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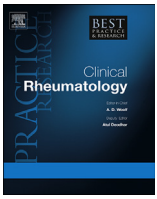

Ultrasound imaging in paediatric rheumatology

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A B S T R A C T

The role of ultrasound imaging in the diagnosis and monitoring of paediatric rheumatic diseases with special emphasis on recent scientific work regarding the evidence base and standardization of this technique is being reviewed. An overview of the most important practical aspects for the use of musculoskeletal ultrasound in a clinical setting is also provided.

Huge scientific efforts and advances in recent years illustrate the increasing importance of musculoskeletal ultrasound in pediatric rheumatology. Several studies focused on setting an evidence-based standard for the ultrasound appearance of healthy and normal joints in children of all age groups. Physiologic vascularization and ossification were two main aspects of these studies. Other publications demonstrate that ultrasound imaging is also an important and useful tool to detect pathology as synovitis, tenosynovitis or enthesitis in children and to monitor pediatric patients with rheumatic conditions. Important practical aspects include training in the use of correct ultrasound techniques, as well as knowledge and experience of normal pediatric sonoanatomy and the appearance of pathological findings on ultrasound.

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Introduction

Over the last 15 years musculoskeletal ultrasound (MSUS) has become the most important technical tool for the examination of joints in pediatric patients [1–5]. By using MSUS routinely to examine painful joints in the upper and lower extremities, many pediatric rheumatologists report significant improvements in the precise diagnosis of various joint conditions like arthritis, tenosynovitis or enthesitis compared to the clinical examination alone [6–10]. Unlike conventional radiography, MSUS has a higher sensitivity to detect any soft tissue lesions or even early cartilage or surface bone damage, without using ionizing radiation. The on-going development of high frequency transducers and high resolution ultrasound (US) devices has led to an image resolution comparable and in fact superior to MRI. MSUS is a well-tolerated non-invasive diagnostic tool in paediatrics which does not require sedation. Unlike MRI, MSUS can easily be performed at the point of care by clinicians routinely at the time of the physical examination, providing the advantage of a real-time multi-joint assessment. In addition, a dynamic MSUS evaluation can significantly improve the interpretation of findings seen on a static image. For example, the dynamic assessment of patients allows a quick and reliable distinction of joint effusion, synovial thickening and epiphyseal cartilage, which is of particular importance when examining the growing skeleton. Despite its many strengths, MSUS has some limitations in the complete evaluation of musculoskeletal systems (Table 1). Since US waves cannot penetrate bone, MSUS is unable to assess bone marrow edema, deep intra-articular regions and specific joints (e.g. the spine and sacroiliac joints). MRI remains the gold standard for detecting temporomandibular joint (TMJ) and axial inflammation [2,4,5,7]. In addition, the diagnostic potential of MSUS is strongly related to the type of equipment available and to the skill of the examiner using it.

Several studies have demonstrated the importance of MSUS in evaluating rheumatic conditions in children, particularly juvenile idiopathic arthritis (JIA) [2,3,5]. Evidence for using MSUS routinely in pediatric rheumatology is currently increasing on the basis of several studies providing MSUS normative data and international consensus standards for MSUS examination, interpretation and scoring of inflammation [11–20].

MSUS technique in children

MSUS requires a solid knowledge in ultrasound technique for safe and accurate results. The correct scanning technique and choice of resolution and calibration of the US equipment are crucial to avoid the most frequent artefacts that can mimic disease.

Table 1
Advantages and disadvantages of musculoskeletal ultrasound in children with juvenile idiopathic arthritis.

Advantages	Limitations
• High-resolution soft tissue imaging. • Non-invasive. • Lack of exposure to ionizing radiation. • No need to sedate children. • Ability to image in real-time. • Possibility of examining multiple joints at one time. • Enables rapid contralateral limb examination for comparison. • Dynamic examination of anatomic structures. • Ability to guide procedures (e.g., aspirations, injections). • Repeatability. • Portable. • Relatively inexpensive. • Demonstration of soft tissue inflammation. • Early detection of bone erosions and cartilage damage.	• Limited field of view. • Acoustic shadowing from overlying bones. • Inability to assess the whole joint space. • Limited value in the assessment of axial skeleton and temporo-mandibular joints. • Operator dependency. • Absence of standardized paediatric-specific imaging protocols and guidelines. • Lack of validated scoring systems to grade the severity of US abnormalities.

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Scanning younger children with painful joints is sometimes a challenge and parents play an important part in creating a comfortable examination environment for the child. Warm US gel, any toy or a monitor to distract children may help to achieve the optimal conditions for the US examination.

For the best resolution, high US frequencies are used. The smaller geometric dimensions of joints in younger patients benefit from the use of higher frequencies (up to 22 MHZ), which can demonstrate all aspects of joints and tendons at high resolution. MSUS in pediatric rheumatology is generally performed with different linear probes depending on the joint region and depth. For smaller joints of the wrist, hand and foot, frequencies of 12–22 MHz are recommended. Medium-sized joints such as the knees and shoulders are normally examined with 10–15 MHz, and deeper joint regions like the anterior hip recess are best scanned with probes between 5 and 10 MHz. In some adolescent patients, higher penetration with lower frequency is needed.

Some articles already suggest standard positioning for pediatric patients and standard planes for different joint regions as a basis for the US examination [12,13,21]. Recently, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) group has studied different scanning planes of knee joints affected by arthritis [21]. However, an international standard to examine affected joints and tendons in children does not exist at this point.

To examine potentially involved joint regions, both B-Mode and Doppler-Mode (Color Doppler, CD or Power Doppler, PD) have to be used. B-Mode resolution has to be set at the highest possible resolution and Doppler Mode at the highest sensitivity to adjust for the very low velocity blood flow in the small vessels inside the synovium (pulse repetition frequency between 0,6 and 0,8 kHz) [22]. Increased blood flow on Doppler Mode should only be considered as a marker for inflammation if it is detected within the synovial proliferation. Additional positive Doppler signals in children may also occur from intraarticular or periarticular physiologic feeding vessels [12,13].

The intravenous administration of a microbubble-based US contrast agent may be of benefit in identifying disorders with abnormal blood flow by enhancing the blood pool echoes. Doria et al. used contrast-enhanced color Doppler US to evaluate the knees in 22 children with JIA and found improved detection of active synovial inflammatory disease in patients in apparent clinical remission [23]. Further studies are required to prove any real benefit for the use of contrast-enhanced ultrasound (CEUS) compared to CD or PD in the routine setting to examine pediatric joints.

Importance of MSUS in JIA

JIA is the most common rheumatic disorder in the pediatric population and it is characterized by an inflammatory process primarily targeting the synovial membrane and the periarticular tissues. JIA is not a single disease but a diagnosis of exclusion which includes all forms of chronic arthritis that begin before the age of 16 years, persist for more than 6 weeks and are of unknown origin. The current classification for JIA recognizes several disease categories with distinct clinical features and, in some cases, genetic background. Despite the heterogeneity, all forms are characterized by chronic synovial and/or entheseal inflammation, which, if not adequately controlled, may ultimately lead to cartilage loss and bone damage and subsequent long-term functional disability. The disease course of JIA is highly unpredictable: in some patients it is characterized by self-limiting disease and in others by unremitting disease with substantial risk of joint destruction. Over the last decades the prognosis of the disease has improved dramatically due to the availability of novel drugs, such as biological agents, which are able to selectively inhibit the cytokines involved in the pathogenesis of the disease. However, not all patients require an aggressive treatment. Therefore, methods to improve diagnosis and prognosis as well as sensitive tools to assess treatment efficacy have become a high priority in order to tailor treatment strategies. From this perspective, MSUS is playing an expanding role in diagnosing, managing and monitoring the course of JIA [1,2,4,5]. MSUS is increasingly being utilised whenever there is a clinical diagnostic doubt in children with suspected JIA [24]. Important differential diagnoses like soft tissue infections, traumatic lesions or other inflammatory conditions can be safely excluded in most cases by MSUS. In addition, MSUS plays a pivotal role to precisely identify the site of inflammation by differentiating between synovial, tendinous and entheseal involvement, especially in complex joints such as the ankles [25].

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Several studies have already demonstrated that US has a better sensitivity for the evaluation of joint inflammation than the physical examination [26–29]. The high sensitivity of MSUS in detecting joint inflammation may be useful to avoid a delay in JIA diagnosis and to take advantage of the "window of opportunity" in early disease. From a similar perspective, US has been incorporated into the diagnostic algorithm of the 2010 revised diagnostic criteria for rheumatoid arthritis (RA), with the aim to favour early diagnosis and an accurate assessment of the extent of joint involvement.

Pilot studies have shown that MSUS, by directly visualizing inflammation at the primary site of pathology, is more sensitive than clinical findings to track changes in response to treatments. Lanni et al. have recently demonstrated an excellent sensitivity to change of MSUS in the assessment of synovitis in a cohort of new onset JIA patients who started treatment for their disease. Of note, the authors found that more than 60% of patients considered to be in remission based on clinical evaluation showed persistent inflammation on MSUS examination, with potential implications for treatment strategy [28]. A study into the impact of the detection of subclinical disease by MSUS has recently been published [30]. Results of this study have demonstrated that US-detected residual synovitis significantly increased the risk of disease flare in a large cohort of clinically inactive JIA patients. Particularly, positive Doppler signals within the hypertrophic synovium seem to play a main role for predicting disease relapse. Persistent Doppler signals have also been shown to correlate with recurrence of synovial inflammation and the development of structural damage in RA [31,32].

It remains unclear whether subclinical synovitis in JIA also entails a risk of silent progression of joint damage and whether it should influence the physician's decision to discontinue therapies.

Despite the fact that the value of MSUS in the assessment of JIA is well established, MSUS remains underused in the assessment of patients with JIA in both clinical practice and the research setting [33]. Possible explanations include the lack of paediatric-specific imaging protocols and guidelines. Another key point concerns the shortage of US-trained pediatric rheumatologists. The training required to identify the specific changes of the immature skeleton is, in fact, lengthy and very challenging. There are some typical differences in pediatric joints on MSUS images, which are very important to recognize in order to avoid misinterpretation. For a better discrimination between physiologic or pathologic findings in JIA, several studies focused on physiologic MSUS findings in children in recent years [11–20].

- MSUS is playing an expanding role in diagnosing, managing and monitoring the course of JIA.
- Several studies have already reported that US has a better sensitivity for the evaluation of joint inflammation than the physical examination.
- MSUS remains underused in the assessment of patients with JIA in both clinical practice and research setting.

Physiologic MSUS findings in pediatric joints

The musculoskeletal system undergoes dramatic changes during growth. At birth, most of the skeleton is cartilaginous and cortical bone is present in most long bone diaphyses, which represents the primary area of ossification. With the advance of skeletal maturity the ephiphyseal secondary ossification center will appear. Being familiar with the evolving patterns of normal development is paramount for a correct interpretation of MSUS images and to avoid misdiagnosis. Before describing abnormalities in pathological conditions, it is important to define B-mode and Doppler US findings in healthy children, including different age groups. For this reason, a few national and international pediatric MSUS working groups, e.g. the Pediatric Task Force of the OMERACT US Group, were created to validate the use of US in the assessment of joints in healthy children. For example, the work of the OMERACT Pediatric US Task Force has involved several steps and publications towards this goal. Definitions of US findings in healthy children were developed and confirmed by consensus [11]. A standardized US scanning procedure for children of different age groups was created, images showing physiologic ossification and vascularization at different joint sites were collected followed by an international multi-observer test and necessary amendments to the definitions [11–13,34]. To collect more normative MSUS data about important joint sites, national working groups collaborated to provide data for the knee, shoulder, hip, elbow, hand and wrist joints [14,16,18–20]. A common finding in all joints was the prominent cartilage in younger children due to the incomplete ossification of the

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epiphyses and apophyses. Discrimination between synovial inflammation and the adjacent unossified cartilage is particularly difficult in very young children, because all these structures may have a similar, hypoechoic appearance. Dynamic evaluation is particularly helpful to accurately distinguish different joint structures. In fact, the unossified cartilage will retain the contour during joint movement, whereas fluid will change its shape. These studies have also highlighted the fact, that in children cartilage vascularization patterns differ from those in adults and show age- and joint-related variability in US. A sound knowledge of the physiological vascularization of the immature skeleton is essential for correct interpretation of the articular Doppler signal in JIA patients. The physiological vascularization of the growing cartilage must be distinguished from the disease-related synovial hyper-vascularization associated with inflammation (Fig. 1). Finally a visible fluid accumulation in different joint recesses has been described in a significant proportion of healthy children using high-resolution B-mode MSUS (Fig. 2). These normative data support a more reliable distinction of pathologic MSUS findings in children and provide further evidence for the use of MSUS in pediatric rheumatology practice and research settings [12–20,34,35].

- Common findings in all joints were the prominent cartilage in younger children due to the incomplete ossification of the epiphyses and apophyses
- Knowledge of the physiological vascularization of the immature skeleton is essential for correct interpretation of the articular Doppler signals in JIA patients
- Visible fluid accumulation in different joint recesses has been described in a significant proportion of healthy children

Pathologic MSUS findings in pediatric joints

Based on the normative data of healthy pediatric joints, several groups have recently worked on the standardization of the assessment and interpretation of pathologic MSUS findings in pediatric joints.

Synovitis

Synovitis is clinically defined by the presence of swelling or effusion with increased temperature, limitation of motion and/or pain in one or more joints. However, there are several non-rheumatic conditions potentially presenting with the same symptoms, for example soft tissue infections, bone inflammation, traumatic lesions or edema. As anticipated, MSUS is more sensitive than the clinical evaluation in detecting synovial inflammation. An international consensus for the US appearance of synovitis in patients with JIA was recently reached by the Pediatric Task Force of the OMERACT US Group [35]. The assessment of synovitis by US requires the use of both B-mode and Doppler mode. B mode findings include synovial effusion (defined as an abnormal, intraarticular, anechoic or hypoechoic material that is displaceable) and synovial hypertrophy (defined as an abnormal, intraarticular, hypoechoic material that is non-displaceable). As expected, children show a variable degree of physiologic blood flow within the joint but only the Doppler signals within an area of synovial hypertrophy are clearly indicative of increased blood flow as part of the inflammatory process. The clear emphasis on the precise intrasynovial and not just intraarticular location of the Doppler signals represents a differentiation from the existing definition in RA (Figs. 3–5).

US Scoring systems are essential to quantify pathological findings and to evaluate the efficacy of therapeutic interventions during longitudinal follow-up. The OMERACT US pediatric subtask group is currently working on a general pediatric synovitis score to quantify the grade of inflammation in small and large joints of JIA patients. In addition, a new score specific to the knee joint was recently published by the North American CARRA working group [21] (Fig. 6).

Another unanswered question regarding the use of MSUS for monitoring treatment efficacy is, which set of joints should be optimally imaged. In theory a scan of all accessible joints would be ideal but certainly not feasible in routine practice. Of interest, Collado et al. have shown that a limited US-exam of 10 joints (both knees, ankles, wrists, elbows and the second MCP joints), reflected the overall inflammatory activity similarly well as the 44-joint comprehensive MSUS assessment [36].

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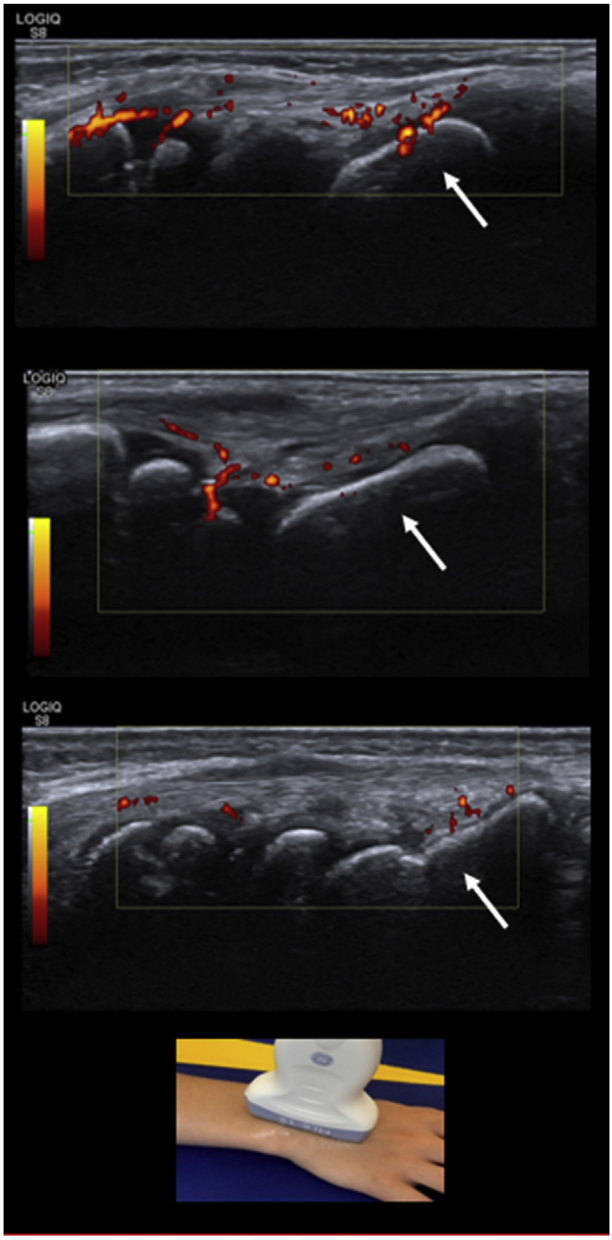

Fig. 1. Development of the wrist on ultrasound. US images showing the cartilaginous midhand in the dorsal longitudinal scan with physiologic feeding vessels from toddlers (upper image) to adolescent age (lower image). Ossification and growth of os capitate (arrows).

Tenosynovitis

Ultrasonography represents the gold standard technique for tendon assessments. Tenosynovitis is common in JIA patients from the early stages of the disease, evolving in parallel with joint

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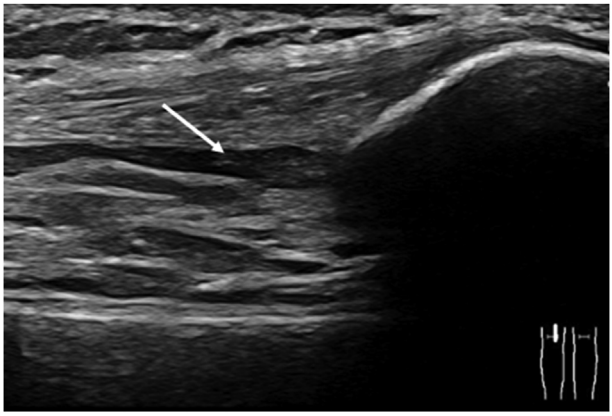

Fig. 2. Suprapatellar longitudinal scan of a healthy knee of a 12 years old girl showing physiologic effusion (arrow) in the suprapatellar recess.

inflammation. Tenosynovitis is frequently missed in clinical practice and a poor concordance between clinical and US detection of tenosynovitis has been reported in JIA [37]. Rooney et al. evaluated 49 swollen ankles of patients with JIA with MSUS; unexpectedly, tenosynovitis was found to be the dominant finding, observed in 35 ankles (71%) [25]. Tenosynovitis occurred often as an isolated manifestation with potential implications for therapeutic intervention. It has been suggested, that MSUS should be performed prior to all ankle injections, as isolated tibiotalar joint disease is relatively uncommon and tenosynovitis occurs more frequently than is clinically recognized. Differentiating tenosynovitis and underlying arthritis on clinical ground alone may be difficult because these structures are in close proximity and both may cause diffuse swelling and decreased function (Fig. 7).

The OMERACT ultrasound group has defined tenosynovitis in RA as hypoechoic or anechoic thickened tissues with or without fluid within the tendon sheath that may exhibit Doppler signals, excluding normal feeding vessels [38]. These definitions seem to correlate very well with our observations of tenosynovitis on MSUS in children. Currently the pediatric task force of the OMERACT group is testing the accuracy of these definitions for the pediatric population. This will improve the knowledge on the patterns of tendon involvement in JIA and help to define its potential role in diagnosis, classification and prognosis.

Enthesitis

The entheses are excellent targets for US imaging because of their superficial location. They can be easily evaluated with high-frequency transducers. The detection of enthesitis in a child with recent-onset inflammatory arthritis might contribute substantially to the correct classification of JIA, which in turn influences treatment decisions. JIA patients with enthesitis-related arthritis or psoriatic arthritis may show enthesitis in different joint regions (Figs. 8 and 9). Pilot studies have demonstrated, that the clinical diagnosis of enthesitis is often challenging. A poor concordance between clinical and ultrasound detected enthesitis was reported by Jousse-Joulin et al., who showed that 50% of the sites with sonographic evidence of enthesitis were missed by physical examination [39].

MSUS definitions of enthesitis include the loss of the normal fibrillar echotexture and thickening of the tendon. Increased Doppler signals within the insertion very close to the bone are considered to be specific for enthesitis. However, it is important to highlight that children's enthesis may show physiological vascularization that may interfere with the correct interpretation of pathologic Doppler signal as an expression of enthesitis. Physiologic Doppler signals usually occur within the cartilage into which the tendon inserts, along the tendon as well as inside the tendon itself at various distances from its insertion. The US definition of enthesitis also includes the presence of structural abnormalities such as

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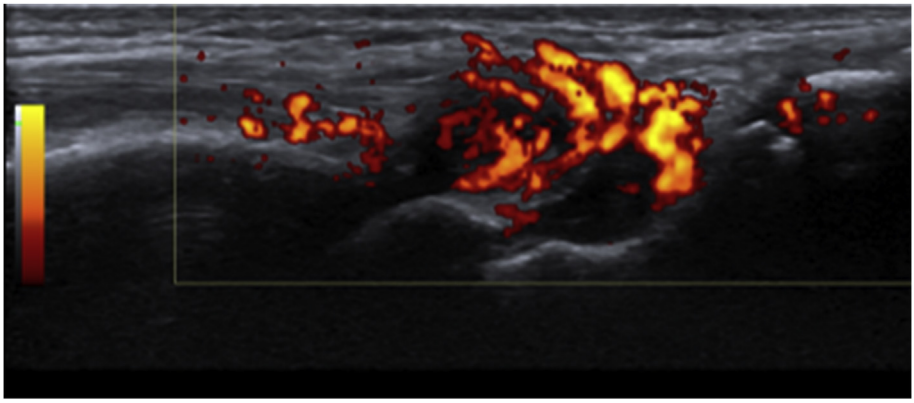

Fig. 3. Dorsal longitudinal scan of the wrist of an 11 years old girl with severe polyarticular arthritis showing synovial hypertrophy with intrasynovial hypervascularization.

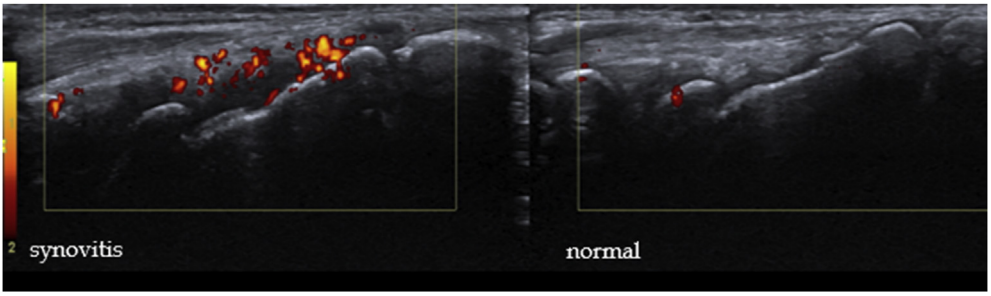

Fig. 4. Dorsal longitudinal scan of the wrist of a patient with carpalarthritis (left image) showing the comparison to the healthy side (right image).

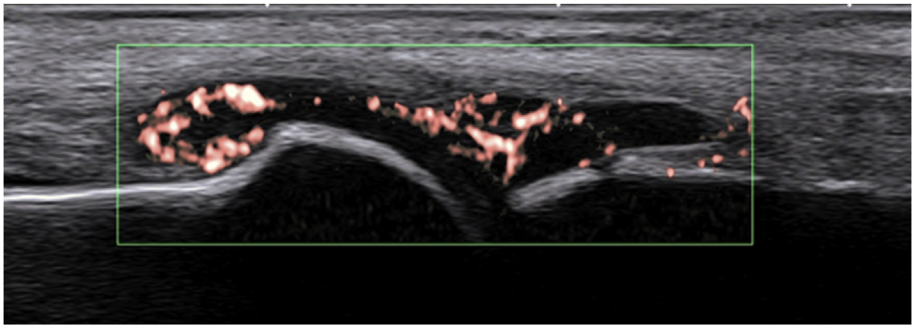

Fig. 5. Synovitis of the first metatarsophalangeal joint of a 13 years old girl with polyarticular arthritis.

erosions, enthesiophytes or calcifications at the insertion of the tendon. The evaluation of these pathological changes in children represents a real challenge due to the age-related physiologic irregularities of the bone-cartilage interface.

So far only a few studies have provided normative data for the pediatric entheses on MSUS and overall the literature about enthesitis in JIA patients in particular remains very limited [40,41].

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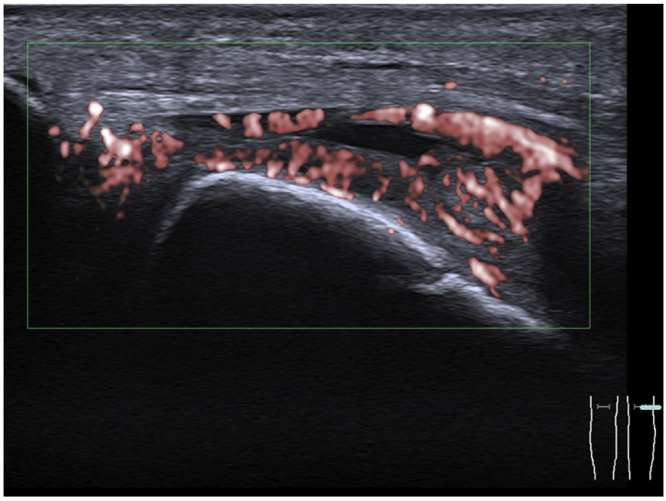

Fig. 6. The recommended parapatellar transversal scan of the parapatellar recess with synovitis and hypervascularization in a girl with JIA.

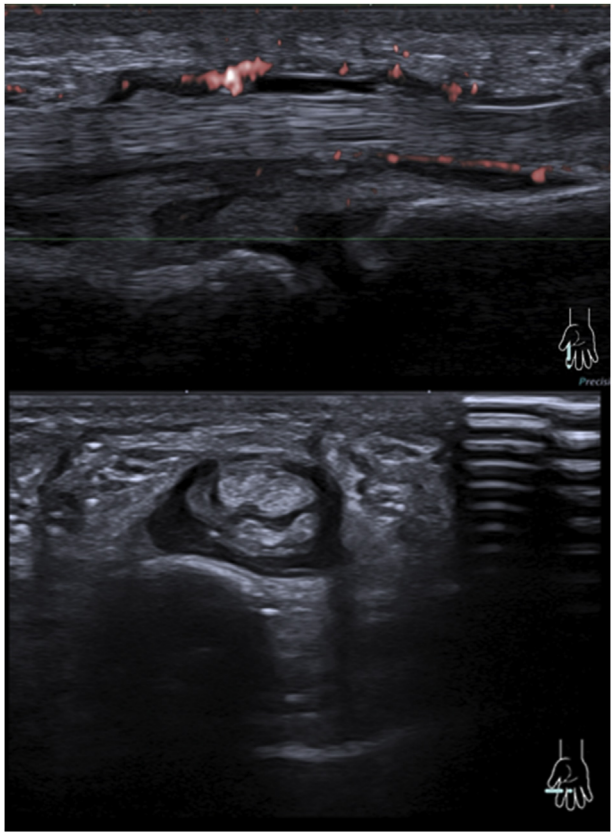

Fig. 7. Longitudinal and transversal scan of flexotenosynovitis (Digitum II) in a 5 years old boy with oligoarthritis.

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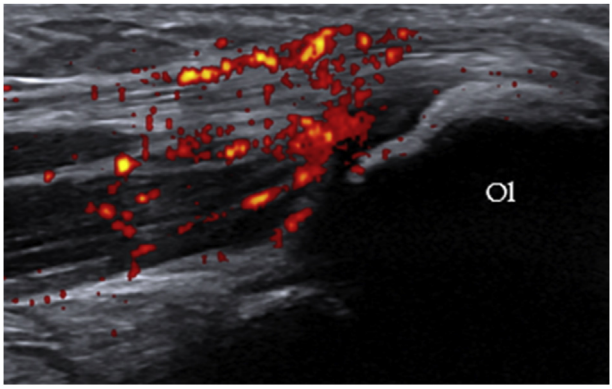

Fig. 8. Enthesitis of the musculus triceps tendon enthesis with its insertion to the olecranon (ol) in a girl with enthesitis related arthritis.

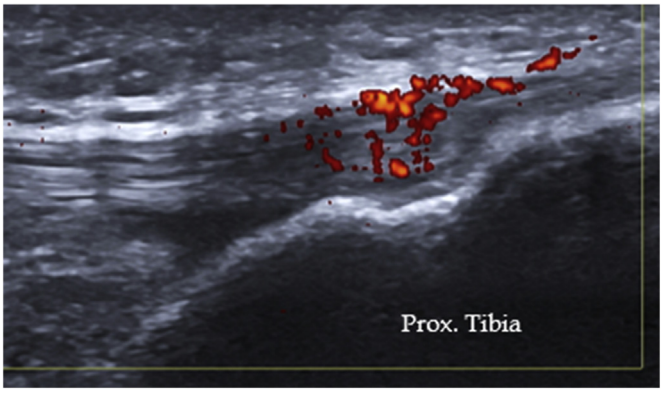

Fig. 9. Enthesitis of the patella tendon enthesis with its insertion to the tuberosities tibiae in a boy with enthesitis related arthritis.

Cartilage and bone lesions

Articular cartilage is one of the main targets of the erosive process in JIA. Cartilage damage can be visualized on MSUS with blurring of the outer or subchondral margin and the thinning or loss of homogeneity of the technostructure. The assessment of the integrity of the articular cartilage in JIA is a real challenge due to the physiological reduction in cartilage thickness during the skeletal maturation process. Several studies have provided normative data on the cartilage thickness in small and large joints of healthy children of different ages [15–19]. These standards are of potential value as a reduction in cartilage thickness from the reference interval could indicate a sign of structural damage progression. An excellent agreement between MRI and US measurements of the distal femoral cartilage thickness in JIA patients has been described [42], providing evidence that MSUS is a reliable tool for the assessment cartilage damage in JIA patients.

MSUS, by visualizing articular changes in multiple planes of view, has proved to be more sensitive than plain radiographs in detecting bone erosions in the metacarpophalangeal [43] and carpal bones [44] of JIA patients (Fig. 10). Bone erosions on MSUS are defined as a discontinuity of the cortical surface. Scanning in more than one plane can prevent overdiagnosis of erosions, particularly in children. However, caution is required when MSUS is used for the assessment of bone damage in the growing skeleton because of the significant changes in bone morphology during skeletal maturation. In

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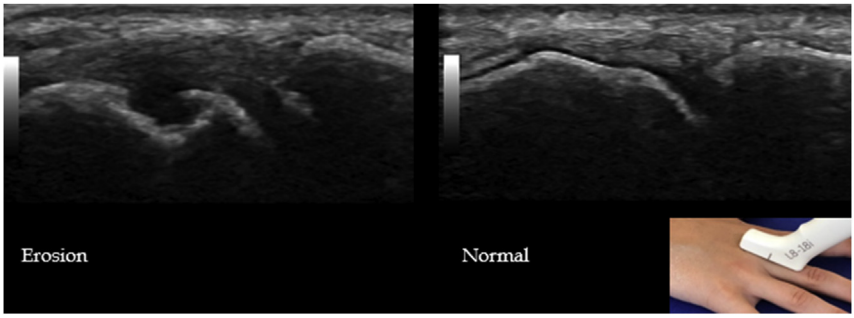

Fig. 10. Erosion of the second metacarpal bone (comparison to the healthy side) in a girl with polyarticular arthritis.

fact, the open physis may be confused with erosions and developing bone may appear to be very irregular. Another peculiar aspect of JIA relates to the fact that the disease may interfere with the skeletal maturation process leading to the development of unique radiological findings, such as disturbance of bone growth, which have no equivalent in adults with RA. Persistent joint inflammation and consequent hyper-vascularization of affected joints may cause an acceleration of the ossification process resulting in an advancement of the skeletal age that can be reliably detected by ultrasound [12].

Ultrasound-guided joint injections

Ultrasound imaging guidance of needles introduced for the purpose of joint aspiration or joint injection is becoming increasingly popular. The use of ultrasound increases the safety and efficacy of joint injections in pediatric rheumatology. Needle guidance may be important for diagnostic purposes (fluid aspiration) as well as therapeutic interventions. Intraarticular corticosteroid (CS) injections can be used acutely for short-term relief or longer-term management of either limited disease or treatment resistant multi-joint disease. Ultrasound guidance can also be used to inject steroids into tendon sheaths or around entheses in inflammatory conditions. In oligoarticular JIA in particular, injections of corticosteroids into joints play an important and established role in anti-inflammatory treatment. The knee is the most commonly affected and injected joint in JIA, but all peripheral joints can be safely and effectively injected with CS via ultrasound guidance. Ultrasound guidance improves the precise identification of the target as well as the accuracy of the needle placement within the joint space, tendon sheath, or around the enthesis (Figs. 11 and 12). It can be challenging to inject very small joint

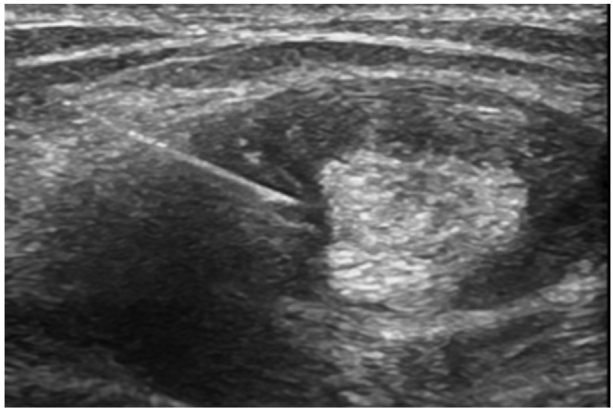

Fig. 11. Needle placement into the tibialis posterior tendon sheath in a girl with tenosynovitis and polyarticular arthritis.

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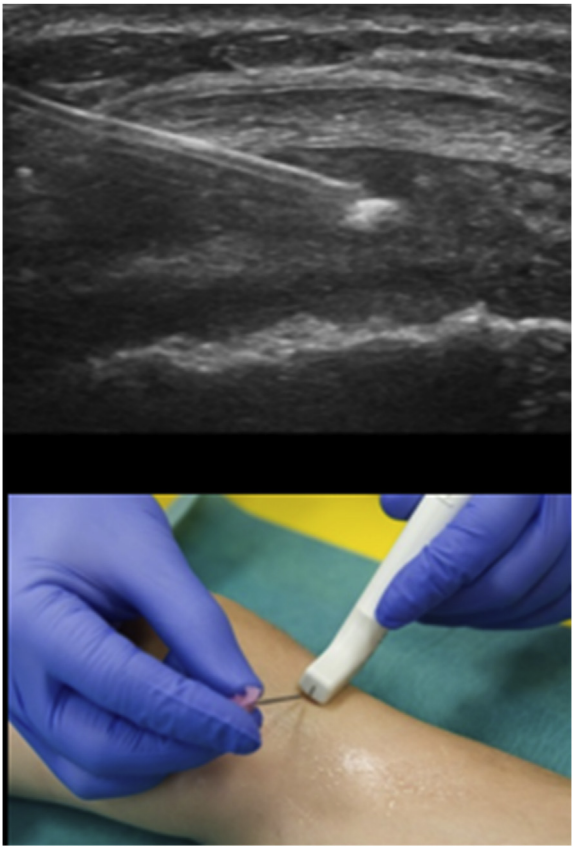

Fig. 12. Injection of the infrapatellar bursa with ultrasound guidance.

regions in younger children without any imaging guidance, and incorrectly placed CS injections can potentially permanently damage the cartilage and soft tissue structures in these younger patients. Ultrasound techniques have undergone marked development over the last two decades, so that all joint and tendon structures are clearly shown by the newer high-resolution ultrasound devices. High-frequency ultrasound probes with frequencies of up to 22 MHz help to safely guide the needle into the targeted structure. Studies have shown that ultrasound guidance increases the safety and efficacy of intraarticular injections in rheumatic patients. Ultrasound guidance of the needle has no negative side effects in pediatric patients, and does not increase the time required for the injection procedure [45–49].

Summary

MSUS is emerging as an important diagnostic tool with the potential to enhance disease assessment and management in patients with JIA. The unique aspects of the growing skeleton make the interpretation of ultrasound images in children more challenging than in adults. Becoming familiar with the normal sonoanatomy throughout the paediatric age range is essential in order to avoid misinterpretation. The development of US definitions for pathology and refining scoring systems in JIA represents a high priority for swift and smooth integration of MSUS into clinical workflow. The assessment of the diagnostic accuracy of MSUS is an essential prerequisite for the evaluation of its potential to inform the decision-making process and impact the patient management plan.

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The correct use of ultrasound imaging in pediatric patients with rheumatic diseases has many advantages for patients which include diagnostic certainty, better discrimination between different pathological findings, and the ability to monitor and follow-up the patient safely while on treatment and in remission.

Praticice points

- MSUS is a powerful tool for the assessment and monitoring of synovitis, tenosynovitis and enthesitis in patients with JIA.
- US guidance may enhance the efficacy of local glucocorticoid injection therapy in JIA.
- A deep knowledge in ultrasound technique and normal paediatric sonoanatomy is required for an accurate interpretation of US images.

Research agenda

- The development and validation of scoring systems in JIA is high priority for optimizing the role of US as a robust outcome measure to assess treatment efficacy.
- Testing the diagnostic accuracy of MSUS to detect bone and cartilage damage is a prerequisite to use US for identifying patients with a severe disease who should receive early aggressive therapy in order to prevent joint destruction.
- The integration of US findings with immune biomarkers could provide more disease-specific information that may be useful to develop patient-specific treatment strategies.

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