Ultrasound imaging in juvenile idiopathic arthritis for the rheumatologist

P. Collado Ramos

Department of Rheumatology / Paediatric Rheumatology Unit, Hospital Universitario Severo Ochoa, Madrid, Spain.

Paz Collado Ramos, MD, PhD
Consultant Rheumatologist and Paediatric Rheumatologist

Please address correspondence to:
Paz Collado Ramos,
C/ Corazón de María 55, 2ºA,
28002 Madrid, Spain.
E-mail: paxcollado@yahoo.es

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ABSTRACT

The present review provides an update of the currently available data and discusses research issues of US imaging in juvenile idiopathic arthritis (JIA). This review also includes a brief description of the normal sonoanatomy of healthy joints in children in order to avoid misinterpretation.

Musculoskeletal ultrasound (US) is a quick, inexpensive, bedside method for evaluating children with no need for anaesthesiological support. Until now, the major objective in the application of US in children is to improve clinical diagnosis and patient care in daily practice. Articular disorders in children affect the epiphyseal cartilage leading to alterations in maturation and growth. US imaging allows distinguishing between synovitis and joint cartilage as well as between articular and peri-articular structures. Currently the principal applications for using US in patients with JIA include: detection of synovitis, tenosynovitis, enthesitis and cartilage and bone abnormalities. US is also used to guide needle injection. To date, the role of US in therapy monitoring has not been fully established.

Future topics for study include: establishing international definitions (B-mode and Doppler) for joint components in healthy children and for US findings in JIA patients, consensus on scanning protocols and scoring systems, evaluation of the role of US with power Doppler in the assessment of the real state of disease (activity/remission) and developing a specific training programme for paediatric rheumatologists performing US in patients with JIA.

Introduction

Musculoskeletal ultrasound (US) is a quick, inexpensive, bedside method for evaluating children with no need for anaesthesiological support. US is routinely used by increased number of rheumatologists and paediatric rheumatologists in their clinical practice. The major objective in the application of US in children is to improve clinical diagnosis and patient care.

The US evaluation of articular disorders in children differs from adults in several important aspects. Aside from the articular cartilage, articular disorders in children affect the epiphyseal cartilage and the shape and contour of the epiphysis and the growth plate. Arthritis can have a profound and lasting effect on maturation and growth.

The steady advance in US investigation in the paediatric rheumatology field has allowed it define its usefulness in inflammatory diseases (*e.g.* juvenile idiopathic arthritis) and infectious diseases (*e.g.* osteomyelitis) (1-13).

The term juvenile idiopathic arthritis (JIA) encompasses a group of clinically heterogeneous arthritides characterised by a chronic inflammatory process of the synovium and periarticular tissue that can lead to structural damage. The International League of Association for Rheumatology (ILAR) proposed a current classification for JIA that aims to enable identification of homogeneous groups of children suitable for etiopathogenetic studies (14).

The presence of joint involvement in JIA may be expressed by ultrasonographic findings such as synovial proliferation, effusion, cartilage thinning and bone erosions. US has demonstrated higher sensitivity in detecting synovitis compared to clinical examination (1-4). US has proven earlier detection of synovial and bone abnormalities than conventional radiology (5). Repeatability and the possibility of examining several joint regions at one session are of paramount importance for monitoring joint damage in JIA. US can be used to assess tenosynovitis and enthesitis and to guide needle aspiration or injection (6, 7). In addition, the use of Doppler techniques facilitates detection of synovial vascularisation in identifying

active disease (8). However, the real validity of US for assessing inflammation activity, monitoring therapeutic response and prognostic evaluation has not been defined yet.

The present review provides an update of the available data and discusses research issues of US imaging in JIA. This review also includes a brief description of the normal sonoanatomy of healthy joints in children in order to avoid misinterpretation.

Clinical applications

Currently, from a paediatric rheumatologic perspective, the principal indication of US in JIA is direct visualisation of synovitis (*i.e.* effusion and synovial hypertrophy) in peripheral joints and tendon sheaths in a few minutes, even when clinical examination does not evidence abnormalities. Whereas the major limit in US joint accessibility is its applicability in the temporomandibular joint (15). US allows the differentiation between synovial and entheseal inflammation. In addition, US may enable precise and earlier classification of a patient with JIA into different JIA categories because multiple joints can be assessed during a single session. That is why US might be particularly relevant in the current ILAR classification. Consequently, it would have important implications for early therapy management and follow-up (16).

US is the best available technique for imaging guidance of needle position within inflamed joints and tendon sheaths for aspiration of effusion and local injection of steroids, providing better outcomes in JIA and reducing the risk of damaging epiphyseal cartilage (7). This is also important for patients with the enthesitis-related arthritis subtype characterised by tendineous and entheseal involvement. They may get great benefit from accurate perilesional (*i.e.* enthesitis) therapy.

As in other inflammatory arthritis, other main indications for US examination in JIA are detection of tendonitis, bursitis and synovial cysts, as well as bone erosions earlier than conventional radiography (5). Colour and Power Doppler (PD) techniques provide information on the vascularisation of the synovial and soft tissues reflecting vascular abnormalities and active inflammation.

Over the last few years, the clinical application of US in JIA has extended to the defining of US pathologic findings and therapy monitoring in JIA patients. Future potential applications are the determination of a scoring system for the assessment of synovitis, as well as, the demonstration of early detection of changes in the epiphyseal cartilage

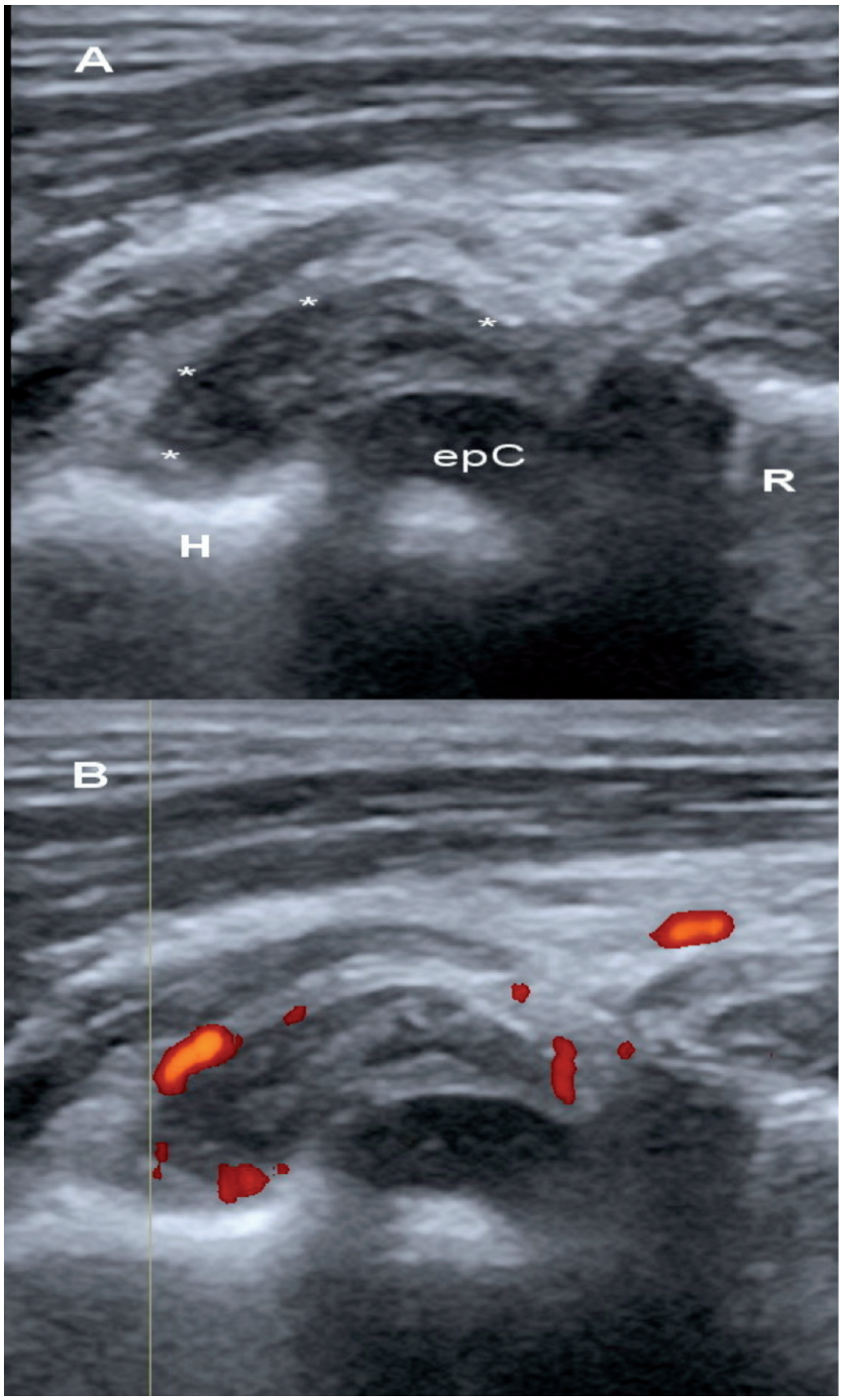

Fig. 1. Juvenile idiopathic arthritis. Longitudinal scan of the elbow joint (anterior radiocapitellar joint) in a 4-year-old child.
A. B-mode US sonogram shows effusion and synovial hypertrophy (*) extending on the cortical of humeral (H) bone, the epiphyseal cartilage of the humeral capitullum (epC) and the cartilaginous non-ossified radial head (R). Note the interface sign between the synovial hypertrophy and the epiphyseal cartilage of the capitullum.
B. Doppler-US. Synovial vascularisation detected by power Doppler reflects disease activity.

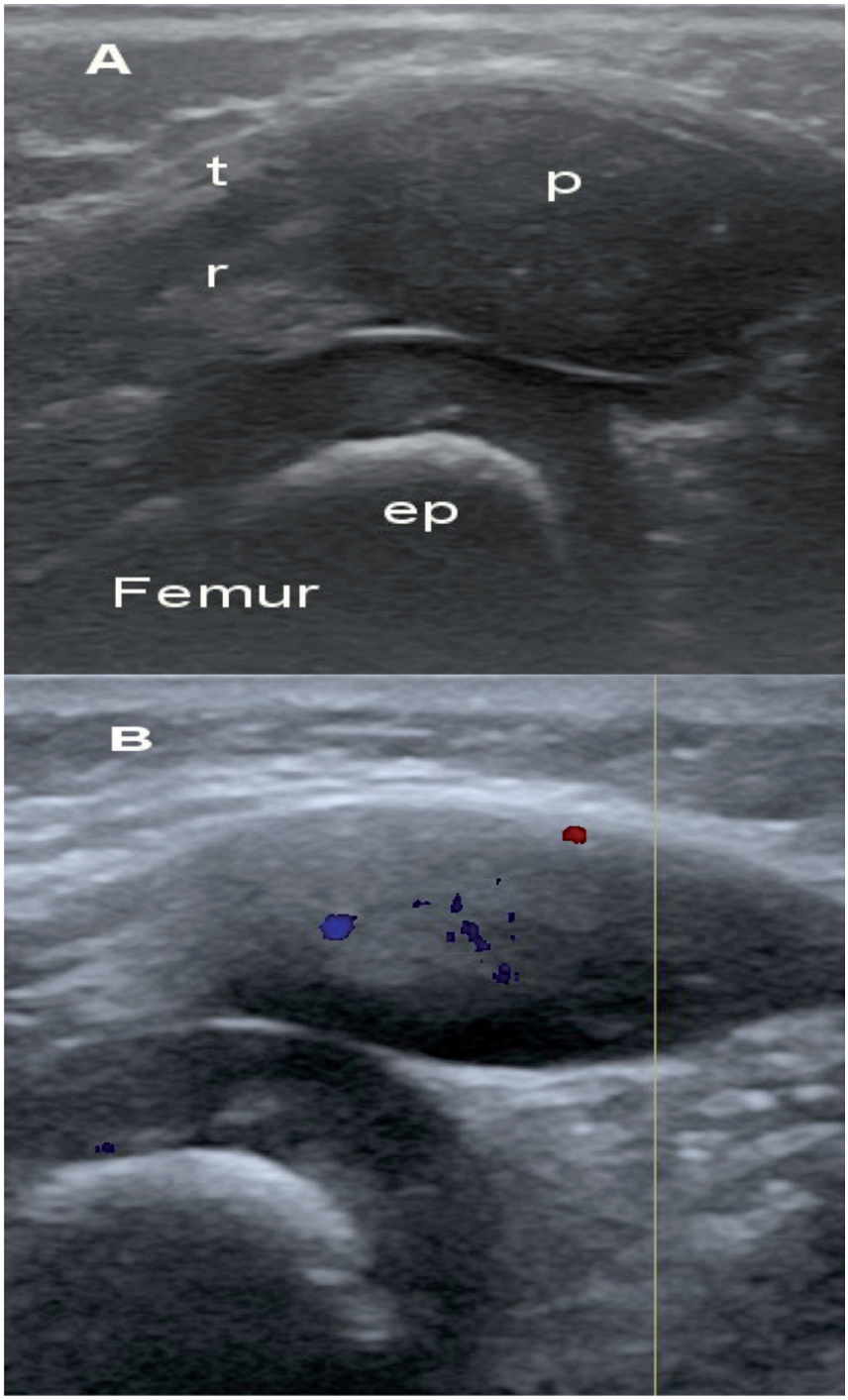

Fig. 2. Anterior longitudinal US scan of the knee in a healthy 2.5-year-old child.
A. B-mode US. The anechogenic anterior structure (p) is the cartilaginous non-ossified patella. Note the presence of mild physiologic fluid in the suprapatellar recess (r) and the surface of cartilaginous structures detected as a hyperechoic line (or interface sign). The epiphyseal cartilage is surrounding ossific centre of epiphysis (ep) of the femoral bone. t: quadriceps tendon.
B. Doppler-US. Note the two Doppler signals within the cartilaginous non-ossified patella due to vascularisation of feeding vessels.

taking into account normal age-related variations of the growing skeleton. Ultrasonographic assessment of structural damage in JIA is challenging due to the lack of studies documenting the sonoanatomy in healthy children (17-20).

Sonographic findings

Synovitis

Effusion and synovial hypertrophy can easily be imaged in peripheral joints of patients with JIA (Fig. 1A-B). Definitions of JIA pathology have varied in different US studies as a recent systematic review showed (21). Nevertheless, the current tendency is to apply the definitions of synovitis provided for adult rheumatoid arthritis (RA) by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Special Interest Group for musculoskeletal US in rheumatology (22). In children, it is crucial to keep in mind the US image of cartilaginous ends of long bones forming joint in order to distinguish it from synovitis. Since growth cartilage contains a high amount of water; it usually appears as an anechoic, well-defined shaped structure. The US appearance of joint cartilage in children seems thicker than in adults because the individual components of the joint cartilage (articular and growth cartilages) are initially continuous with each other. They are usually displayed as a single anechoic structure, particularly in early ages. The challenge in assessing synovitis has been dramatically minimised thanks to technology that has considerably evolved US equipment. Nevertheless, real time (or dynamic) examination is the most reliable method of scanning in children in order to distinguish between synovitis and joint cartilage.

Over the last two years, the paediatric subgroup of the OMERACT-US group has been working on providing preliminary definitions of the individual components of the healthy joint on B-mode US (or grey-scale US) that might support the interpretation of US findings in children with JIA. Synovial effusion is defined as compressible and displaceable, synovial hypertrophy as poorly compressible whereas the epiphyseal cartilage is not. Preliminary definition for the growth cartilage on B-mode describes it as a well-defined anechoic structure that is non-compressible and whose surface can (but does not have to) be detected as a hyperechoic line (Fig. 2A). On Doppler-US, preliminary definition has not been provided yet. Unlike adults, Doppler signal within the joint cavity does not only mean inflamed synovial proliferation, as vascularisation can be present in both proliferation of synovial membrane and cartilaginous epiphyses. The latter can show Doppler signal due to the vascularisation of feed-

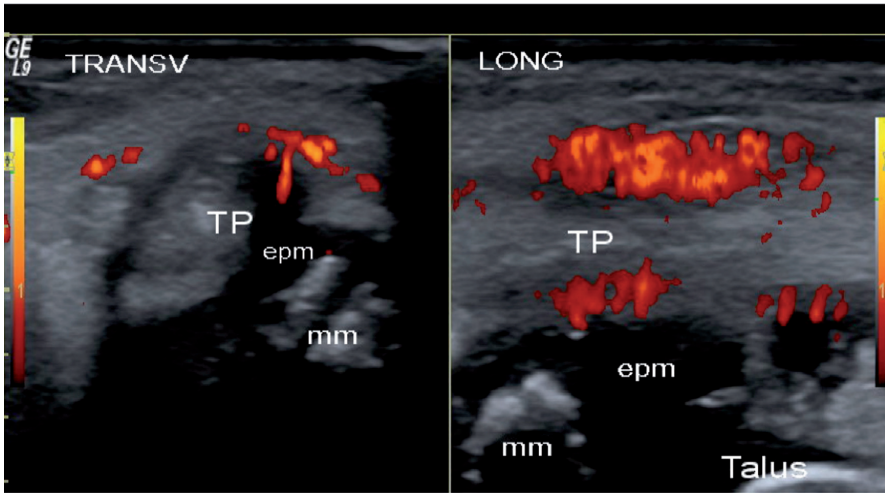

Fig. 3. Juvenile idiopathic arthritis. Longitudinal (left image) and transverse (right image) scans of the ankle joint at the level of the medial malleolus (mm) shows tenosynovitis of tibialis posterior (TP) in a 9-year-old child. Synovial vascularisation detected in the tendon sheath by power Doppler reflects disease activity. The epiphyseal cartilage of malleolus (epm) is visible in both transverse and longitudinal scans as an anechoic structure. Dynamic examination allows distinguishing the epiphyseal cartilage of malleolus from effusion/synovitis.

ing vessels (Fig. 2B). The literature has reported that the presence of enhanced vascularisation of the growth cartilage or hyperaemia of the hypertrophic synovium indicate joint inflammation (23). It is important to consider the existence of both findings when interpreting US images in patients with JIA. This is particularly needed for the youngest children in order to distinguish between active synovitis and inactive residual hypertrophic synovium when disease remission is evaluated (24, 25).

Tenosynovitis

Tendon sheath widening is the hallmark of tenosynovitis that can be detected by US in JIA patients, particularly in the ankle region (7, 10, 11) (Fig. 3). The US appearance of tenosynovitis is the same in patients of all ages. Studies focusing on the US detection of tenosynovitis in hands are scarce and some data have shown the presence of small amount of fluid within tendon sheath as physiological finding (18, 26). Tendinosis can be also detected by US. According to the tendon involved by inflammation, tendon thickening can be associated to tendon sheath widening or not. Isolated tendon thickening can be visualised particularly in Achilles tendon (6). Tendon thickening is often associated with decreased echogenecity. US is a sensitive method for detecting synovial cyst and bursae as pouch of hypo/anechoic material that can present associated Doppler signal in active disease (6, 27-29).

Enthesitis

Enthesitis, *i.e.* the inflammation of the insertion of tendons, ligaments, aponeuroses and joint capsules on bones, is a common feature in children with enthesitis-related arthritis (ERA) and some juvenile spondyloarthritis (SpA), involving mainly the lower limbs (6). A definition of enthesitis has been provided by the OMERACT US group for adults (22). The US appearance of enthesitis on B-mode is the same in all patients with inflammatory disease irrespective of age. Nevertheless, the role of Doppler technique in giving additional information about active inflammation of infantile entheses has not been established yet. When a growing child is examined by Doppler-US, peripheral flow on the non-ossified apophysis can be detected indicating blood flow at feeding vessel level. On the other hand, even though Doppler use in the evaluation of enthesitis seems to be important in adults, a wide heterogeneity in its use has been recorded recently (30). Doppler sensitivity to inflammatory flow (low-velocity-flow) depends partly on the settings and partly on the equipment.

Erosion

According to the OMERACT-US definition in adults, erosion is a break or discontinuity of the bone surface (22). However, the physis (or the growth plate) is visualised as a discontinuity of cortical bone throughout the childhood until the child's skeleton reaches maturity. In addition, the US appearance of physiological bone irregularities at the ossification centre might be misinterpreted as bone erosions. The presence of other pathologic findings along with erosion avoids those mistakes (Fig. 4).

US findings including definitions in joints, tendons and entheses used in patients with JIA are summarised in Table I.

Literature review

Ultrasound for detecting synovitis

US validity for the diagnosis and follow-up of synovitis in JIA has been recently reviewed by Collado *et al*. (21). US has been found to be a valuable tool for the detection of synovitis in JIA. However, the reliability and responsiveness of US in evaluating changes in synovitis over time should be further assessed. As US has demonstrated higher sensitivity in detecting synovitis than physical examination (PE), some authors have found a prevalence from low to moderate of subclinical synovitis on B-mode US, particularly in the small joints of hands and feet (1-4, 11). Only two of the studies mentioned reported some data of joints involved with positive PD (1, 4). In 32 patients with active JIA, Magni-Manzoni *et al*. (1) assessed a total of 1664 joints both clinically and with US. Of the 1560 clinically normal joints, US examination detected synovitis in 86 (5.5%). Nevertheless, they did not provide separate data for the presence of PD alone or associated with US synovitis in grey-scale. Similarly, Filippou *et al*. (2) reported a low percentage of joints with subclinical synovitis (1%, calculated from data reported in the paper, of 1195 joints with negative PE only detected 12 joints with synovitis on B-mode US) in 31 children evaluated. However, the study population included a heterogeneous group of diseases given that the inclusion criteria were patients with suspected JIA referred by their family paediatrician

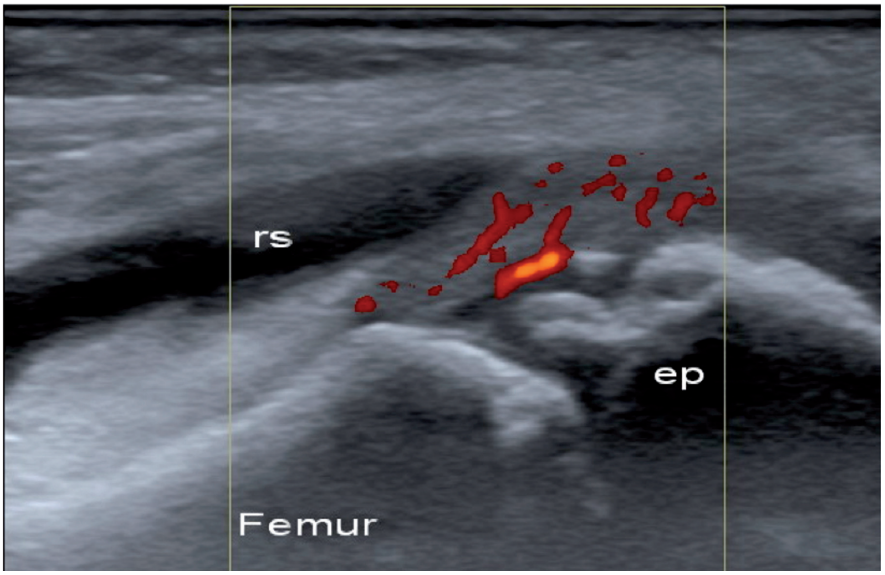

Fig. 4. Juvenile idiopathic arthritis. Anterior longitudinal US scan of the knee in a 7-year-old child. Bone erosion in ossific centre of epiphysis (ep) of the femur surrounded by hypertrophied synovial tissue with hyperaemia. Power Doppler examination also shows vascularisation at the level of the erosive lesion and cartilage surface. Note the presence of pathological effusion in the suprapatellar recess (rs).

Table I. Pathological findings in juvenile idiopathic arthritis (JIA) and corresponding definitions for ultrasound (US) pathology according to OMERACT Special Interest Group.

US pathological findings in JIA	
Joint effusion	Abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible, but does not exhibit Doppler signal;
Synovial hypertrophy	Abnormal hypoechoic intra-articular tissue that is non displaceable and poorly compressible and may exhibit Doppler signal;
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath that is seen in two perpendicular planes and which may exhibit Doppler signal;
Tendinosis	Focal or global thickening and hypoechogenicity of the tendon with abnormal heterogeneous echotexture which may exhibit a hypervascular pattern at Doppler US;
Enthesitis	Abnormal hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament as its bone attachment (may contains hyperechoic foci consistent with calcification) seen in two perpendicular planes that may exhibit a Doppler signal and/or bony changes such as enthesophytes, erosions, or irregularities;
Cartilage thinning	Alteration in the contour seen as blurring and obliteration of the normally sharp margins of the cartilage surface;
Bone erosions	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes.

and presenting ≥1 painful joint with or without swelling for more than 2 weeks. In Haslam's study, 17 patients with early oligoarticular JIA (a total 680 joints) were evaluated, 6 of patients had synovitis only on US (3). Breton *et al*. (4) compared PE and US examination for evaluation of synovitis, limiting their study to metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints. Thirty-one JIA patients were included and 558 joints were evaluated. US synovitis was found in 38 (7%) of the 512 joints without clinical swelling. Regarding the role of Doppler in their study, they reported that synovial vascularisation was significantly associated with JIA but it was not seen in the healthy controls. There was no specific mention about PD in joints with subclinical synovitis.

A plausible explanation for the subclinical synovitis in JIA has been suggested by Janow *et al*. (31). Fourteen joints exhibited sonographic findings of active disease but were inactive on PE (9 knees, 5 ankles), but on follow-up PE, 35.7% (5/14) developed signs of active arthritis, suggesting the probable presence of subclinical disease at the time of the initial PE. Moreover, identification of subclinical synovitis on US leads to early and accurate patient classification that may support treatment decision in clinical setting and inclusion of patients in clinical trials (1-3, 16). Nevertheless, the prognostic significance of such subclinical synovitis still needs to be determined. On the contrary, some papers aboved mentioned reported a small number of joints classified as having clinically synovitis but had no evidence of US synovitis (1-4).

Ultrasound for detecting tenosynovitis

Tendons can be affected throughout the whole course of JIA. US is able to distinguish articular and peri-articular inflammation. Using US, Rooney *et al*. (10) evaluated the prevalence of synovitis and tenosynovitis in 34 JIA patients who had clinically detected swelling in 49 ankles. Only 29% of ankles had tibiotalar effusion alone, whereas associated tenosynovitis and tenosynovitis alone were detected in 71 and 39% of ankles, respectively. Pascoli *et al*. (11) compared the PE and US examination in 61 swollen/painful ankles. US demonstrated no signs of tibiotalar disease in 32% of the ankles considered clinically involved, whereas involvement of medial and lateral tendons was detected in 42% and less than 50% of ankles were recorded as clinically normal.

Ultrasound for detecting enthesitis

Although enthesitis is a common feature of ERA and the juvenile form of SpA (14), the scarcity of studies focusing on US evaluation of this entity in childhood is surprising. Jousse-Joulin *et al*. (6) compared US with PE in the detection of enthesitis in 26 patients (213 enthesal sites) with JIA. The authors defined enthesitis as a PD signal at the insertion into the cortical bone. It was detected in 20 (9.4%) sites, particularly in patients with oligoarthritis and polyarthritis. Additionally, cartilage

vascularisation was noted at only 3% of entheseal sites in JIA, but it was not associated with PD-US enthesitis. They found that clinical entheses involvement and HLA-B27-positive status were significantly associated with enthesitis detected by PD US. Subclinical enthesitis was reported in 10 (50%) of the 20 sites exhibiting PD-US enthesitis (6). Unlike adults, there is no gold standard MRI technique that fully supports the claim that subclinical synovitis and enthesitis detected in childhood truly represent active disease.

In a fully descriptive study, Laurell *et al*. (32) documented all possible imaging findings of JIA (*i.e*. considering synovial hypertrophy, synovial perfusion/enhancement, effusion, bone erosions, and bone oedema). Eleven JIA patients with clinically active joints (2 ankles, 3 knees and 6 wrists) were assessed by US and MRI. Additionally, they used healthy controls belonging to another hospital. They investigated whether the US and MRI findings involved the same areas. The conformity of both imaging findings in the areas examined was high except for erosions. Doppler flow was detected in 86% of the 22 diseased areas with synovial hypertrophy on US. No synovitis (synovial hypertrophy and/or synovial perfusion) or erosions were detected in any healthy controls. Slight effusion was the only finding detected in healthy controls (5 joints by US and 6 by MRI). The authors acknowledged that it is a study with several limitations, and thus their results need to be confirmed in a larger prospective clinical investigation.

Ultrasound for multiple joint examining

One of the advantages of US is the potential for multiple joint examining. US assessment of a large number of joints at one session in order to evidence active disease is clearly tedious and time-consuming in daily practice. To determine the number and which specific joints to examine with US for detecting synovitis have been currently addressed. A recent study highlighted the usefulness of a reduced US assessment (33). The authors reported that a number of 10 joints, including bilateral knee, ankle, wrist, elbow and the 2nd metacarpal joints, yielded excellent sensitivity for detecting grey-scale synovitis and PD signal in patients with JIA. Reduced US assessment showed a high correlation with a comprehensive assessment of 44 joints at a 3- and 6-month follow-up. The authors suggested that a targeted approach to US joint examination is comparable to a more comprehensive assessment.

Ultrasound for treatment monitoring

To date, except for US-guided injections, as a form of treatment in JIA, few papers on US therapy monitoring have been published. Short-term monitoring with US has show significant changes in joint inflammation after the administration of steroids and NSAIDs (7, 26, 34-36). A reduction of effusion, synovial hypertrophy and intraarticular Doppler signal has been demonstrated with intraarticular steroid injection. Data from a recent study supports the evidence that US-guided injections in the talocrural and subtalar joints resulted in better outcome of injections in ankle disease in JIA (7). The same author has carried out injections in the radiocarpal joint, the midcarpal joints and tendon sheaths at the wrist level (26). Kakati *el al*. (34) examined the knee joints in 30 patients (14 monoarticular and 16 with bilateral knee involvement) treated with naproxen (15–20mg/kg/day). Quantitative assessment of effusion and synovial thickness (anterioposterior diameter) were evaluated at the six-month follow-up, demonstrating statistical changes in the US findings detected. Similarly, a positive therapeutic effect was obtained with anti-TNF-alpha therapy for enthesitis in a 13-year-old boy with ERA and HLA-B27-positive who was serially evaluated at a two-year follow-up (37).

Ultrasound for detecting cartilage and bone damage

As US clearly displays the cartilage of unossified epiphyses, it may be appropriate for the evaluation of cartilage thinning as an early marker of joint damage in JIA. US is able to show the ossific nuclei much earlier than when it becomes visible radiographically in the immature skeleton. Spannow *et al*. (19) were the first authors to delineate the normal ranges of cartilage thickness in the small and large joints in healthy children by US. They reported a good intra- and interobserver agreement in the evaluation of cartilage thickness in several joints, using US standard scans according to EULAR guidelines. More recently, Spanoff *et al*. (20) studied a large cohort of healthy children to establish normal age- and sex-related standards for cartilage thickness. They reported thicker cartilage measurements in boys than girls in the knee, ankle, wrist, second MCP and second PIP joints. They also documented a progressive reduction in the thickness with age. Although those values are of potential interest to provide reference values in various joints to evaluate children with JIA, further investigations that focus on patients with JIA are needed. Malattia *et al*. (5) studied the sensitivity of imaging modalities, including conventional radiography, US and MRI, in the detection of erosion at wrist and MCP joints in JIA patients. They found that more than 90% of the children evaluated showed one or more erosions as detected by MRI, whereas conventional radiography and US revealed erosions in 50%, showing that MRI has better sensitivity in patients with a shorter disease duration. Interestingly, the authors also reported that US was superior to conventional radiography in the detection of bone lesions in some carpal bones that are more accessible for US evaluation. More recently, Muller *et al*. (38) studied the wrists of healthy children and documented some bone changes resembling small erosions. Therefore, longitudinal studies are needed to establish the real significance of bone erosions detected only by MRI.

Ultrasound-evaluated disease remission

The traditional method used to evaluate disease remission in patients with JIA is based on clinical and laboratory parameters (39). US has recently been used to attempt to detect patients in disease remission, as the traditional method does not seem to be sufficient in

ensuring full biologic inactivity of disease. Some studies have demonstrated that a clinically important number of patients in remission continue to have abnormal US findings, particularly in the wrist and ankle joints, including positive PD signals (24,25). Magni-Manzoni *et al*. (25) studied 39 JIA patients (52 joints) who had clinically defined inactive disease for a minimum of 3 months for US assessment of synovitis and tenosynovitis. Synovial hyperplasia, joint effusion, PD signal and tenosynovitis in at least one joint were detected in 76.9%, 66.7%, 33.3% and 15.4% of patients, respectively. Additionally, the patients were followed clinically for up to 2 years. Although the patient group with persistent inactive disease had a greater frequency of PD signal than patients with synovitis flare, the frequency of the rest of the findings was comparable between the two groups. Nevertheless, the author concluded that the presence of those US abnormalities on US did not predict subsequent synovitis flare in JIA. This finding contrasts with the observation in adult RA in which vascularisation detected by PDUS has been shown to be a predictor of the conversion of subclinical synovitis to clinically overt synovitis (40). The clinical relevance of this observation for JIA patients in clinically remission remains a critical issue that needs to be addressed.

Research agenda

The use of US in JIA has several limitations including the lack of a scanning protocol and scoring system for the main abnormalities which can be visualised. Furthermore, due to the already-mentioned peculiarities of the growing skeleton, knowledge of the normal paediatric sonoanatomy is mandatory in order to establish whether the visualised findings are pathological or not.

Recently, a paediatric US subgroup within the OMERACT Special Interest Group for musculoskeletal US has been developed. Currently, great efforts are being made to reach a consensus on the definitions of the individual components of the healthy joint that might support a correct interpretation of findings in children with JIA. Longitudinal studies are required to determine the clinical importance of Doppler US findings in children, particularly those who are asymptomatic.

One of the advantages of US in children is the potential for multiple joint examination. As there is some evidence to suggest that a targeted approach of 10 joints for US-determined synovitis in JIA is comparable to a comprehensive assessment, its applicability in a clinical setting would be a support for demonstrating its usefulness as screening in patients with active disease.

Given that US is the most operator-dependent modality, specific training should be introduced for paediatric rheumatologists. Over the next few years, a great deal of effort should be made to standardise and validate the methodology for performing US and scoring US findings in children. In addition, further studies are needed to enhance the reliability of US in JIA and to establish its validity in the assessment of therapeutic response.

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