Review

The recent evolution of ultrasound in juvenile idiopathic arthritis

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common chronic joint disease in paediatric rheumatology. Over the last two decades, ultrasound (US) has emerged as a tool with the potential to enhance disease assessment and management of JIA. This imaging modality is safe and well tolerated by children and can be easily applied bedside in the clinical setting. Owing to the lack of published studies regarding the validity and reproducibility of US in JIA and the difficulties in interpreting images of children, US was initially perceived like an art rather than a science. In recent years, a great deal of efforts has been made in order to fill the gap of scientific knowledge on US between paediatric and adult rheumatology. This has yielded significant breakthroughs, such as the achievement of valuable information about the anatomical peculiarities of the growing skeleton on US, including internationally agreed definitions on B-mode and Doppler US of components for the normal joints, and the development of a standardised scanning protocol for US examination suitable for use in children. The precise role of US in JIA, however, is yet to be fully defined. Although further research regarding the use of US in joint inflammatory pathology in paediatrics is required, this imaging modality may well possess the necessary properties to pursue the best practice in the care of children with JIA in the near future.

The present review provides information on the recent advances that have made the application of US increasingly promising for the management of JIA.

Introduction

Juvenile idiopathic arthritis (JIA) is a clinical entity which encompasses a heterogeneous group of disorders (1). Joint inflammation is the most common feature across all JIA subtypes (2). Synovial proliferation is a consequence of persistent articular inflammation and can lead to cartilage and, ultimately, bone damage. Thus, the disease may become a potential cause of permanent joint inability in childhood (1, 3).

It is widely agreed that early identification and treatment of affected joints throughout the natural history of JIA plays a key factor to spare patients the institution of non-reversible osteostructural damage and improves the outcome of the disease (1, 4). Nowadays, this goal has become achievable in the majority of patients with JIA, thanks to the development of new drugs that show capacity to reduce significantly and quickly joint inflammation, and to the availability of imaging modalities that enable better and earlier assessment of disease activity and treatment efficacy than clinical examination (5).

In recent years, the properties of ultrasound (US) have driven the interest of paediatric rheumatologists towards an increasing application of this imaging technique in the management of JIA (5-8). The advantages and limitations of US in JIA are reported in Table I.

Ultrasound is of potential value in the diagnostic work-up, since it allows to identify non-rheumatic conditions mimicking JIA, such as soft tissue infections, traumatic lesions or oedema (9, 10). Data from surveys on US in paediatric rheumatology have shown that a part of practitioners has recently started training in order to achieve the skills necessary to perform US in patients with JIA in daily clinical practice (11, 12). This trend has been also simplified by the large technological developments by manufactures that have led to the availability of high-quality and more easily interpretable images. In addition, miniaturisation of some components of the machines, and in particular the production of smaller, handy and higher frequency probes, have made

Table I. Advantages and limitations of US in the assessment of children with JIA.

Advantages	Limitations
- Non-invasiveness	- Operator dependency
- Relatively inexpensive	- Reliability dependent on sensitivity of US equipment
- Lack of exposure to ionising radiation	- Not all joints assessable
- No need to sedate children	- Inability to assess the whole joint space
- Possibility to assess several joint regions in a single scanning session	- Relatively small field of view
- Capability of dynamic and real-time assessment	- Acoustic shadowing from overlying bones
- Potential guidance for corticosteroid injections in joints, tendon sheaths or synovial bursas	- Difficult to carry out in case of joint functional limitation and/or pain
- Portability	- Lack of validated scoring systems to quantify US abnormalities
- Rapidity of performance	- Difficult to standardise and centralise for clinical trials
- Ease of repeatability	
- Visualisation of soft tissue inflammation	

US equipments by far more suitable for the assessment of small joints, tendons and other tiny anatomical structures of children (5, 13).

Normal US features in children

The anatomical peculiarities of the growing skeleton make interpretation of US images in children more challenging than in adults, and misinterpretation between normal and pathologic features is a matter of concern to sonographers who are not experienced in scanning paediatric subjects.

When dealing with US in children, it is important to underline that skeletal maturation has a significant impact on US findings, since appearance of normal anatomical structures on US, such as cartilage, bone and adjacent feeding vessels that enter with a direct trajectory into the cartilaginous epiphyses (Fig. 1), change very quickly with increasing in age. Therefore, thorough knowledge of normal paediatric sonoanatomy at different ages is pivotal to discern whether the observed changes are pathological or part of normal development of children (5-8).

Over the last decade, a working group for US in paediatrics within the Outcome Measures in Rheumatology (OMERACT) task force has been created in order to overcome the gap of scientific knowledge on US between paediatric and adult rheumatology. As a result of the activity of such group, definitions for the sonographic features of joints in healthy children on B-mode US were first developed and validated (14). The US definitions include the description of the hyaline cartilage, the normal joint capsule and synovial membrane, the epiphyseal secondary ossification centre, and the ossified portion of articular bone. In a subsequent study, the same group described the vascularity and developed additional definitions of normal findings on Doppler US in healthy joints to add to the preliminary B-mode US definitions of joint components (15). In particular, it has been highlighted that physiological intraarticular blood flow can be normally detected on US in chil-

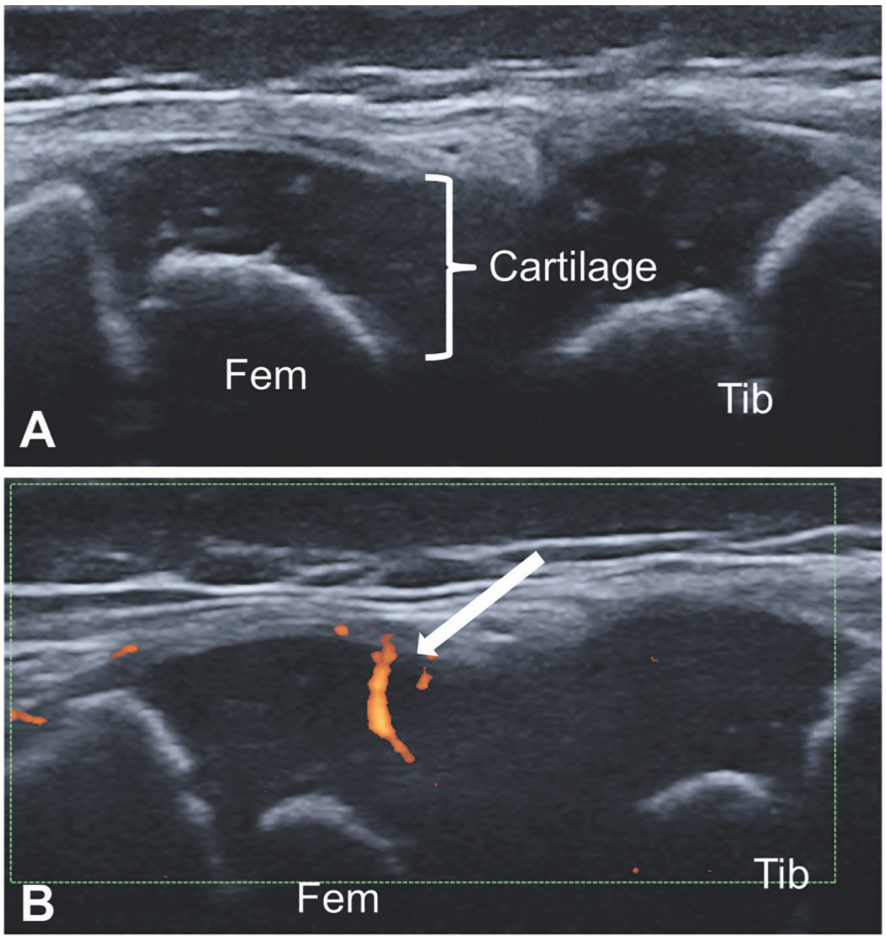

Fig. 1. Longitudinal US scan of the normal lateral aspect of the knee in a 2-year-old girl. The distal femur and the proximal tibia appear on B-mode US (**A**) mostly unossified. It is detectable on PD US (**B**) an adjacent physiological feeding vessel (arrow) that enters with a direct trajectory into the cartilaginous femoral condyle. Fem: femur; Tib: tibia.

dren of different age groups within the fat pads and unossified joint structures (physis, the cartilage of epiphysis and of the short bones). Reliability of US on identification of normal joint vascularisation in healthy children was then tested in another investigation in the wrist, knee, tibiotalar and second metacarpophalangeal (MCP) joint, and resulted good except for the MCP joint, for which agreement was moderate (16). Overall, these steps have provided an essential contribution toward a more reliable use of US in children, and represent a solid platform for studying US abnormalities in JIA.

Children are known to be active, as they run and play at length in the daytime. Furthermore, given to the physiological laxity of periarticular structures, some of them present a small degree of hypermobility. Such mechanical factors may, at least in part, explain why a certain amount of fluid and distension of a synovial recess can be frequently detected on US in healthy joints of paediatric subjects. Therefore, during scanning with US the question often arises as to whether intraarticular fluid is of normal range or a sign of joint inflammation. Several efforts have been recently exerted in order to define cut-off values of normality for different joints and age groups of children (17-23). However, a paucity of data is still being published for a limited set of joints, and no agreement has been so far reached regarding joint positioning in some similar studies (17, 18). Although these reports provide information with the aim of helping discrimination between normal and pathological findings of joints in children, they currently represent starting points and assessment of changes of US features in an individual subject over time sometimes may be even more informative than a simple comparison with a cut-off value. Hence, further studies are needed in order to fill the gap of standardised normal findings.

Standardisation of US assessment in children

The majority of reports on US in JIA have the shortcoming of the absence of standardisation of the US exam in children at the time of conducting those studies. US evaluations usually relied on the scanning OMERACT guidelines developed for adults which may not be entirely suitable for use in paediatric subjects (24).

In order to overcame this problem, recently the OMERACT working group for US in paediatrics has developed a standardised US examination method to collect images in children of the most common peripheral joints involved in JIA (the knee, ankle, wrist, second MCP joint), which includes patient position, transducer placement based on visible reference points for each scanning approach, and joint positioning (25).

Similarly, a subsequent study was conducted in order to obtain information useful to standardise US image acquisition of the subtalar joint (STJ) in JIA (26). In particular, in the study cohort of 50 ankles with clinically active JIA, a comparison among a medial, lateral and posterior scanning approach to the STJ was carried out. US evaluation detected synovitis in 27/50 (54%) STJs. Of interest, all patients with US abnormalities in the medial and/or posterior side of the STJ were always found to have US abnormalities using the lateral scanning approach, but not vice versa. In addition, the amount of inflammation as detected on US was greater using the lateral scanning approach than the medial and posterior. From a practical point of view, the ability to scan only the more comprehensive and representative aspect of a joint may help to shorten the length of the US session, especially when managing younger and poorly cooperative children.

A more recent investigation has proposed a novel protocol for acquisition of US images in the knee of patients with JIA (27). Through an accurate multi-step process covering a comprehensive literature review, practical exercises and a consensus process, a standardised scanning method specific for the assessment of arthritis in the paediatric knee including the suprapatellar and the parapatellar recesses was devised. Of interest, using the same methodology, the investigators developed in parallel in the same study a semiquantitative scoring system for B-mode and Doppler US assessment. Both the scanning protocol and scoring system were based on clear and easily recognisable landmarks, making the method quick and feasible irrespective of bone ossification and, then, of age of patients. Noticeably, interobserver reliability for the scoring system on B-mode US ranged from good to excellent for all views of the knee. The assessment of the medial and lateral parapatellar recesses with power Doppler (PD) US confirmed a good-to-excellent interobserver reliability, which resulted indeed fair for the suprapatellar view. This finding is likely related to the higher sensitivity of US in capturing pathological Doppler signal in the parapatellar recesses, since they are generally more superficial compared to the deeper suprapatellar recess. Overall, this study suggests that a single standard scoring system may not be adopted for all joints in children. Thus, it would be advisable in the future to develop specific scanning protocols and scoring systems that are tailor-made to all different joints that are target of JIA.

Once the scanning technique is standardised, another relevant point to address is how many joints need to be examined with US in JIA to precisely test disease remission and therapeutic response. Theoretically, identifying a unique target joint that is able to reflect the entire state of disease activity would be ideal. In a report from Collado *et al*. a minimal set of 10 joints, including a bilateral assessment of elbow, wrist, second MCP joint, knee and tibiotalar joint, was compared to a more extensive US examination of 44 joints (28). The reduced US protocol allowed the identification of the totality of patients who had B-mode and PD abnormalities in the 44-joints US exam. Furthermore, the reduced model showed a higher responsiveness to change than evaluating the larger number of joints. Overall, these findings suggest that a US assessment centered on a reduced joint count and including the sites that are more frequently affected in JIA may provide information of the whole burden of disease activity. However, additional investigations on different sets of joints are warranted to confirm these preliminary data.

Cartilage and bone injury

Unlike adults, children have different degrees of maturation of hyaline articular cartilage and secondary ossification centres according to age. In fact, during the child's growth hyaline cartilage gradually declined as it is progressively replaced by bone formation, and at the end of the maturation process only a small stripe of joint cartilage remains. In a recent study a semiquantitative US scoring system for assessing physiological development of skeletal maturation of 4 joints (the knee, tibiotalar, wrist, and second MCP joint) has been proposed and applied in a practical exercise on 12 healthy children (16). The proposed scoring system was based on 4 degrees of ossification depending on the appearance on US of ossification centres, thickness of cartilage and growth plate and showed in the practical exercise a high intraobserver reliability and an acceptable interobserver reliability. However, the fact that such scoring system does not take into account other factors influencing the ossification of bones in childhood, such as sex, hormonal status (29), limits its current use in clinical practice and suggests conducting future investigations including these items.

Since loss of cartilage thickness and integrity are early markers of joint damage in chronic inflammatory arthritis, a thorough knowledge of normal sonoanatomy in children is crucial to discriminate a decrease in cartilage thickness related to the physiological development of the immature skeleton from a loss of US-detected cartilage due to pathology.

Initially, studies were conducted in order to validate US assessment of cartilage thickness using a cohort of healthy children (30, 31). They showed an overall satisfactory intra- and inter-observer agreement on US measurements of cartilage thickness for all the examined joints except for the wrist. Subsequently the same group of investigators further validated US evaluation of cartilage thickness in healthy children by comparing US and magnetic resonance imaging (MRI) measurements (32). In addition, age- and sex-related normal standards on US for cartilage thickness were established for a limited set of joints (33).

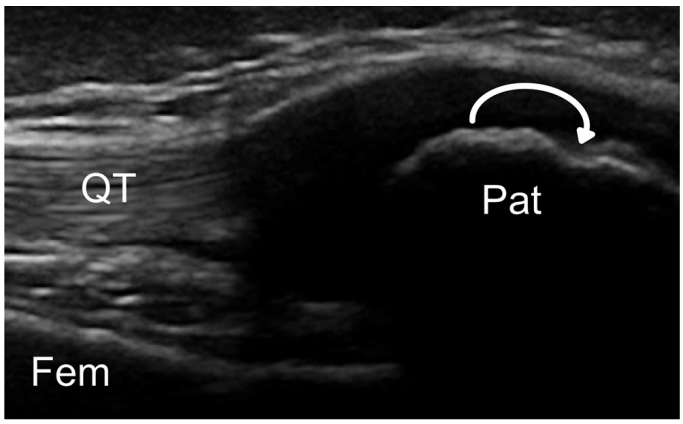

Fig. 2. Physiological bone findings. Longitudinal US scan of the knee in a 5-year-old girl showing physiological irregularities of the bony profile (curved arrow) of the partially ossified patella.
Fem: femur; Pat: patella; QT: quadriceps tendon.

Recently, studies on US evaluation of hyaline articular cartilage have been centered around patients with JIA. In particular, a report documented a decreased cartilage thickness in a set of joints of children with JIA, compared to healthy controls (34). Noteworthy, this finding was observed regardless of whether the examined joints were ever previously affected by arthritis. Furthermore, the group of the study patients with the shortest history of disease was found to have the lowest cartilage thickness in the knee, ankle and second PIP, which suggests that the degradation of cartilage is more related to disease activity rather than to the length of time since disease onset. The fact that patients with the systemic and polyarticular subtypes of JIA, that are known to have a more aggressive disease course among all subsets of JIA, were found to have a significantly decreased cartilage thickness of the knee compared to the oligoarticular JIA subgroup, further corroborates this assumption. From a clinical point of view, altogether the findings of these studies suggest that assessing cartilage and bone maturation on US may be useful in JIA, since children may have accelerated bone development and decrease in cartilage thickness associated with inflammation.

Earlier comparative studies have documented good levels of agreement in cartilage thickness measurements between US and MRI/radiography also in patients with JIA (35, 36). Of interest, the US measurement of the distal femoral cartilage at the level of the intercondylar area has been suggested to be the best anatomical site to assess cartilage thickness with US for the knee in JIA (35), since this area resulted easier to locate exactly on US and with less variability when compared to MRI measurements. Similar investigations should also be conducted for other sets of joints in JIA.

Although the difficulties in identifying cortical erosions in childhood because of their similarity to the physiological wavy and fragmented irregularities of surfaces of partially ossified bones in the growing skeleton (Fig. 2), recent data support the utility and reliability of US in detecting bony erosive changes in JIA (37, 38).

Synovitis

Joint disease is the principal hallmark of JIA. Several studies have demonstrated that synovitis detected by US but not by clinical evaluation (subclinical synovitis) is common in small and large joints of children with JIA (37, 39-43) (Fig. 3). Thus, the application of US in the assessment of JIA may have important implications. Early identification of synovitis on US may impact significantly on disease classification, that is based on the number of the affected joints (2), and may induce theoretically to reclassify some patients with JIA (39, 40). Furthermore, the detection of subclinical synovitis may potentially alert the physician and lead to escalate the treatment with the aim of reducing long-term damage (38). However, it is still unclear whether targeting US remission may lead to a lower risk of developing structural damage progression, and then should influence treatment decision, or may produce

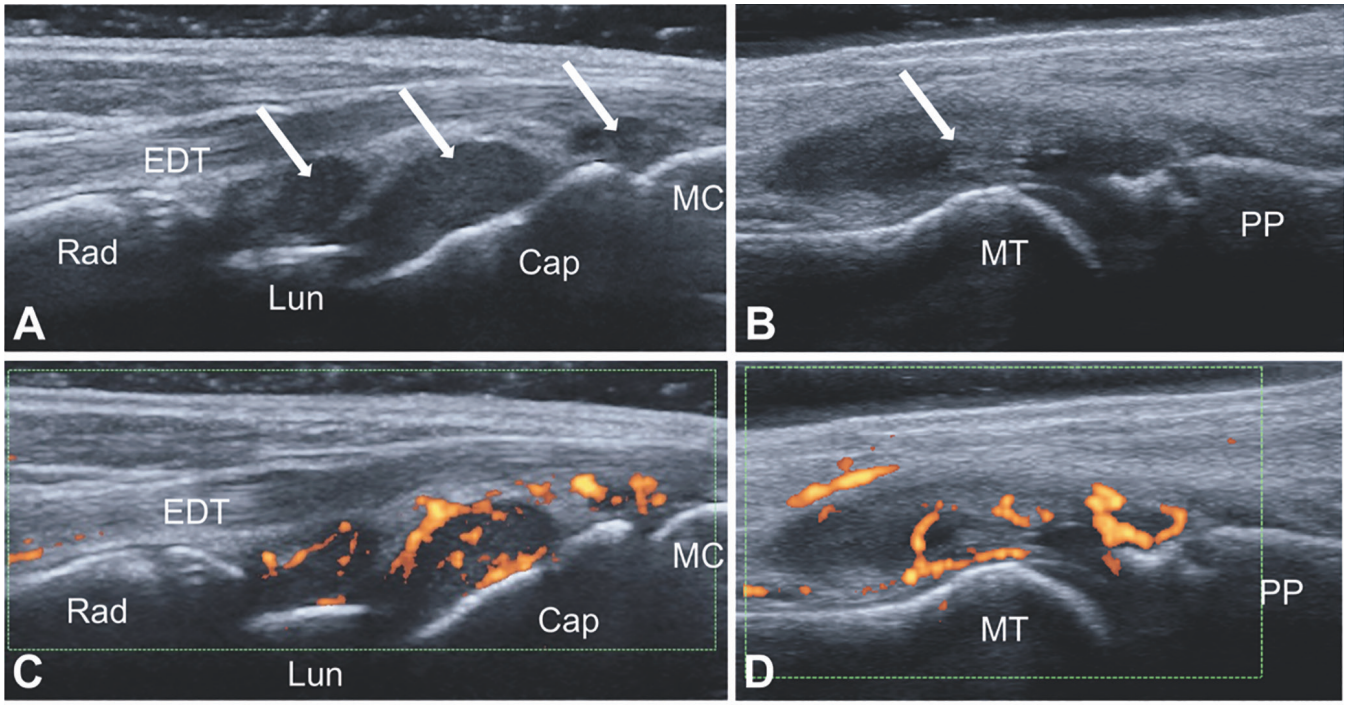

Fig. 3. Synovitis of a large and small joint. Longitudinal US scan of the wrist in a 12-year-old girl with JIA showing a multicompartmental synovitis on B-mode US (**A**) and on power Doppler US (**C**), involving the radiocarpal, midcarpal and carpometacarpal joints. Longitudinal US scan of the first metatarsophalangeal joint in a 10-year-old boy with JIA showing synovitis on B-mode US (**B**) and on power Doppler US (**D**).
EDT: extensor digitorum tendon; Cap: capitate; Lun: lunate; MC: metacarpal bone; MT: metatarsal bone; PP: proximal phalanx; Rad: radius; arrows: synovitis.

overtreatment and be both time consuming and economically unsound.

Since US enables direct visualisation and quantification of synovitis, a potential indication for the use of this imaging modality in JIA is the evaluation of therapeutic efficacy. Previous studies have assessed the response to corticosteroid injections in the wrist and ankle regions (44, 45), and in the knee and hip joints (46). In these studies short-term monitoring with US documented significant changes in joint inflammation with normalisation or partial regression of the baseline synovial abnormalities in the majority of the affected sites that were injected. A more recent investigation has shown a strong sensitivity to change for US in monitoring the 6-month follow-up after therapy in 83 joints of 33 children with new-onset JIA (47). In particular, standardised response mean for B-mode and PD US resulted 2.44 and 1.23, respectively, which suggests the capacity of US to detect improvement of synovial abnormalities induced by treatment. Of note, a considerable number (65%) of the joints with synovial abnormalities on US at 6 months were judged in remission on clinical examination, and 6/21 (28.6%) patients who were American College of Rheumatology Paediatric 90 responders showed persistence of residual findings on US.

Nowadays, the predictive significance of the presence of synovial abnormalities on US in patients with JIA in clinical remission has not been clarified yet. In a first longitudinal study, the detection of abnormalities on US, including PD signal, in a cohort of 39 patients with JIA in clinical remission did not predict subsequent early flare of synovitis (48). Moreover, the study patients with persistent inactive disease had a greater frequency of PD signal than patients with synovitis flare. Conversely, in a subsequent investigation from De Lucia *et al*. that enrolled 88 clinically inactive children with JIA, 75% of patients who had US abnormalities at the baseline visit experienced a flare of synovitis during the follow-up period of 4 years, compared to 38.2% of flares recorded in children without US abnormalities at study entry (49). Furthermore, among joints that were initially US positive and flared in the follow-up, detection of both B-mode and PD abnormalities on US at baseline yielded a much higher predictive value of relapse than finding B-mode abnormalities alone. The paucity of data concerning this topic fosters conducting further studies in order to address this controversial issue in children with JIA, thus covering the current inability to predict synovitis flare based on US findings.

Indeed, discrepancies in results among studies concerning the assessment of synovitis with US in JIA may be partially related to the higher difficulty in interpreting Doppler findings in children than in adults with chronic inflammatory arthritis. Over the last few years, an important breakthrough has been made by the OMERACT group for US in paediatrics that has issued preliminary definitions for the sonographic features of synovitis in children (50). In particular, through the definitions it has been clarified that only Doppler signals detectable within an area of synovial hypertrophy are pathological and evocative of an increased vascularisation in the context of synovitis. The particular stress on the intrasynovial and not just intraarticular location of pathological Doppler signals is rel-

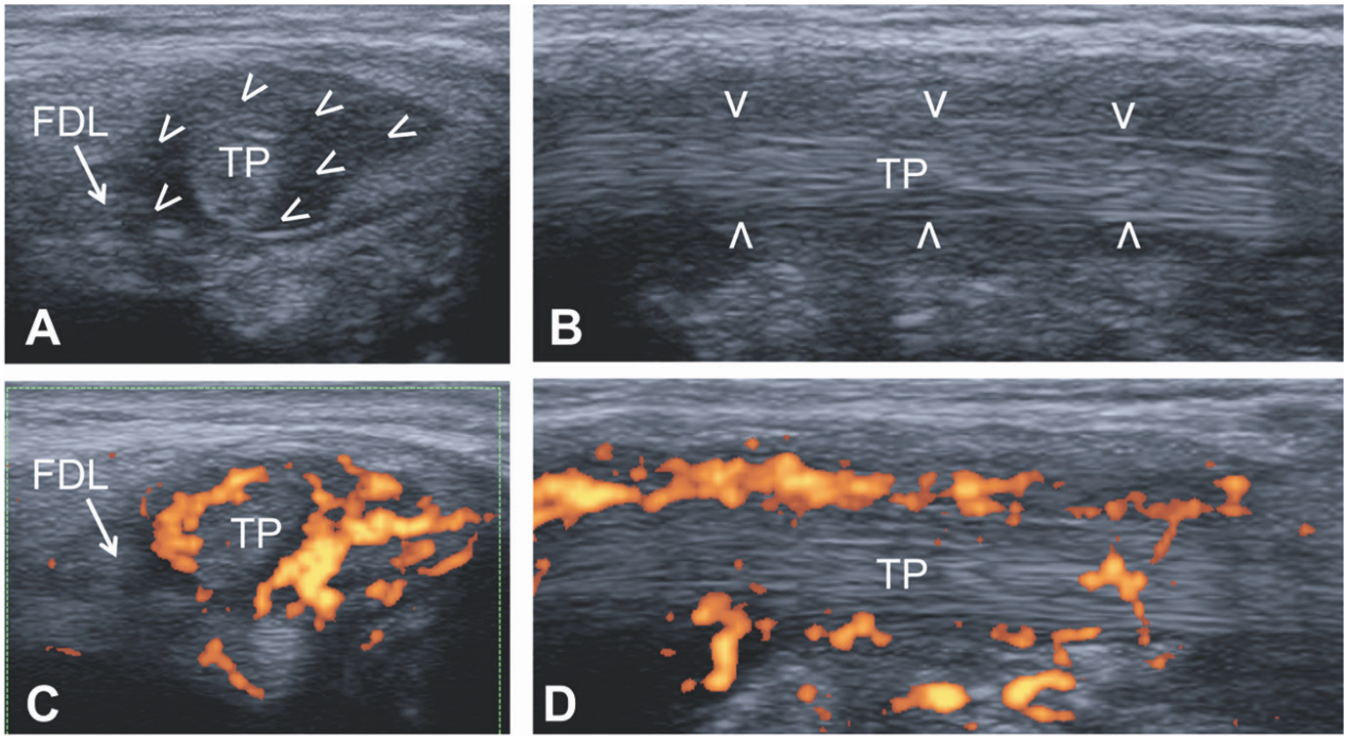

Fig. 4. Tenosynovitis. Transverse (**A**, **C**) and longitudinal (**B**, **D**) US scans of the tibialis posterior tendon in a 5-year-old girl with JIA showing tenosynovitis on B-mode US (**A**, **B**) and on power Doppler US (**C**, **D**).
FDL: flexor digitorum longus tendon; TP: tibialis posterior tendon; arrowheads: distension of the tendon sheath.

evant, given the existence in children of Doppler findings that are intraarticular but represent only physiological blood flow (*i.e.* feeding vessels that cross the synovial recess before entering into the bone/cartilage). However, because of the higher sensitivity of US in capturing pathological Doppler signals in the more superficial structures, it is anticipated that deeper joints show hardly Doppler findings even in presence of an overt synovial inflammation. This aspect has been also addressed in the paediatric definitions that clearly allow the diagnosis of synovitis on the base of findings on B-mode US alone.

A point that still needs to be investigated longitudinally is the interpretation of juxta-articular Doppler signal, since it may either represent normal flow of the well-vascularised epiphyseal cartilage or a sign of ongoing inflammation (5, 42, 48).

Tenosynovitis

Over the last two decades, there have been increasing data emphasising the ability of US to aid the clinicians to identify precisely not only articular, but also periarticular sites with inflammation in JIA. This is particularly true for joints that are complex or difficult to assess clinically, owing to the presence of multiple joint recesses and numerous adjacent tendons (5, 26, 51-54). Among these joints, the ankle is certainly one of the most commonly affected in JIA (51-53), and is surrounded by many tendons.

By enabling precise mapping of the tendons inflamed, assessment with US of the ankle has led to understand that tenosynovitis of this anatomical site is a frequent finding in JIA (Fig. 4), both isolated and associated with joint disease (51-53).

Recently, the utility of US in identifying tenosynovitis has been confirmed in a study that evaluated the agreement between clinical and US assessment for the detection of joint and tendon disease in a large sample of ankles with clinically active JIA (51). Concordance between the clinical exam and US was less than acceptable for both joint and tendon compartments. In addition, in the 105 ankles included in the study, the simple clinical evaluation was able to detect tenosynovitis to a lesser extent than US (32.4% and 70.5%, respectively).

Taken together, these findings may have important implications. The detection of clinical synovitis without evidence of US synovitis may be explained by the presence of tenosynovitis on US. Modifications of the current ILAR classification for JIA, that refers only to joint involvement without taking into account tendon disease (2), may therefore be required in light of this observation. Secondly, until now tenosynovitis is not part of the criteria for defining patients with JIA in remission (55). Thus, given the frequency of tendon involvement in JIA, it would be advisable to plan specific studies aimed to define the role of US-detected tenosynovitis in the definition of disease activity and remission in JIA.

Enthesitis

US allows an accurate visualisation of B-mode alterations in the entheseal echotexture, such as thickening of the tendon and loss of the fibrillar pattern. However, the assessment of enthesitis in children is particularly challenging, since the contribution of Doppler findings in defining active inflammation of the infantile enthesis has not established

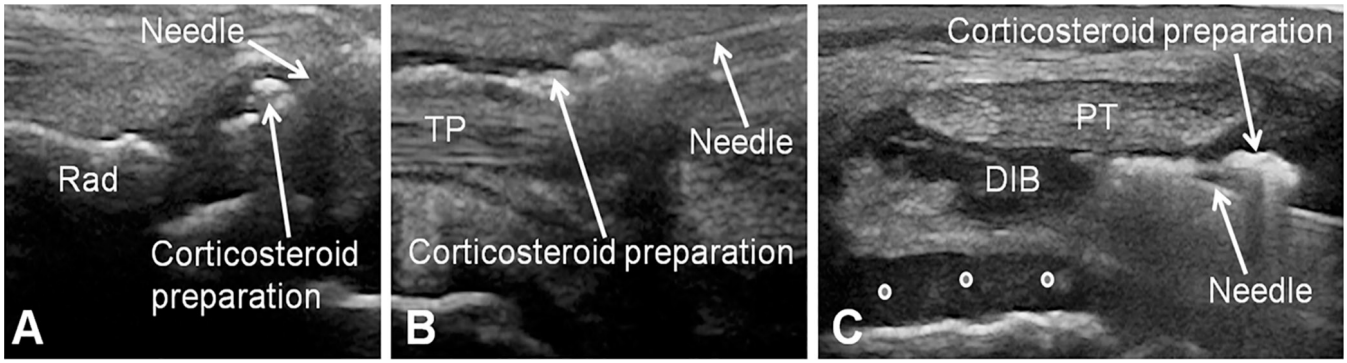

Fig. 5. Representative examples of US-guided corticosteroid injections: injection of the radiocarpal joint (**A**) in an adolescent girl with JIA (longitudinal US scan of the region); injection of the tibialis posterior tendon sheath (**B**) in a 7-year-old girl with JIA (longitudinal US scan of the region); injection of the deep infrapatellar bursa (**C**) in a 4-year-old boy with JIA (transverse US scan of the region).
DIB: deep infrapatellar bursa; PT: patellar tendon; Rad: radius; TP: tibialis posterior tendon; °: cartilage.

yet. In the growing skeleton the insertion area of tendons, ligaments, joint capsules and aponeuroses on the non-ossified portion of the apophysis may display peripheral physiological signal on Doppler US examination which is consistent with the presence of blood flow at the feeding vessel level (56). Discriminating between flow of normal nutrition vessels and vascularisation due to entheseal inflammation requires therefore considerable experience of the sonographer in scanning children, and depends partially on the setting and quality of US equipment.

Data from a past report suggested that the detection of enthesitis on PD US was not always coupled with clinical enthesitis in patients with JIA (57). On the other hand, in the control group of that study no signal was detected at the entheseal level. Nevertheless, a subsequent publication has shown that peritendinous and intra-tendon vascularity in certain entheseal sites can be regarded as a normal finding in healthy children (58). Furthermore, in a more recent study by Roth *et al*. Doppler signal was assessed at various distances from the enthesis of the quadriceps tendon, proximal and distal patellar tendon, and Achilles tendon in healthy children (59). The authors found that physiological vascularisation was present mostly in the quadriceps and distal patellar tendon, and was located close the enthesis within a distance of 2 or 5 mm. Overall these findings provide valuable new insights into the assessment of the enthesis in children where, unlike adults (60-63), a definition for the sonographic enthesitis has not been developed so far. There is an equal need to clearly define enthesitis on US in children. This may contribute to refine clinical assessment and classification of patients with the enthesitis-related arthritis JIA category, in which enthesitis is a central feature of the disease.

Injection therapy

Local injection therapy is commonly used to manage JIA (64). Blinded injections are challenging in children, due to the small size of sites to inject and to the physiological abundant fat masking bony landmarks. Thus, by enabling clear visualisation of needle placement within the target (Fig. 5), US-guidance increases the chance of success of corticosteroid injections and minimises the risk of subcutaneous atrophy (44, 45). Furthermore, the use of US during tendon sheath injections prevents accidental needle entry into the tendon fibres (65). The possibility to document with US the correct location of the injected medication is an added value (8). Despite the recent development of newer high-resolution US devices that facilitate US-guided procedures, thorough training is mandatory before achieving the necessary skills to perform injections under US-guidance in JIA.

Conclusions

Increasing interest is being encountered for US in JIA. Research activities have recently yielded important breakthroughs in several issues, making US a promising tool to implement the care of children with JIA. Nevertheless, US is underused in JIA due to the difficulty of access to specific training. Furthermore, some topics need to be further addressed. There is still need to conduct studies aimed to clarify the prognostic value of US findings at all stages of JIA. In addition, validation of US with MRI findings or histology in JIA is still scarce. The lack of internationally agreed definitions for the paediatric tenosynovitis and enthesitis is another gap in knowledge to fill. A great deal of efforts should also be exerted in future to devise and validate US scoring systems for joint pathological findings that are suitable for use in trials testing treatment response in JIA.

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