have been evaluated in pediatrics for diagnosis and monitoring (Table 2). For instance, in transient hip synovitis, a strain of the joint capsule secondary to the synovial effusion can be detected and typically resolves after 10-15 days.[1,2] In septic arthritis, arthrocentesis and culture of the joint fluid are needed, and MSUS shows joint effusion, sometimes with a hyperechogenic content.[1,2] Ultrasound is especially valuable for performing different guided procedures such as arthrocentesis and joint infiltration with greater precision.

Future applications of MSUS could include assessment of the nail bed in pediatric patients with distal interphalangeal joint involvement (as in psoriatic JIA), or the evaluation of salivary glands in patients with Sjogren's syndrome.

Anatomical peculiarities of the growing skeleton of children and its differences with adults

Children have significant skeletal differences compared with adults. These will vary depending on the child's age and bone maturation.[4] Bones in children are growing structures that are not fully ossified until maturation is completed. Therefore, when performing MSUS in pediatrics, we will have to consider the existence of hyaline cartilage in the epiphysis and secondary ossification center, and these will vary throughout bone maturation (Figure 1).

Table 2. Indications for the use of musculoskeletal ultrasound in children with suspected pediatric rheumatology conditions.

For identifying pathologic findings and the involved structures	• Synovitis • Tenosynovitis • Enthesitis • Calcifications • Joint structural damage (e.g., erosions, loss of cartilage thickness) • Synovial cysts • Inflammatory muscle injuries
For diagnosis and monitoring by pathology	• Peripheral chronic arthritis, typically present in JIA and in many other inflammatory rheumatic diseases • Transient hip synovitis • Avascular necrosis • Joint infections and osteomyelitis • Overuse and traumatic-related injuries (e.g., Osgood-Schlatter disease, Sinding-Larsen-Johansson syndrome and iliotibial belt syndrome)
For guided procedures	• Diagnostic arthrocentesis • Intra-articular infiltrations

JIA, juvenile idiopathic arthritis.

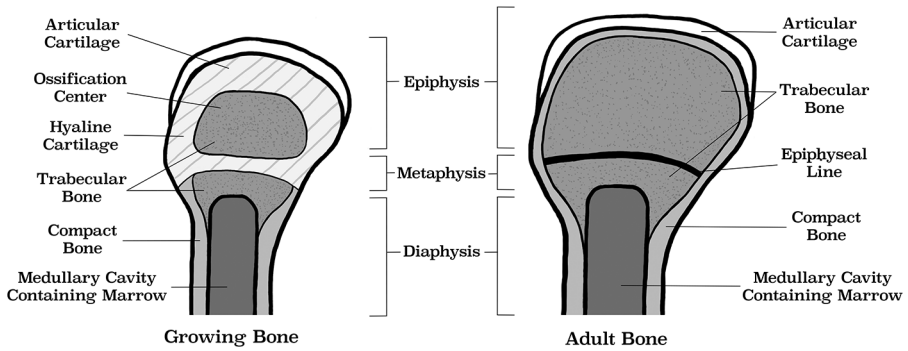

Figure 1. Anatomical differences in a growing and adult long bone. Schematic outline of the structure of a typical long bone shows the gross anatomical characteristics of the distal part of the bone that will interact with the joint.

The secondary ossification centers can be found in different mature states depending on the age of the patient and the anatomical area (Figure 2). When growing, bones exhibit greater vascularization of the unossified epiphyseal, physeal cartilage, and fat pad.[5] For all of the above, a comprehensive anatomical and physiological knowledge of the growing joints is important in order to correctly study and interpret children's ultrasound images.

Assessing normality in the MSUS examination of the joints

In order to detect joint pathology with MSUS, it was necessary to establish definitions for every structure in the joints of healthy children (Figures 1 and 2). In 2010, Spannow et al.[6] established an age- and sex-related normal standards for cartilage thickness in different joints. In 2015, Roth et al.[4] published the definitions of five joint features in healthy children as follows:

1. The normal hyaline cartilage appears as a well-defined homogeneous hypoechoic/anechoic structure (with/without bright echoes/dots) that is non-compressible, and the cartilage surface can be detected as a hyperechoic line.
2. With advancing maturity, the epiphyseal secondary ossification center appears as a hyperechoic structure, with smooth surface or irregular surface within the cartilage.
3. The normal joint capsule can be seen as a hyperechoic band over bones and cartilage of the joint.
4. Under normal circumstances, the thin synovial membrane is undetectable, but in case of hypertrophy, it can be detected as a hypoechoic structure (relative to adjacent hypoechoic tissues).
5. The articular bone surface appears as a sharp hyperechoic line (relative to adjacent hypoechoic tissues).

The OMERACT group defined the characteristics of joint ultrasound in both B-mode (grey-scale) and Power Doppler (PD) in healthy children.[7] They agreed that physiological vascularity could be detected as PD signal during growth within the joint, fat pads, and unossified joint structures, particularly in the youngest children, as it was joint and age dependent. Also, physis could be detected in children as an anechoic unossified structure, intra- or extra-articular according to its anatomical location. Fat pad was defined as an intra-articular structure with heterogeneous echotexture. They stated that ossification grade is age and joint dependent, and ossification centers can be detected with different maturation states.

Recently, the OMERACT pediatric ultrasound task force has proposed a score to determine the degree of maturation of the ossification nucleus with a semiquantitative scale ranging from 0 to 3. The definitions of grades 0-3 were as follows[5]:

- Grade 0: nonossified epiphyseal bone, short bones, or patella.
- Grade 1: small ossification centers, dominant cartilage, and visible growth plate.
- Grade 2: large ossification centers, thin cartilage, and visible growth plate.
- Grade 3: complete ossification.

Standardized joint evaluation with MSUS in children

At present, OMERACT has descriptions of standardized scan positions for evaluating four joints in children.[8] For the remaining joints, until we have a proper examination system designed for children, it seems logical to use the positions that have been proposed for adults. For these four joints, the standardized scan positions are as follows:

- Knee: anterior suprapatellar recess and lateral parapatellar recess.
- Wrist: lateral/midline/medial dorsal examination.
- Second metacarpophalangeal (MCP): dorsal/lateral/volar.
- Ankle: medial/midline/lateral/dorsal.

Additional studies are required to standardize findings and the interpretation of PD in healthy children. This will subsequently help to detect and correctly interpret pathological findings (Figure 3). Likewise, standardized ultrasound scanning positions for all joints are necessary to improve the robustness of the data and the reproducibility of the results.

Synovitis: Definitions for children and adults

The widespread use of MSUS in the management of inflammatory arthritis has led OMERACT to develop consensus definitions for sonographic findings of bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis, and enthesopathy.[9] These definitions have

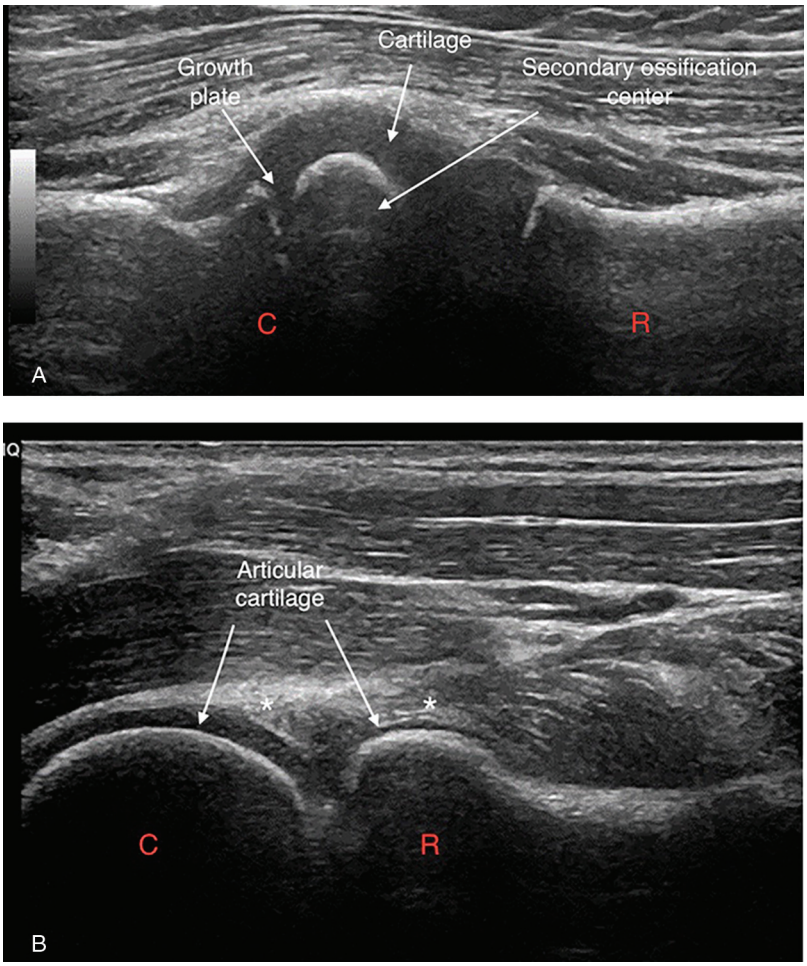

Figure 2. A, B. Ultrasound images (grey-scale) of the radiocapitellar joint, showing normal anatomy of the elbow in a longitudinal-anterior view. (A) Three-year-old patient with incompletely ossified epiphysis. Notice the anechoic image of the metaphysis with the growth plate, along with the secondary ossification center in the epiphysis, surrounded by hyaline cartilage. (B) Sixteen-year-old patient with completely ossified epiphysis. Notice the anatomic changes in the epiphysis and how the articular cartilage has a different thickness. Asterisks (*) indicate a hyperechoic regular line, which is an interface artifact on hyaline cartilage. Images obtained using a GE Logiq S8 ultrasound with a linear probe of 4-15 MHz frequency. C, capitulum (humerus); R, radius.

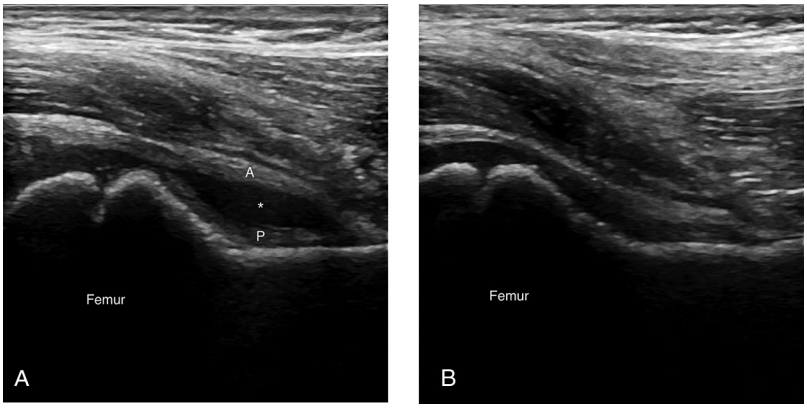

Figure 3. A, B. Sagittal ultrasound images (grey-scale) of the hip of a 3-year-old Juvenile idiopathic arthritis girl who had synovitis of the hip during the disease course. (A) Right hip with anechoic joint effusion (*) and synovial thickening. The anterior (A) and posterior (P) layers of the joint capsule are separated by the effusion, and there is distension of the joint capsule above the femoral neck. (B) Contralateral left hip (healthy) of the same patient. Images obtained using a GE Logiq S8 ultrasound with a linear probe of 4-15 MHz frequency.

been shown to be essential for good inter-reader reliability and represented a good starting point for conducting outcome studies based on MSUS. In adults, the initial definition of synovitis included two elementary lesions: synovial effusion and synovial hypertrophy. Either of these individually or both together could indicate synovitis. In 2019, OMERACT Ultrasound group updated these definitions guided by a stepwise validation process consisting of a web-based Delphi exercise testing the validity and reliability of those lesions. Because synovial effusion did not prove to be reliable and was frequently detected in healthy subjects, synovitis in adults was redefined as the presence of a hypoechoic synovial hypertrophy, regardless of the presence of effusion or any grade of Doppler signal.[10]

These adult definitions could not be simply adapted for pediatric patients, mainly because of the significant changes related to cartilage maturation and blood flow.[4] MSUS definitions for synovitis in children were developed and validated through an international consensus process (Table 3). The definition of synovitis is encompassed by synovial effusion and synovial hypertrophy. The combined scoring system for synovitis using B-mode and PD signal is stratified from 0 to 3 according to the severity of the findings (Table 3).

As in adults, the assessment of synovitis by MSUS requires the use of both B-mode and Doppler, and it cannot be detected based on PD findings alone. It is very important to clearly identify the synovial recess on B-mode and to differentiate this recess from the connective tissue. This distinction is especially significant for the correct interpretation of PD signal (Figure 4). In children, intra-articular PD signal must be found within an area of synovial hypertrophy to consider it pathogenic.[11]

Despite the efforts conducted by OMERACT Ultrasound Task Force to overcome the challenges of MSUS, this field is still underinvestigated, and the majority of the studies that have been performed are cross-sectional. Future longitudinal studies could help to clarify the significance of periarticular hyperemia and perisynovial vessels observed during inflammation.

Role of MSUS in children with arthritis and differences with adults

There are many differences between JIA and RA patients inherent to the disease characteristics (e.g., JIA is a more heterogeneous disease than RA) or to the biologic mechanisms of the disease (e.g., the presence of anticyclic citrullinated peptide antibodies is common

Table 3. Pediatric definition for synovitis detected by ultrasound, and combined scoring system for synovitis in children.

Definition for synovitis on ultrasonography in children
• Synovitis detected by US in children includes the assessment of B-mode and PD mode (color or power Doppler) findings. • Synovitis can be detected on the basis of B-mode findings alone. Synovitis cannot be detected based on color/PD findings alone. • B-mode findings include synovial effusion and synovial hypertrophy. • Synovial effusion is defined as an abnormal, intra-articular, anechoic, or hypoechoic material that is displaceable. • Synovial hypertrophy is defined as an abnormal, intra-articular, or hypoechoic material that is nondisplaceable. • Color/power Doppler signals must be detected within synovial hypertrophy to be considered a sign of synovitis.

OMERACT Combined Scoring System for Synovitis in Children

Grade	B-Mode	PD
0 (absence)	No signs of synovial effusion or synovial hypertrophy	Absence of color/power Doppler signal within synovial hypertrophy with or without detection of normal physiological Doppler signals
1 (mild)	Synovial effusion and/or synovial hypertrophy that leads to a mild change of the joint recess appearance	Detection of up to three single Doppler signals within the area of synovial hypertrophy with or without normal physiological Doppler signals
2 (moderate)	Synovial effusion and/or synovial hypertrophy that leads to a moderate change of the joint recess appearance	Detection of more than three single Doppler signals but less than 30% of the area of synovial hypertrophy with or without normal physiological Doppler signals
3 (severe)	Synovial effusion and/or synovial hypertrophy that leads to a severe change of the joint recess appearance	Detection of Doppler signals at more than 30% of the area of synovial hypertrophy with or without normal physiological Doppler signals

US, ultrasound; PD, power-Doppler.
Adapted from Roth et al.[11] and Bruyn et al.[10]

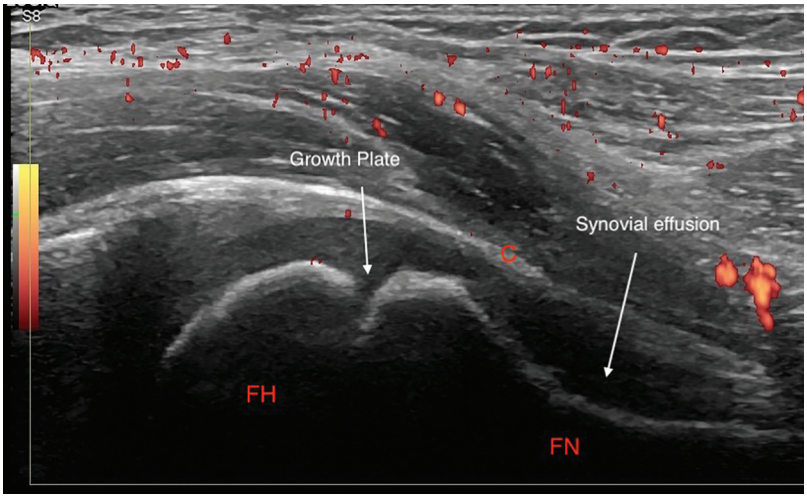

Figure 4. Ultrasound image (grey-scale and power Doppler) of the hip of a 4-year-old juvenile idiopathic arthritis patient who had synovitis of the joint during the disease course. Sagittal ultrasonography of the femoral head (FH), femoral neck (FN), the joint capsule (C), and an anechoic synovial effusion. Notice the bulging in the capsule above the femoral neck caused by the joint effusion. Doppler signal observed in the image is an artifact not related in this case with the pathological findings. Images obtained using a GE Logiq S8 ultrasound with a linear probe of 4-15 MHz frequency.

among patients with RA, while in JIA, they have been described in some of the patients classified as polyarticular JIA rheumatoid factor (RF) positives). Only polyarticular RF positive JIA clearly resembles adult RA. Among the patient-dependent differences in JIA and RA, age is the most important: by definition, JIA has to start before 16 years of age. In both of them, chronic synovitis is the cardinal feature, but RA is typically a polyarticular and symmetric disease, while JIA patterns of joint affection are very heterogeneous (Figure 5).

Role of MSUS in JIA diagnosis

Ultrasonography is more sensitive at detecting synovitis than clinical examination, adding value in monitoring both adult RA and pediatric JIA patients. At diagnosis, MSUS could help to better determine the extent of the arthritis and to improve certainty in diagnosis when in clinical doubt.[3,12] This is relevant in JIA because children are classified as having oligoarthritis or polyarthritis based on the number of affected joints on clinical examination.[13] Furthermore, current American College of Rheumatology (ACR) JIA treatment recommendations differ depending on the number of joints with synovitis.[14,15] The role of MSUS in classifying patients with JIA is still unclear. Some data indicate that MSUS ability to detect subclinical synovitis may reclassify some JIA patients from oligoarticular to polyarticular if performed early at disease onset.[16,17] Potential changes in classification can lead to significant variations in the treatment and prognosis of these children.

The role of MSUS performed at diagnosis to classify JIA patients and how this could influence their clinical outcome need to be explored.

Role of MSUS in subclinical synovitis

Subclinical synovitis can be defined as inflammation detected in a joint by MSUS when a trained rheumatologist/pediatric rheumatologist fails to detect inflammation by clinical examination. Current scientific evidence indicates that a significant percentage of patients with JIA in clinical remission and a significant percentage of clinically inactive joints exhibit subclinical inflammatory activity by MSUS.[17–22] There are some remarkable

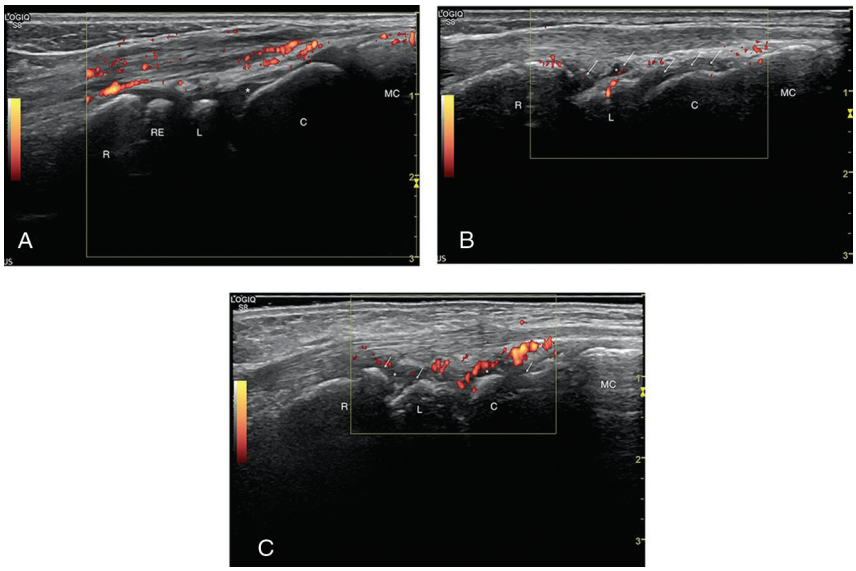

Figure 5. A–C. Midsagittal ultrasound images (grey-scale and power Doppler) of dorsal wrists of juvenile idiopathic arthritis (JIA) patients of different ages. Images showing radiocarpal and midcarpal joints. (A) Five-year-old girl with oligoarticular JIA: anechoic synovial effusion (*) synovial hypertrophy and hypervascularization (part of the signal corresponds to physiological blood vessels and part of the signal is pathological); (B) 15-year-old girl with JIA: anechoic synovial effusion (*) synovial hypertrophy (arrows) and hypervascularization; (C) 19-year-old girl with polyarticular rheumatoid factor positive JIA: anechoic synovial effusion (*) synovial hypertrophy, hypervascularization and cortical bone irregularities (arrows), compatible with bone erosions (images of perpendicular planes not shown). R, radius; RE, distal-radial epiphysis; L, lunate; C, capitate; MC, metacarpal. Images obtained using a GE Logiq S8 ultrasound with a linear probe of 4-15 MHz frequency.

limitations when evaluating these studies, e.g., variations in the joints and the number of joints explored, a lack of agreement on synovitis definition, and differences in PD assessment. Altogether, it is very challenging to compare their data. The most relevant studies examining subclinical synovitis in JIA are summarized in Table 4. Later, we expand on many aspects of this highly interesting topic.

Subclinical synovitis can be detected in healthy subjects

In healthy adults, some subjects could present a positive PD signal in the joints,[23] while this finding was not observed in healthy children.[24] Ultrasound abnormalities were observed in 35.9% of healthy children, and all MSUS alterations were scored as low-grade.[22] These observations set the basis for further investigation in patients affected with chronic arthritis, especially to determine how to value the importance of low-level MSUS findings in JIA. It could be interesting to carry out a study that follows healthy subjects presenting with MSUS abnormalities, to check whether these deviations are transient, or if they remain stable over time.

Subclinical synovitis is more frequent in polyarticular JIA, in both active and inactive patients

Subclinical synovitis is more frequent in patients exhibiting a polyarticular course than in those who had an oligoarticular course.[20,25] RA typically has a polyarticular course, and the percentages of patients/joints with subclinical activity are higher or at least similar to those reported in JIA studies.[26,27] Subclinical synovitis can be present in joints of both active and inactive patients. Available data suggest that active patients with RA present subclinical synovitis more frequently than those in remission; however, this has not been yet fully confirmed in JIA patients (Table 4).

Joints most commonly affected by subclinical synovitis

In JIA, the frequency of subclinical synovitis in different joints greatly varies between studies, but, in general, it has been more frequently described in wrist, ankle, and small joints of hands and feet.[16,17,25] The assessment of ankles can be particularly challenging because of the higher frequency of tenosynovitis detected by MSUS when compared with clinical examination.[28] In RA, subclinical synovitis is detected most frequently in wrist, MCF, ankle, and metatarsophalangeal joints.[29]

In JIA, some data indicate that subclinical synovitis could be more frequently observed in joints that have previously had inflammation.[30] Ultrasound's ability to differentiate acute from chronic synovitis is unclear. A recent prospective study found residual synovial abnormalities in one-fifth of joints that were in clinical remission after 6 months of clinical intervention.[31] One possible explanation could be that, in some joints, the recovery seen in imaging is slower than the physical clinical recovery. However, in Magni-Manzoni's prospective study where 39 clinically inactive patients were included (2,028 joints assessed), just 19.9% (56/282) of the joints that had been clinically involved in the past had MSUS abnormalities, and these represented 43.2% (60/139) of the total of joints with subclinical synovitis[22] (Table 4).

Subclinical synovitis may be predictive of flare in JIA

In RA patients, the presence of subclinical synovitis, particularly PD signal, is predictive of flares,[29,32] while in JIA, we have conflicting data. Many studies did not confirm ultrasound's value to predict a flare, as was the case for Magni-Manzoni's, where during a 2-year follow-up, 38.5% (15/39) of the inactive JIA patients flared, and none of the MSUS parameters had prognostic value.[22] A misinterpretation of physiological low-grade PD signal could be the reason for the lack of association between subclinical activity and JIA risk of flare in other studies.[33] Contrarily, a prospective study of 35 patients in clinical remission followed-up for up to 30 months concluded that subclinical synovitis with positive PD is a predictor of flare in JIA patients in clinical remission.[25] Janow et al.[34] described that out of 14 knees and ankles that exhibit MSUS abnormalities while clinically inactive, five (35.7%) developed clinically active arthritis during the follow-up. In a recent study of 88 patients with inactive disease followed-up for 4 years, De Lucia et al.[19] observed that subclinical activity detected by MSUS increased by about four times the risk of flare. Interestingly, the joints where the disease relapsed were not necessarily the joints that presented MSUS alterations, which may indicate a higher systemic inflammation in these patients. Importantly, in this study, the combination of grey-scale and PD abnormalities displayed a much higher predictive value of relapse (65%, 13/20) than grey-scale alone (33%, 6/18).[19]

Subclinical synovitis may be predictive of damage in JIA

Subclinical synovitis in RA patients in remission is a predictor of radiological progression. It may explain the observed discrepancy between disease activity and outcome, but the mechanisms are not yet fully understood.[26,27] Part of the alterations observed with MSUS in grey-scale could correspond to a thickening and residual fibrosis of the synovial membrane. However, histological studies

Table 4. Summary of relevant studies that assessed multiple joints in JIA patients to analyze the prevalence, characteristics, and clinical value of subclinical synovitis determined by ultrasound.

					Subclinical Synovitis		
Author and Year	Design	N JIA Patients/N Joints	JIA Subtype	Clinical Activity*	N (%) Patients	N (%) Joints with GS	N (%) Joints with PD
De Lucia et al., 2018[19]	Prospective	88/3 872	All categories	Inactive and remission	20 (22.7)	38 (0.98)	20 (0.52)
Bugni-Mioto e Silva et al., 2017[25]	Prospective	35/3 298	Oligoarticular and polyarticular	Remission	24 (68.6)	NA	NA
Bugni-Mioto e Silva et al., 2014[20]	Cross-sectional	36/1 224	Oligoarticular and polyarticular	Remission	15 (41.7)	38 (3.1)	NA
Collado et al., 2014[21]	Cross-sectional	34/1 496	Oligoarticular and polyarticular	Remission	13 (38.2)	37 (2.5)	18 (1.2)
Magni-Manzoni et al., 2013[22]	Prospective	39/2 028	All categories	Inactive and remission	30 (76.9)	131 (6.5)	30 (1.5)
Janow et al., 2011[34]	Cross-sectional	19/76	All categories	Active	NA	14 (30)	NA
Haslam et al., 2010[16]	Cross-sectional	17/680	Oligoarticular	Low activity and inactive	6 (35.3)	15 (2.28)	NA
Magni-Manzoni et al., 2009[17]	Cross-sectional	32/1 664	Nonsystemic JIA	Active and inactive	NA	86 (5.5)	NA

Nonsystemic JIA can include oligoarthritis (persistent and extended), rheumatoid factor-positive polyarthritis and rheumatoid factor-negative polyarthritis, psoriatic JIA, enthesitis-related arthritis, and undifferentiated JIA.
GS, grey-scale abnormalities (synovial hypertrophy and/or joint effusion for most of the studies); JIA, juvenile idiopathic arthritis; N, number of; N joints, number of joints in JIA patients; NA, not available; PD, power doppler signal.
*Defined by clinical criteria, the patients could be on treatment or out of treatment.
†The percentage was calculated among the total number of inactive joints.

in RA demonstrated the presence of active inflammation in synovial samples of patients in remission,[35] and some traits characteristic of inflammation, as the presence of macrophage infiltration and increased vascular components (also present in clinically active joints, but not in controls).[36] This may or may not be the case for JIA patients, since the mechanism and site of onset of erosions are different. The correlation between subclinical synovitis and damage in patients with JIA has just been explored by Miotto e Silva et al.[25] in a prospective study published in 2017. Thirty-five JIA patients in clinical remission were followed for 12 months, and 2 108 joints were evaluated to assess damage progression. Erosions were observed in 25 (1.2%) joints. Subclinical synovitis increased the risk of developing an erosion in these JIA patients, and unlike in RA, this risk was independent of the positive PD signal.[25]

There are several unmet needs to further understand subclinical synovitis meaning and value in JIA. Prospective studies could further investigate how subclinical synovitis predicts the risk of flare and damage in inactive JIA patients, to determine the weight of PD in assessing this risk and to correlate MSUS findings with other biomarkers. Also, the clinical meaning of subclinical synovitis in active and inactive JIA patients should be clarified in order to address treatment strategies accordingly.

Role of MSUS in treat to target strategies and disease monitoring

The primary target recommended by the international Task Force for the treatment of patients with JIA is clinical remission, which means the absence of signs and symptoms of inflammatory disease activity, including extra-articular manifestations.[37] Over the past decade, attention has been focused on the use of MSUS in RA regarding treat-to-target (T2T) strategies. Two randomized clinical trials recently published included early disease onset RA patients and aimed for low disease activity or remission or remission only.[38,39] Both concluded that systematic use of MSUS for treatment decision-making was not superior to tight clinical control in RA, in terms of both clinical or imaging outcomes.[38,39]

MSUS can be applicable to JIA in day-to-day clinical practice,[3] and its role in response to treatment monitoring and decision-making needs to be further explored. Recently, Lanni et al.[31] assessed 83 joints of 33 patients with new-onset JIA by MSUS at study entry and at 6 months after a therapeutic intervention. Grey-scale and PD abnormalities assessed with a semiquantitative scale showed a significant improvement ($P < .0001$) from baseline

to follow-up. It is remarkable that 28.6% of the patients who achieved ACRp90 response did not display a complete resolution of synovial abnormalities by MSUS.[31]

MSUS can also help to anatomically distinguish the structure inflamed in the joint. Rooney et al.[40] evaluated 49 clinically swollen ankles from 34 JIA patients and found that only 29% of the ankles had tibiotalar effusion alone, whereas concomitant tenosynovitis was found in 33% of the cases. Recently, Lanni et al.[28] used MSUS to study 78 patients who had 105 active ankles on clinical examination. Tenosynovitis was found more commonly with MSUS than with clinical examination (70.5% vs 32.4%). Determining the exact location of inflammation has direct implications regarding treatment procedures.

There is no established role for imaging in defining disease remission. We need to better understand how MSUS correlates with clinical tools, like the validated Juvenile Arthritis Disease Activity Score (JADAS), and how it can be used to complement them when necessary. Also, in order to define a T2T strategy, we will need to refine our targets and to precisely define the goals we want to achieve with therapy. More studies are needed to understand particular aspects of disease activity and remission and to establish the impact of MSUS on influencing therapeutic decisions in JIA.

Assessing damage with MSUS in JIA

Cartilage damage

Joint cartilage is a known target in inflammatory arthritis. Even though MSUS does not visualize cartilage completely in all joints, its diminished thickness can represent an early marker of damage in JIA. Spannow et al.[41] were the first to provide normal ranges of MSUS-measured cartilage thickness in small and large joints of healthy children. Later, this group compared these measures with JIA patients, and they found a significantly thinner cartilage in JIA, regardless of whether the examined joints had been previously affected by arthritis.[42] The assessment of cartilage and bone damage in RA, which has traditionally relied on radiographic scores and measurement by MSUS, has not yet been standardized. Recently, definitions of elementary lesions of the cartilage were formulated, and a semiquantitative MSUS score for assessing cartilage pathology in the MCP joints of patients with RA was developed.[43] Designing a semiquantitative MSUS score to assess cartilage thickness in JIA patients can be more challenging due to the presence of irregular ossification centers in the epiphysis in younger children.

Bone erosions

The OMERACT definition of bone erosion is areas of discontinuity of the bone surface that are visible in two perpendicular planes.[9] Even though bone erosions are less common in JIA than RA, they are an important sign of joint damage (Figure 5C). EULAR-PReS points to consider recommend the detection of structural abnormalities or damage when it is suspected, and MSUS could help to detect abnormalities at an earlier stage.[3] Also, when the imaging techniques have been directly compared, MRI and MSUS can detect more joint damage than conventional radiography, especially at the hip and wrist.[44] In children, erosions can be found in the epiphysis rather than the metaphysis, which is more commonly affected in adults.[45]

Growing disturbance in JIA children

Due to children's anatomy and the vascularization of the epiphysis in growing bones, the inflammation affecting the epiphyseal cartilage may spread to the ossification center, causing excessive growth and irreversible deformities in the affected joints.

New imaging tools like high-resolution ultrasound, high-frequency transducers, and 3D-US-MRI fusion techniques are eagerly awaited and could play a role to determine the role of MSUS in assessing damage in children.[46]

Reduced semiquantitative ultrasound scores: From RA to JIA

When and how often the joints of a child with JIA need to be examined by MSUS are still unresolved questions. However, how many and which joints can be assessed to optimize our control over JIA were investigated a few years ago. Reduced ultrasound scores have been designed to determine inflammatory activity in patients with chronic arthritis as precisely as possible, while exploring the fewest number of joints as possible in a reasonable time.

The pioneers in designing reduced ultrasound scores to improve patient outcome and assessment were adult rheumatologists.[47–49] Among the validated reduced ultrasound scores designed for RA, two stand out for their simplicity and results: a 7-joints score[47] and a 12-joints score.[48] This last 12-joint MSUS score proved to be superior to the 7-joint score.[49] A reduced MSUS 10-joint score has been developed to optimize the assessment of JIA patients.[50] It correlates well with the extended MSUS score of 44 joints, and it has been shown to be valid, sensitive to long-term change, and feasible to use in clinical practice. In fact, assessing a reduced number of joints was more sensitive to change than assessing a larger number of joints in children with JIA.[50] In both the 12-joint score designed for RA and the 10-joint score designed for JIA, a semiquantitative value is given to the MSUS findings in the knees, ankles, elbows, wrists, and 2nd MCP joints.[48,50] The main differences between them are the examination of the third MCP joint (only present in the adult score) and in some explored compartments.

For future studies, it could be interesting to validate this reduced MSUS score in JIA prospective cohorts. This would allow us to better assess its performance when used at different time points in the disease course and to correlate it with other biomarkers or clinical validated scores like JADAS.

Conclusion

Ultrasound is an excellent tool used in the management of both adult RA and pediatric JIA patients. Despite the similarities in the pathology, many differences regarding the characteristics of the growing skeleton and the peculiarities of JIA should be taken into account when examining children with this disease. Definitions of pathology, and the clinical and ultrasound scores used in adults are neither precise nor often applicable to pediatric patients with JIA. In children, we still need to fully determine normal MSUS characteristics, including the changes that happen as a result of age and maturation. To perform a reliable examination with ultrasound for JIA patients, the operators need to be properly trained and have a precise knowledge of children's anatomy. Increasing evidence demonstrates how ultrasound is a relevant and safe technique for managing children with JIA: it can be used to evaluate most of the joints, monitor response to treatment, guide local procedures, and detect subclinical inflammation that could be predictive of damage and flare. The specific roles for B-mode and PD signal in JIA evaluation, and the possibility of incorporating imaging to diagnostic criteria in JIA or to monitor and make treatment decisions based on imaging findings have been understudied. Nowadays, many efforts in pediatric rheumatology are moving toward implementing T2T approaches. Establishing the targets that need to be reached will be crucial to that end. In the coming years, ultrasound could be incorporated to complement current clinical tools when applying these T2T strategies.

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References

1. Spârchez M, Fodor D. What's new in musculoskeletal ultrasound in pediatric rheumatology? *Med Ultrason*. 2018;20(3):371-378. [CrossRef]
2. Barbuto L, Di Serafino M, Della Vecchia N, et al. Pediatric musculoskeletal ultrasound: A pictorial essay. *J Ultrasound*. 2019;22(4):491-502. [CrossRef]
3. Colebatch-Bourn AN, Edwards CJ, Collado P, et al. EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. *Ann Rheum Dis*. 2015;74(11):1946-1957. [CrossRef]
4. Roth J, Jousse-Joulin S, Magni-Manzoni S, et al. Definitions for the sonographic features of joints in healthy children. *Arthritis Care Res*. 2015;67(1):136-142. [CrossRef]
5. Windschall D, Collado P, Vojinovic J, et al. Age-related vascularization and ossification of joints in children: An international pilot study to test multiobserver ultrasound reliability. *Arthritis Care Res*. 2020;72(4):498-506. [CrossRef]
6. Spannow AH, Pfeifer-Jensen M, Andersen NT, Herlin T, Stenbørg E. Ultrasonographic measurements of joint cartilage thickness in healthy children: Age- and sex-related standard reference values. *J Rheumatol*. 2010;37(12):2595-2601. [CrossRef]
7. Collado P, Windschall D, Vojinovic J, et al. Amendment of the OMERACT ultrasound definitions of joints' features in healthy children when using the DOPPLER technique. *Pediatr Rheumatol*. 2018;16(1):23. [CrossRef]
8. Collado P, Vojinovic J, Carlos Nieto J, et al. Toward standardized musculoskeletal ultrasound in pediatric rheumatology: Normal age-related ultrasound findings. *Arthritis Care Res*. 2016;68(3):348-356. [CrossRef]
9. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol*. 2005;32(12):2485-2487.
10. Bruyn GA, Iagnocco A, Naredo E, et al. OMERACT definitions for ultrasonographic pathologies and elementary lesions of rheumatic disorders 15 years on. *J Rheumatol*. 2019;46(10):1388-1393. [CrossRef]
11. Roth J, Ravagnani V, Backhaus M, et al. Preliminary definitions for the sonographic features of synovitis in children. *Arthritis Care Res*. 2017;69(8):1217-1223. [CrossRef]
12. Colebatch AN, Edwards CJ, Østergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis*. 2013;72(6):804-814. [CrossRef]
13. Petty RE, Southwood TR, Manners P, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton. *J Rheumatol*. 2004;31(2):390-392.
14. Ringold S, Weiss PF, Beukelman T, et al. Update of the 2011 American college of rheumatology recommendations for the treatment of juvenile idiopathic arthritis: Recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013;65(10):2499-2512. [CrossRef]
15. Ringold S, Angeles-Han ST, Beukelman T, et al. American college of rheumatology/arthritis foundation guideline for the treatment of juvenile idiopathic arthritis: Therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol*. 2019;71(6):846-863. [CrossRef]
16. Haslam KE, McCann LJ, Wyatt S, Wakefield RJ. The detection of subclinical synovitis by ultrasound in oligoarticular juvenile idiopathic arthritis: A pilot study. *Rheumatology (Oxford)*. 2010;49(1):123-127. [CrossRef]
17. Magni-Manzoni S, Epis O, Ravelli A, et al Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. *Arthritis Rheum*. 2009;61(11):1497-1504. [CrossRef]
18. Zhao Y, Rascoff NE, Iyer RS, et al. Flares of disease in children with clinically inactive juvenile idiopathic arthritis were not correlated with ultrasound findings. *J Rheumatol*. 2018;45(6):851-857. [CrossRef]
19. De Lucia O, Ravagnani V, Pregnolato F, et al. Baseline ultrasound examination as possible predictor of relapse in patients affected by juvenile idiopathic arthritis (JIA). *Ann Rheum Dis*. 2018;77(10):1426-1431. [CrossRef]
20. Bugni Miotto e Silva V, de Freitas Tavares da Silva C, de Aguiar Vilela Mitraud S, et al. Do patients with juvenile idiopathic arthritis in remission exhibit active synovitis on joint ultrasound? *Rheumatol Int*. 2014;34(7):937-945. [CrossRef]
21. Collado P, Luz Gamir M, Carlos López-Robledillo J, et al. Detection of synovitis by ultrasonography in clinically inactive juvenile idiopathic arthritis on and off medication. *Clin Exp Rheumatol*. 2014;32(4):597-603.
22. Magni-Manzoni S, Alberto Scirè C, Ravelli A, et al. Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. *Ann Rheum Dis*. 2013;72(2):223-228. [CrossRef]
23. Padovano I, Costantino F, Breban M, D'Agostino MA. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis*. 2016;75(10):1819-1823. [CrossRef]
24. Collado P, Naredo E, Calvo C, Crespo M.. Assessment of the joint recesses and tendon sheaths in healthy children by high-resolution B-mode and power doppler sonography. *Clin Exp Rheumatol*. 2007;25(6):915-921.
25. Miotto e Silva VB, de Aguiar Vilela Mitraud S, Nely Vilar Furtado R, et al. Patients with juvenile idiopathic arthritis in clinical remission with positive power doppler signal in joint ultrasonography have an increased rate of clinical flare: A prospective study. *Pediatr Rheumatol*. 2017;15(1):80. [CrossRef]
26. Saleem B, Brown AK, Keen H, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. *Ann Rheum Dis*. 2011;70(5):792-798. [CrossRef]
27. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum*. 2008;58(10):2958-2967. [CrossRef]
28. Lanni S, Marafon DP, Civino A, et al Comparison between clinical and ultrasound assessment of the ankle region in juvenile idiopathic arthritis. *Arthritis Care Res*. 2021;73(8):1180-1186. [CrossRef]
29. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. et al. Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: A systematic review and meta-analysis. *Rheumatology (Oxford)*. 2014;53(11):2110-2118. [CrossRef]
30. Rebollo-Polo M, Koujok K, Weisser C, Jurencak R, Bruns A, Roth J. Ultrasound findings on patients with juvenile idiopathic arthritis in clinical remission. *Arthritis Care Res*. 2011;63(7):1013-1019. [CrossRef]
31. Lanni S, Pieter van Dijkhuizen EH, Vanoni F, et al. Ultrasound changes in synovial abnormalities induced by treatment in juvenile idiopathic arthritis. *Clin Exp Rheumatol*. 2018;36(2):329-334.
32. Saleem B, Brown AK, Quinn M, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. *Ann Rheum Dis*. 2012;71(8):1316-1321. [CrossRef]
33. Roth J. Predictive value of musculoskeletal ultrasound for flares in juvenile idiopathic arthritis. *J Rheumatol*. 2019;46(1):113-113. [CrossRef]
34. Janow GL, Panghaal V, Trinh A, Badger D, Levin TL, Ilowite NT. Detection of active disease in juvenile idiopathic arthritis: Sensitivity and specificity of the physical examination vs ultrasound. *J Rheumatol*. 2011;38(12):2671-2674. [CrossRef]
35. Anandarajah A, Thiele R, Giampoli E, et al. Patients with rheumatoid arthritis in clinical remission manifest persistent joint inflammation on histology and imaging studies. *J Rheumatol*. 2014;41(11):2153-2160. [CrossRef]
36. Ramirez J, Celis R, Usategui A, et al. Immunopathologic characterization of ultrasound-defined synovitis in rheumatoid arthritis patients in clinical remission. *Arthritis Res Ther*. 2016;18:74. [CrossRef]
37. Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target:

Recommendations of an international task force. *Ann Rheum Dis*. 2018;77(6). [CrossRef]
38. Paulshus SN, Aga AB, Olsen IC, et al. Clinical and ultrasound remission after 6 months of treat-to-target therapy in early rheumatoid arthritis: Associations to future good radiographic and physical outcomes. *Ann Rheum Dis*. 2018;77(10):1421-1425. [CrossRef]
39. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: The results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis*. 2016;75(6):1043-1050. [CrossRef]
40. Rooney ME, McAllister C, Burns JF. Ankle disease in juvenile idiopathic arthritis: Ultrasound findings in clinically swollen ankles. *J Rheumatol*. 2009;36(8):1725-1729. [CrossRef]
41. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Stenbøg E, Herlin T. et al. Inter- and intraobserver variation of ultrasonographic cartilage thickness assessments in small and large joints in healthy children. *Pediatr Rheumatol*. 2009;7:12. [CrossRef]
42. Pradsgaard DO, Spannow AH, Heuck C, Herlin T. Decreased cartilage thickness in juvenile idiopathic arthritis assessed by ultrasonography. *J Rheumatol*. 2013;40(9):1596-1603. [CrossRef]
43. Mandl P, Studenic P, Filippucci E, et al. Development of semiquantitative ultrasound scoring system to assess cartilage in rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(10):1802-1811. [CrossRef]
44. Fedrizzi MS, Ronchezel MV, Hilario MO, et al. Ultrasonography in the early diagnosis of hip joint involvement in juvenile rheumatoid arthritis. *J Rheumatol*. 1997;24(9):1820-1825.
45. Karmazyn B, Bowyer SL, Schmidt KM, et al. US findings of metacarpophalangeal joints in children with idiopathic juvenile arthritis. *Pediatr Radiol*. 2007;37(5):475-482. [CrossRef]
46. Peluso G, Bosello SL, Gremese E, et al. Detection of bone erosions in early rheumatoid arthritis: 3D ultrasonography versus computed tomography. *Clin Rheumatol*. 2015;34(7):1181-1186. [CrossRef]
47. Backhaus M, Ohrndorf S, Kellner H, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: A pilot project. *Arthritis Rheum*. 2009;61(9):1194-1201. [CrossRef]
48. Naredo E, Rodríguez M, Campos C, et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum*. 2008;59(4):515-522. [CrossRef]
49. Mandl P, Naredo E, Wakefield RJ, et al. A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in rheumatoid arthritis according to the OMERACT filter. *J Rheumatol*. 2011;38(9):2055-2062. [CrossRef]
50. Collado P, Naredo E, Calvo C, et al. Reduced joint assessment vs comprehensive assessment for ultrasound detection of synovitis in juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2013;52(8):1477-1484. [CrossRef]