World Journal of Pediatrics
https://doi.org/10.1007/s12519-019-00312-9

REVIEW ARTICLE

Current status and recent advances on the use of ultrasonography in pediatric rheumatic diseases

Li-Xia Zou[1] · Mei-Ping Lu[1] · Lawrence Kwok Leung Jung[2]

Received: 18 August 2019 / Accepted: 26 August 2019

Abstract

Background Ultrasonography has become a useful tool in the clinical rheumatology settings in the last two decades, but its use has only recently been explored by pediatric rheumatologists. The aim of this article is to review the literature on the current status and recent advances on the use of ultrasound in pediatric rheumatic diseases.

Data sources We have retrieved and reviewed the relevant articles from MEDLINE/PubMed databases published so far, on the applications of ultrasound in juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, dermatomyositis, enthesitis, Sjogren's syndrome, and other rheumatic diseases. In addition, articles on novel ultrasound imaging technology of potential use in pediatric rheumatology are also reviewed.

Results In JIA, ultrasound can be used to detect subclinical synovitis, to improve the classification of patients in JIA subtypes, to capture early articular damage, to monitor treatment response, and to guide intraarticular injections. Ultrasound is also considered useful in other rheumatic disorders for the evaluation of musculoskeletal symptoms, assessment of parotid gland pathology, and measurement of skin thickness and pathology. Novel ultrasound techniques developed to augment the functionality of ultrasonography may also be applicable in pediatric rheumatic disorders.

Conclusions Ultrasound shows great promise in the assessment and management of children with rheumatologic disorders. However, standardization and validation of ultrasound in healthy children and in patients with rheumatic diseases are still needed.

Keywords Dermatomyositis · Juvenile arthritis · Lupus · Pediatric rheumatic diseases · Sonoelastography · Ultrasound

Introduction

Ultrasonography has become an important imaging modality that can improve early diagnosis, follow-up and monitor therapy in rheumatic disorders in adults [1–4]. However, the use of ultrasound in the pediatric population is still limited. Recently, pediatric rheumatologists are exploring its use in clinical pediatric practice. One area of concern has been the lack of standards in its use in pediatric rheumatology as normal ultrasound findings had not been well characterized in children. The Outcome Measures in Rheumatology ultrasound pediatric task force was formed to address this issue. Subsequently, a standardized musculoskeletal ultrasound (MSUS) examination procedure, adapted to children, was developed [5]. In addition, ultrasound definitions of normal joint features [6] and definitions for synovitis for children were recently proposed [7].

In this review, we will describe the current status of ultrasound applications in pediatric rheumatology and newer ultrasound technology that may be useful in pediatric rheumatology.

Principles of ultrasound technology

Recent advances in technology had led to the development of ultrasound machines that can produce high quality images and yet are portable enough for office use. The declining cost of the ultrasound machines further boosts their acceptability in routine clinical use.

✉ Lawrence Kwok Leung Jung
lawjunglemd@gmail.com

[1] Department of Rheumatology Immunology and Allergy, Children's Hospital, Zhejiang University School of Medicine, 57 Zhugan Lane, Hangzhou 310003, China

[2] Division of Rheumatology, Children's National Medical Center in Washington D.C., 111 Michigan Avenue NW, Washington, D.C., 20010, USA

Published online: 13 September 2019

The ultrasound technology is based on the generation of ultrasound wave by electrical stimulation of a piezoelectric crystal in the transducer. The wave traverses the target tissue and, depending on the nature of tissue, some of the ultrasound waves are reflected back to the transducer/piezoelectric crystal, where the wave energy is converted back to electric energy which is analyzed and displayed on the ultrasound machine computer screen. When the ultrasound wave travels through liquid, none is reflected and will appear black on the computer screen (anechoic). In contrast, if the wave encounters bone or metal object, it is reflected back to the transducer and results in a bright image on the computer screen (hyperechoeic). The time for the ultrasound to reach the transducer is used to calculate the depth of the reflecting surface. The frequency of the ultrasound wave determines the image quality. The higher the frequency, the higher the resolution, but this comes at the expense of the ultrasound penetration. High-frequency linear transducers (e.g., 10–18 MHz) are thus useful for superficial structures (skin, bone, etc.) and are used for scanning musculoskeletal structures, while low-frequency transducers (e.g., 5–10 MHz) are useful for deeper tissues such as abdominal organs. The "hockey stick" transducer with small-field of view is useful in assessing small joints in children.

Ultrasound machine also utilizes the well-known Doppler effect, in which a moving object reflected sound wave at different frequencies depending on whether it is approaching or receding from the sound source. Thus, the direction of blood flow can be detected (known as Color Doppler). Power Doppler assigns a color to the blood flow regardless of direction and is considered to be more sensitive for small vessels and slow flow. These techniques are useful for detection of small vessels in superficial tissues, as seen in inflamed sites [8]. Along with improvement in computer processing and memory storage capacity, recent novel ultrasound imaging techniques have been developed such as three-dimensional imaging, contrast-enhanced ultrasound (CEUS), and sonoelastography that will improve the application of US in medicine [9].

Advantages and limitations of ultrasound technology in pediatrics

The use of ultrasound in pediatric medicine is gaining favor due to its many favorable attributes over other imaging techniques [10]. It is child-friendly, noninvasive, easily accessible and involves no ionizing radiation. Compared to other imaging modalities, it is relatively low cost and avoids anesthesia and prolonged imaging time. Several joints can be studied in one session, and real-time dynamic study can be done. Ultrasound can be used to detect fluid collection or soft-tissue disease and to visualize musculoskeletal structures, such as muscle, fascia, tendon, ligament, synovium, cartilage, nerve, and bone surfaces. It is also able to detect inflammation and bone erosions before they become clinically evident [11]. In addition, US can be used to guide interventional procedures such as joint aspiration, synovial biopsy, and intraarticular or tendon sheath injections [12]. Therefore, the application of US in pediatric rheumatic diseases is expanding, and can be used not only in juvenile idiopathic arthritis (JIA), but also other rheumatic conditions such as systemic lupus erythematosus (SLE), dermatomyositis, enthesitis, Sjogren's syndrome, among others.

Many of the limitations of ultrasound in pediatric are similar to those in adult medicine: relatively small field of view, inability to assess deformed joints, lack of fine anatomic details compared to magnetic resonance imaging (MRI), inability to view tissue behind bone or other high-density objects, and operator-dependency. However, there are unique challenges in pediatric ultrasonography. In pediatric ultrasound, understanding the changes of anatomic structure with age is essential. This includes age-related variation of articular cartilage thickness, variation in amount of joint fluid, age-related vascularization, and ossification [13–15]. Only with careful collection of normative data, validation and consensus agreement, that the sonographers and pediatric rheumatologists can devise a precise scanning method for different age groups. Although systemic studies of normal sono-anatomy are being carried out, there remain many areas to be developed.

Another challenge is the lack of availability of ultrasonography to pediatricians in some parts of the world due to local regulations and financial constraints. This issue can only be resolved with changes in the political and economic landscapes and in the lowering of equipment costs for wider implementation of this technique globally.

Applications of ultrasound in pediatric rheumatology

Ultrasound in JIA

Juvenile idiopathic arthritis refers to a group of heterogeneous conditions involving chronic inflammatory arthropathy of unknown cause in childhood, with disease incidence of 1.6–23 per 100,000 and a disease prevalence of 3.8–400 in 100,000 [16]. It comprises of seven different clinical subtypes, based on the number of affected joints and the presence of extraarticular clinical manifestations [16]. Ultrasound can be a valuable tool for early diagnosis, evaluation and follow-up of JIA disease activity and for the assessment of treatment response.

Ultrasound in the diagnosis of JIA

Clinical examination in JIA may be imprecise and can underestimate the extent of joint involvement. Ultrasound has the potential to detect significant degrees of synovitis before

clinically evident and to discriminate inflammatory from noninflammatory joint diseases [17, 18]. However, for this goal to be realized, the sonographic characteristics of normal and inflamed joints in children need to be better defined. A number of ultrasound studies evaluating normal wrist, shoulder, knee, and hip as well as vascularization and ossification of joints in normal children had been published [13–15, 15, 19] and are useful references for determining normal sonographic appearances of the various joints. Recently, Roth et al., developed an ultrasound definition of synovitis covering the entire pediatric age range and it was validated in a web-based still images exercise. These results provided the basis for the standardized ultrasound assessment of synovitis in clinical practice and research [7]. Another scoring system of pediatric synovitis (PedSynS) for the elbow, radiocarpal, tibiotalar, mid-foot and finger joints had also been published [21]. Because of the presence of physiological vascularization, the sonographers need to adhere to the principle that synovitis should be detectable on greyscale (B-mode) and not based only on color/power Doppler alone [7].

Using MSUS as a tool, Haslam et al. found that 6 of 17 patients with early oligoarticular JIA (< 12 months) had subclinical synovitis, more frequently detected in the small joints of hands and feet [22]. This had the potential of increasing the joint count and changing the patient's diagnosis. This possibility thus, raised the issue whether MSUS has a role in the classification of JIA subtypes.

Ultrasound can also distinguish whether joint swelling is due to synovitis, tenosynovitis or both [23]. Pascoli et al. have reported that 42% of ankles thought to be clinically normal had ultrasonographic evidence of involvement of medial tendons, while less than 50% of the lateral tendons deemed to be clinically involved were found to be affected on ultrasound [24].

The clinical detection of enthesitis in children is challenging as elicitation of enthesis tenderness by palpation may be confused with fibromyalgia tender points. Detection of enthesitis may be improved with ultrasound. To define the normal greyscale ultrasound characteristics of entheses in the lower extremity, Lin et al. evaluated 702 entheses in 117 normal children and reported that entheseal thickness increased with age and weight [25]. In a study about JIA, 27 (12.5%) of the entheseal sites exhibited clinical enthesitis while 20 (9.4%) had ultrasound evidence of enthesitis by power Doppler (US-PD), including 10 that were considered clinically normal (50%). Clinical enthesitis and HLA-B27-positive status were significantly associated with positive US-PD findings [26]. In patients with enthesitis-related arthritis, recent studies confirmed that ultrasonography was more reliable in detecting enthesitis compared to clinical examination [27, 28].

Cartilage loss in JIA is an early indicator of joint damage before irreversible structural changes develop. However, evaluating cartilage loss in JIA patients is difficult, especially since cartilage thickness normally decreases with skeletal maturity [29]. Ultrasound can detect the cartilage of unossified epiphyses and the osseous nuclei before they become visible on plain radiographs [30]. In this regard, ultrasound is a useful tool for measuring cartilage thickness, and is highly correlated to MRI measurements. The intercondylar notch of the distal femoral cartilage may be the best anatomical point to assess cartilage thickness in the knee [31]. Cartilage thickness in the knee measured with ultrasound was significantly lower in patients with JIA, as compared with the control group, and notably lower in those with polyarthritis and systemic-JIA compared to the oligoarticular group, regardless of whether the examined joints were previously affected [32]. Similar research had shown significant cartilage thinning in JIA patients, particularly in the polyarticular subtype, and more in boys than girls [33].

Ultrasound is also useful for imaging bone erosions in rheumatoid arthritis [34]. However, it is more difficult to evaluate bony erosive changes in children, because irregularities in recently ossified bones can be misinterpreted as cortical erosions [35]. Nevertheless, the reliability of the ultrasound to detect bone erosions was excellent. In a recent study, the investigators observed a low prevalence of bone erosions of metacarpophalangeal (MCP) (10%) in patients with JIA [36]. Further validation and large-scale studies are required to determine the possible role of ultrasound in the detection of bone erosions in children.

Ultrasound-guided interventions

Intraarticular corticosteroid injections (IACI) is a common treatment for patients with JIA. The use of ultrasound-guided joint aspiration and injection can improve its success rate. By ensuring correct needle placement, ultrasound guidance can maximize treatment efficacy and minimize local complications [37]. In patients with inflamed small joints such as MCP and proximal interphalangeal joints, ultrasound improved accurate needle placement from 59% by palpation to 96% by ultrasound guidance [38]. Other studies had also shown significantly better results with ultrasound-guided steroid injections into joints for treatment of JIA in easily palpable joints or complex joints [39–42]. In addition, ultrasound-guided tendon sheath steroid injections were frequently used to treat patients with JIA. The ankle, specifically the medial compartment, was the site most commonly injected with ultrasound guidance in these patients [12]. In addition to IACI, ultrasound had been used to guide joint injection of infliximab in oligoarticular JIA to ensure safety and potential clinical benefit of this treatment [43].

Ultrasound in monitoring treatment response in JIA

Because ultrasound can directly visualize the synovial proliferation and joint effusion, it can be used for monitoring the

response to treatment. Semi-quantitative scoring of disease activity [44, 45] and more quantitative analyses of the vascular activity by monitoring pixel colors [46] are available to monitor response to treatment. Validity of using ultrasound in managing synovitis has been reviewed by Collado et al. [29].

Whether ultrasound findings can be used to predict flares for JIA in remission remains controversial. A number of studies indicated that ultrasound-detected synovial abnormalities were frequent seen in clinically inactive juvenile idiopathic arthritis [47], and these findings did not necessarily predict a flare of synovitis [48–50]. In contrast, De Lucia et al., in a 4-year study, showed that ultrasound abnormalities at baseline were strong predictors of relapse. In addition, irrespective of treatment, the risk of flare in ultrasound-positive patients was almost four times higher than those who were ultrasound-negative [51]. Miotto et al. also reported similar findings [52]. These contradictory findings are puzzling and may relate to different techniques and different definition of "subclinical synovitis" [53]. The current criteria for clinical remission of JIA do not include evaluation by ultrasound, and further studies should be performed to assess the true significance of ultrasound changes in relation to JIA activity and remission.

Ultrasound in juvenile SLE

Musculoskeletal symptoms are common in pediatric SLE and are associated with significant morbidity. In adults, ultrasound, and MRI studies suggested that new approaches to the diagnosis, classification, and evaluation of these symptoms are needed [54]. Recently, a study revealed an unexpectedly wide heterogeneity of pathologic ultrasound findings in the joints and tendons of patients with SLE, including synovial effusion, synovial hypertrophy, joint dislocation, bone erosion, calcifications, cartilage damage, tenosynovitis, tendon tear, and tendinitis/peritendinitis [55]. Furthermore, there was poor to moderate association between ultrasound abnormalities and disease activity indices and immunological findings [56]. However, comparing articular manifestations of lupus vs mixed connective tissue disease (MCTD) on ultrasound, the frequency and extent of joint involvement was much higher in MCTD [57].

There are very few studies of MSUS in pediatric lupus. Demirkaya et al. had noted effusions in the knee, ankle, elbow, wrist, flexor, and extensor tendons in pediatric SLE with 60% of the subjects having knee effusions [58]. Further research and validation are needed in children to define the role of ultrasound as an outcome measure for the musculoskeletal manifestations in pediatric SLE [59].

Using ultrasound to evaluate carotid intima-media thickness (CIMT) as the surrogate markers of atherosclerosis has been useful in identifying risk factors for atherosclerosis [60]. Recent studies have corroborated that higher CIMT and carotid arterial stiffness in active and inactive pediatric SLE may be early risk factors of atherosclerosis [61].

Ultrasound in juvenile myositis

Muscle and soft-tissue changes in myositis can take the form of edema within and around muscles, fatty infiltration, subcutaneous reticulation, and calcification. Ultrasound was used as early as 1988 to image muscles and abnormal signals were noted in the 3/5 patients with dermatomyositis [62]. There was gradual adaption of its use in this disorder [63]. Using quantitative muscle ultrasonography, studies had shown that muscle echo-intensity in patients with juvenile dermatomyositis first increased then normalized with successful therapy [64, 65]. In chronic myositis, the muscle could appear hyperechoic with decreased thickness due to fatty infiltration [66]. Recently, a study reported that ultrasound could readily differentiate muscle involvement from cellulitis and from deep venous thrombosis, the two conditions that are most commonly confused with focal myositis [67]. Thus, ultrasound could be used to diagnose focal myositis due to its greater availability and lower cost as compared to MRI. It could also guide aspiration of fluid/abscess and/or muscle biopsy and for follow-up [68].

Use of ultrasonography in other rheumatic conditions

Measuring skin thickness using ultrasound dated back to the mid-1980s and had been very reproducible [69, 70]. Its use in pediatric rheumatology had been adopted to evaluate patients with localized scleroderma [71] in terms of (1) tissue thickness, (2) tissue echogenicity, and (3) tissue vascularity by color Doppler. It showed great promise in clinical assessment of disease activity and a cooperative effort had resulted in a standardized protocol for acquisition and interpretation of ultrasound images for use in clinical and research settings [72].

The use of ultrasound in assessing parotid gland pathology in Sjogren syndrome had been ongoing in adult rheumatology community. Studies had shown that salivary gland ultrasonography (SGUS) may be useful in evaluating the presence of parotid gland involvement in patients with suspected or established primary Sjogren's syndrome [73, 74]. It could also be used for monitoring response to therapy [75, 76].

Ultrasound features seen in Sjogren's syndrome included multiple hypoechoic areas, hyperechoic lines of spots, and obscuration of gland configuration [77]. Scoring systems were devised to semi-quantify the degree of salivary gland involvement according to parenchyma homogeneity, echogenicity, gland size and posterior glandular border, presence of degenerative changes, fibrosis, and calcification ranging

from Grade 0 (normal salivary glands) to Grade 4 (diffuse structural damage of the glandular parenchyma) [77–79]. The addition of Doppler to evaluate parotid gland vascularity improved the sensitivity and accuracy of B-mode (greyscale) ultrasound and in the diagnosis of Sjogren's syndrome [80].

Ultrasonographic analysis of parotid gland is being introduced into the field of pediatric rheumatology [81, 82]. However, these are mostly case reports and a systemic study of this issue has not been done. As recurrent parotid swelling in childhood are often seen by pediatric rheumatologists due to concern for Sjorgren's syndrome, a proper study is urgently needed. Furthermore, since other diseases affecting the parotid glands such as sialadenitis or infection can be easily differentiate from juvenile Sjorgen's, the use of SGUS in pediatrics seems reasonable [83].

Novel ultrasound imaging technology in pediatric rheumatology

There are various ultrasound techniques which have been developed to augment the functionality of ultrasonography. Of these, sonoelastography and CEUS are of particular interest.

Sonoelastography is a novel quantitative ultrasound technique that provides additional information about soft tissue elasticity. The two most frequently used elastography techniques are strain (or compressive) elastography (SE) and shear-wave elastography (SWE) [9]. SE analyses the strain or displacement in response to freehand compression on the transducer and shows the relative tissue elasticity within a selected region of interest). SWE measures the compression of an automated pulse through the tissue and the shear-wave velocity is a measure of the tissue elasticity. These techniques complement the data acquired using gray-scale (B-mode), power, and color Doppler ultrasound by quantifying mechanical and elastic tissue properties [84].

Studies had been done using sonoelastography to characterize a variety of tissues such as tendons, muscles, and skins in children. Using SE, to evaluate juvenile dermatomyositis, a group of investigators had found that it only had a sensitivity of 40% and specificity of 67%. They concluded that SE could not replace MRI as the imaging standard for detecting myositis. But these investigators noted an association between abnormal ultrasound elastography and increased muscle echogenicity and suggested that SE elastography was capable of detecting muscle derangement in patients with myositis [85]. However, SE is subjective and a recent study in adults using the more objective SWE, showed that it could detect abnormal muscle stiffness which correlated with muscle weakness and MRI signs of edema and atrophy in idiopathic inflammatory myopathy [86]. Thus, further study using SWE in juvenile dermatomyositis is warranted.

In localized/systemic sclerosis, SWE has been used to detect skin stiffness in different clinical stages and to monitor disease severity and progression with high specificity, sensitivity and reliability [87, 88]. In Sjogren syndrome, SWE can provides further information compared to B-mode ultrasound, for the evaluation of salivary gland involvement. It was shown to be the most important tool, next to histological examination, for identifying early stage disease in primary Sjogren's syndrome [89]. In tendonosis, there was good correlation between SE and histologic evaluation as well as clinical markers of tendon pain and dysfunction [90].

CEUS increases the ability of sonography to evaluate tissue perfusion. During CEUS, a contrast agent consisting of microbubbles, which are 1–5 μM in diameter with a shell of lipids or protein and a core of inert gas of perfluorocarbon or sulfur hexfluoride, is injected intravenously. The microbubbles stay within the blood vessels and interact with the ultrasound pulse to generate a signal. CEUS can provide better evaluation of inflammatory arthritides in diagnosis, monitoring of disease progression, and assessment of response to therapy when compared with gray-scale ultrasound and power Doppler [91–93]. It also has potential of evaluating the vessel wall abnormalities and may be useful in managing vasculitic disorders [94]. The disadvantage of this technique is that the contrast needs to be injected and thus reduces it acceptability and convenience in pediatric medicine.

In Takayasu arteritis (TA), CEUS could help clinicians to monitor response to treatment. It could identify active lesions in the carotid by visualizing neovascularization as a consequence of arteritis even when erythrocyte sedimentation rate and C-reaction protein improved with treatment. Thus, CEUS can be used as an alternative method to assess disease activity and treatment response for TA patients [95, 96].

Because the microbubbles used in CEUS has the ability incorporate biologic molecules such as ligands for endothelial cell surface molecules, it can be used to study the molecules of interest in vivo. As an example, in a murine model of inflammatory bowel disease, targeted CEUS imaging enabled noninvasive in vivo quantification and monitoring of P-selectin expression in inflammation [97].

Conclusions

Ultrasound is likely to play an increasing role in the diagnosis and disease monitoring in children with rheumatologic disorders. It has many advantages over other imaging modalities including low cost, easy accessibility, real-time assessment, non-invasiveness and obviates the need for

sedation. Conventional and novel ultrasound imaging techniques continue to improve and show great promise in clinical medicine. However, as it is a relatively new approach in pediatric rheumatology, more work on the standardization and validation of ultrasound use in healthy children and in patients with rheumatic diseases are needed. In addition, further research and educational efforts are required for integrating ultrasound into routine clinical practice.

Author contributions LXZ collected and analyzed data and prepared the manuscript. MPL supervised the drafting and revision of the manuscript. LXZ and MPL contributed equally to this work. LKLJ contributed to the conception, drafting and revision of the manuscript. All authors approved the final version of the manuscript.

Funding This study is funded by Zhejiang Basic Public Welfare Research Project (LGF19H100002).

Compliance with ethical standards

Ethical approval Ethical approval was not obtained, since this is a literature review article.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Möller I, Janta I, Backhaus M, Ohrndorf S, Bong DA, Martinoli C, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. Ann Rheum Dis. 2017;76:1974–9.
2. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce—part 1: definition and development of a standardised, consensus-based scoring system. RMD Open. 2017;3:e000428.
3. Jeka S, Dura M, Żuchowski P, Zwierko B, Wojciechowski R. The role of ultrasonography in monitoring long-standing rheumatoid arthritis: a pilot study. Reumatologia. 2017;55:177–82.
4. D'Agostino MA, Wakefield RJ, Berner-Hammer H, Vittecoq O, Filippou G, Balint P, et al. Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Ann Rheum Dis. 2016;75:1763–9.
5. Collado P, Vojinovic J, Nieto JC, Windschall D, Magni-Manzoni S, Bruyn GA, et al. Toward standardized musculoskeletal ultrasound in pediatric rheumatology: normal age-related ultrasound findings. Arthritis Care Res (Hoboken). 2016;68:348–56.
6. Collado P, Windschall D, Vojinovic J, Magni-Manzoni S, Balint P, Bruyn GAW, et al. Amendment of the OMERACT ultrasound definitions of joints' features in healthy children when using the DOPPLER technique. Pediatr Rheumatol Online J. 2018;16:23.
7. Roth J, Ravagnani V, Backhaus M, Balint P, Bruns A, Bruyn GA, et al. Preliminary definitions for the sonographic features of synovitis in children. Arthritis Care Res (Hoboken). 2017;69:1217–23.
8. Ranjan S, Jahan A, Yadav TP, Sachdev N, Dewan V, Singh S. Evaluation of synovial inflammation in juvenile idiopathic arthritis by power color Doppler and spectral Doppler ultrasonography. Indian J Pediatr. 2014;81:29–35.
9. Nwawka OK. Update in musculoskeletal ultrasound research. Sports Health. 2016;8:429–37.
10. Magni-Manzoni S. Ultrasound in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2016;14:33.
11. Collado Ramos P. Ultrasound imaging in juvenile idiopathic arthritis for the rheumatologist. Clin Exp Rheumatol. 2014;32(1 Suppl 80):S34–41.
12. Peters SE, Laxer RM, Connolly BL, Parra DA. Ultrasound-guided steroid tendon sheath injections in juvenile idiopathic arthritis: a 10-year single-center retrospective study. Pediatr Rheumatol Online J. 2017;15:22.
13. Windschall D, Trauzeddel R, Haller M, Krumrey-Langkammerer M, Nimtz-Talaska A, Berendes R, et al. Pediatric musculoskeletal ultrasound: age- and sex-related normal B-mode findings of the knee. Rheumatol Int. 2016;36:1569–77.
14. Trauzeddel R, Windschall D, Trauzeddel RF, Nirschl C, Ganser G, Palm-Beden K, et al. Arthrosonographic reference values of the shoulder joint in healthy children and adolescents: a cross-sectional multicentre ultrasound study. Klin Padiatr. 2017;229:293–301.
15. Windschall D, Collado P, Vojinovic J, Magni-Manzoni S, Balint P, Bruyn GAW, et al. Age-related vascularization and ossification of joints in children: an international pilot study to test multi-observer ultrasound reliability. Arthritis Care Res (Hoboken). 2017. https://doi.org/10.1002/acr.23335.
16. Petty R, Laxer RM, Wedderburn LR. Juvenile idiopathic arthritis. In: Petty R, Laxer RM, Lindsley C, Wedderburn LR, editors. Textbook of pediatric rheumatology. 7th ed. Amsterdam: Elsevier; 2016. p. 188–204.
17. Damasio MB, Malattia C, Martini A, Tomà P. Synovial and inflammatory diseases in childhood: role of new imaging modalities in the assessment of patients with juvenile idiopathic arthritis. Pediatr Radiol. 2010;40:985–98.
18. Janow GL, Panghaal V, Trinh A, Badger D, Levin TL, Ilowite NT. Detection of active disease in juvenile idiopathic arthritis: sensitivity and specificity of the physical examination vs ultrasound. J Rheumatol. 2011;38:2671–4.
19. Żuber Z, Owczarek A, Sobczyk MI, Migas-Majoch A, Turowska-Heydel D, Sternal A, et al. Establishing percentile charts for hip joint capsule and synovial cavity thickness in apparently healthy children. Pediatr Rheumatol Online J. 2017;15:8.
20. Rosendahl K, Bruserud IS, Oehme N, Júlíusson PB, de Horatio LT, Müller LO, et al. Normative ultrasound references for the paediatric wrist; dorsal soft tissues. RMD Open. 2018;4:e000642.
21. Collado P, Naredo E, Calvo C, Gamir ML, Calvo I, García ML, et al. Reduced joint assessment vs comprehensive assessment for ultrasound detection of synovitis in juvenile idiopathic arthritis. Rheumatology (Oxford). 2013;52:1477–84.
22. Haslam KE, Mccann LJ, Wyatt S, Wakefield RJ. The detection of subclinical synovitis by ultrasound in oligoarticular juvenile idiopathic arthritis: a pilot study. Rheumatology (Oxford). 2010;49:123–7.
23. Rooney ME, Mcallister C, Burns JF. Ankle disease in juvenile idiopathic arthritis: ultrasound findings in clinically swollen ankles. J Rheumatol. 2009;36:1725–9.
24. Pascoli L, Wright S, Mcallister C, Rooney M. Prospective evaluation of clinical and ultrasound findings in ankle disease in juvenile idiopathic arthritis: importance of ankle ultrasound. J Rheumatol. 2010;37:2409–14.
25. Lin C, Diab M, Milojevic D. Grey-scale ultrasound findings of lower extremity entheses in healthy children. Pediatr Rheumatol Online J. 2015;13:14.
26. Jousse-Joulin S, Breton S, Cangemi C, Fenoll B, Bressolette L, de Parscau L, et al. Ultrasonography for detecting enthesitis in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2011;63:849–55.

27. Weiss PF, Chauvin NA, Klink AJ, Localio R, Feudtner C, Jaramillo D, et al. Detection of enthesitis in children with enthesitis-related arthritis: dolorimetry compared to ultrasonography. Arthritis Rheumatol. 2014;66:218–27.
28. Shenoy S, Aggarwal A. Sonologic enthesitis in children with enthesitis-related arthritis. Clin Exp Rheumatol. 2016;34:143–7.
29. Collado P, Malattia C. Imaging in paediatric rheumatology: is it time for imaging? Best Pract Res Clin Rheumatol. 2016;30:720–35.
30. Collado P, Jousse-Joulin S, Alcalde M, Naredo E, D'Agostino MA. Is ultrasound a validated imaging tool for the diagnosis and management of synovitis in juvenile idiopathic arthritis? A systematic literature review. Arthritis Care Res (Hoboken). 2012;64:1011–9.
31. Pradsgaard DØ, Fiirgaard B, Spannow AH, Heuck C, Herlin T. Cartilage thickness of the knee joint in juvenile idiopathic arthritis: comparative assessment by ultrasonography and magnetic resonance imaging. J Rheumatol. 2015;42:534–40.
32. Pradsgaard DØ, Spannow AH, Heuck C, Herlin T. Decreased cartilage thickness in juvenile idiopathic arthritis assessed by ultrasonography. J Rheumatol. 2013;40:1596–603.
33. Mitra S, Samui PP, Samanta M, Mondal RK, Hazra A, Mandal K, et al. Ultrasound detected changes in joint cartilage thickness in juvenile idiopathic arthritis. Int J Rheum Dis. 2019;22:1263–70.
34. Szkudlarek M, Terslev L, Wakefield RJ, Backhaus M, Balint PV, Bruyn GA, et al. Summary findings of a systematic literature review of the ultrasound assessment of bone erosions in rheumatoid arthritis. J Rheumatol. 2016;43:12–21.
35. Chauvin NA, Doria AS. Ultrasound imaging of synovial inflammation in juvenile idiopathic arthritis. Pediatr Radiol. 2017;47:1160–70.
36. Ventura-Rios L, Faugier E, Barzola L, De la Cruz-Becerra LB, Sánchez-Bringas G, García AR, et al. Reliability of ultrasonography to detect inflammatory lesions and structural damage in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2018;16:58.
37. Young CM, Shiels WE 2nd, Coley BD, Hogan MJ, Murakami JW, Jones K, et al. Ultrasound-guided corticosteroid injection therapy for juvenile idiopathic arthritis: 12-year care experience. Pediatr Radiol. 2012;42:1481–9.
38. Raza K, Lee CY, Pilling D, Heaton S, Situnayake RD, Carruthers DM, et al. Ultrasound guidance allows accurate needle placement and aspiration from small joints in patients with early inflammatory arthritis. Rheumatology (Oxford). 2003;42:976–9.
39. Laurell L, Court-Payen M, Nielsen S, Zak M, Fasth A. Ultrasonography and color Doppler in juvenile idiopathic arthritis: diagnosis and follow-up of ultrasound-guided steroid injection in the wrist region. A descriptive interventional study. Pediatr Rheumatol Online J. 2012;10:11.
40. Young CM, Horst DM, Murakami JW, Shiels WE 2nd. Ultrasound-guided corticosteroid injection of the subtalar joint for treatment of juvenile idiopathic arthritis. Pediatr Radiol. 2015;45:1212–7.
41. Baikar T, Chhabra A, Yadav TP, Sachdev N, Dewan V. Power color Doppler and spectral Doppler ultrasonography to evaluate response to intra-articular steroid injection in knee joints in juvenile idiopathic arthritis. Indian J Pediatr. 2017;84:826–32.
42. Habibi S, Ellis J, Strike H, Ramanan AV. Safety and efficacy of US-guided CS injection into temporomandibular joints in children with active JIA. Rheumatology (Oxford). 2012;51:874–7.
43. Vidovic M, Lamot L, Lamot M, Harjacek M. Intraarticular infliximab therapy in patients with juvenile idiopathic arthritis: the role of musculoskeletal ultrasound and disease activity scores in monitoring therapy response. Clin Exp Rheumatol. 2018;36:676–82.
44. Magni-Manzoni S, Epis O, Ravelli A, Klersy C, Veisconti C, Lanni S, et al. Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. Arthritis Rheumatol. 2009;61:1497–504.
45. Ting TV, Vega-Fernandez P, Oberle EJ, De Ranieri D, Bukulmez H, Lin C, et al. Novel ultrasound image acquisition protocol and scoring system for the pediatric knee. Arthritis Care Res (Hoboken). 2019;71:977–85.
46. Terslev L, Torp-Pedersen S, Qvistgaard E, Bliddal H. Spectral Doppler and resistive index. A promising tool in ultrasonographic evaluation of inflammation in rheumatoid arthritis. Acta Radiol. 2003;44:645–52.
47. Rebollo-Polo M, Koujok K, Weisser C, Jurencak R, Bruns A, Roth J. Ultrasound findings on patients with juvenile idiopathic arthritis in clinical remission. Arthritis Care Res (Hoboken). 2011;63:1013–9.
48. Magni-Manzoni S, Scirè CA, Ravelli A, Klersy C, Rossi S, Muratore V, et al. Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. Ann Rheum Dis. 2013;72:223–8.
49. Zhao Y, Rascoff NE, Iyer RS, Thapa M, Reichley L, Oron AP, et al. Flares of disease in children with clinically inactive juvenile idiopathic arthritis were not correlated with ultrasound findings. J Rheumatol. 2018;45:851–7.
50. Nieto-González JC, Rodríguez A, Gámir-Gámir ML, Boteanu A, López-Robledillo JC, Garulo DC, et al. Can ultrasound-detected subclinical synovitis be an indicator of flare recurrence in juvenile idiopathic arthritis remission patients on tapered TNFi? Clin Exp Rheumatol. 2019;37:705–12.
51. De Lucia O, Ravagnani V, Pregnolato F, Hila A, Pontikaki I, Gattinara M, et al. Baseline ultrasound examination as possible predictor of relapse in patients affected by juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2018;77:1426–31.
52. Miotto E, Silva VB, Mitraud SAV, Furtado RNV, Natour J, Len CA, Terreri MTSELRA. Patients with juvenile idiopathic arthritis in clinical remission with positive power Doppler signal in joint ultrasonography have an increased rate of clinical flare: a prospective study. Pediatr Rheumatol Online J. 2017;15:80.
53. Roth J. Predictive value of musculoskeletal ultrasound for flares in juvenile idiopathic arthritis. J Rheumatol. 2019;46:113.
54. Mahmoud K, Zayat A, Vital EM. Musculoskeletal manifestations of systemic lupus erythematosus. Curr Opin Rheumatol. 2017;29:486–92.
55. Di Matteo A, De Angelis R, Cipolletta E, Filippucci E, Grassi W. Systemic lupus erythematosus arthropathy: the sonographic perspective. Lupus. 2018;27:794–801.
56. Zayat AS, Md Yusof MY, Wakefield RJ, Conaghan PG, Emery P, Vital EM. The role of ultrasound in assessing musculoskeletal symptoms of systemic lupus erythematosus: a systematic literature review. Rheumatology (Oxford). 2016;55:485–94.
57. Gunashekar S, Prakash M, Minz RW, Sharma A, Sharma S, Dhir V. Comparison of articular manifestations of mixed connective tissue disease and systemic lupus erythematosus on clinical examination and musculoskeletal ultrasound. Lupus. 2018;27:2086–92.
58. Demirkaya E, Ozçakar L, Türker T, Haghari S, Ayaz NA, Bakkaloglu A, et al. Musculoskeletal sonography in juvenile systemic lupus erythematosus. Arthritis Rheumatol. 2009;61:58–60.
59. Wong PC, Lee G, Delle Sedie A, Hanova P, Inanc N, Jousse-Joulin S, et al. Musculoskeletal ultrasound in systemic lupus erythematosus: systematic literature review by the Lupus Task Force of the OMERACT Ultrasound Working Group. J Rheumatol. 2019. https://doi.org/10.3899/jrheum.181087.
60. Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, et al. Premature atherosclerosis in pediatric systemic lupus erythematosus: risk factors for increased carotid intima-media thickness in the atherosclerosis prevention in pediatric lupus erythematosus cohort. Arthritis Rheumatol. 2009;60:1496–507.
61. Su-Angka N, Khositseth A, Vilaiyuk S, Tangnararatchakit K, Prangwatanagul W. Carotid intima-media thickness and arterial

stiffness in pediatric systemic lupus erythematosus. Lupus. 2017;26:989–95.
62. Heckmatt JZ, Pier N, Dubowitz V. Real-time ultrasound imaging of muscles. Muscle Nerve. 1988;11:56–65.
63. Zaidman CM, van Alfen N. Ultrasound in the assessment of myopathic disorders. J Clin Neurophysiol. 2016;33:103–11.
64. Bhansing KJ, Hoppenreijs EP, Janssen AJ, van Royen-Kerkhof A, Nijhuis-Van der Sanden MW, van Riel PL, et al. Quantitative muscle ultrasound: a potential tool for assessment of disease activity in juvenile dermatomyositis. Scand J Rheumatol. 2014;43:339–41.
65. Habers GE, Van Brussel M, Bhansing KJ, Hoppenreijs EP, Janssen AJ, Van Royen-Kerkhof A, et al. Quantitative muscle ultrasonography in the follow-up of juvenile dermatomyositis. Muscle Nerve. 2015;52:540–6.
66. Weber MA. Ultrasound in the inflammatory myopathies. Ann N Y Acad Sci. 2009;1154:159–70.
67. Aslam F, Fox M, Chang-Miller A. Ultrasound for the rheumatologist—focal myositis. Acta Reumatol Port. 2017;42:336–8.
68. Nair JR, Nijjar M, Chiphang A, Binymin KA. Ultrasound-guided closed muscle biopsy: a useful tool for rheumatologists: case report: recurrent focal myositis of the gastrocnemius muscle. Rheumatol Int. 2013;33:799–801.
69. Tan CY, Statham B, Marks R, Payne PA. Skin thickness measurement by pulsed ultrasound: its reproducibility, validation and variability. Br J Dermatol. 1982;106:657–67.
70. Serup J. Localized scleroderma (morphoea): thickness of sclerotic plaques as measured by 15 MHz pulsed ultrasound. Acta Derm Venereol. 1984;64:214–9.
71. Li SC, Liebling MS, Haines KA. Ultrasonography is a sensitive tool for monitoring localized scleroderma. Rheumatology (Oxford). 2007;46:1316–9.
72. Li SC, Liebling MS, Ramji FG, Opitz S, Mohanta A, Kornyat T, et al. Sonographic evaluation of pediatric localized scleroderma: preliminary disease assessment measures. Pediatr Rheumatol Online J. 2010;8:14.
73. Mossel E, Delli K, van Nimwegen JF, Stel AJ, Kroese FGM, Spijkervet FKL, et al. Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjögren's syndrome. Ann Rheum Dis. 2017;76:1883–9.
74. Cornec D, Jousse-Joulin S, Marhadour T, Pers JO, Boisramé-Gastrin S, Renaudineau Y, et al. Salivary gland ultrasonography improves the diagnostic performance of the 2012 American College of Rheumatology classification criteria for Sjögren's syndrome. Rheumatology (Oxford). 2014;53:1604–7.
75. Jousse-Joulin S, Devauchelle-Pensec V, Cornec D, Marhadour T, Bressollette L, Gestin S, et al. Brief report: ultrasonographic assessment of salivary gland response to rituximab in primary Sjögren's syndrome. Arthritis Rheumatol. 2015;67:1623–8.
76. Fisher BA, everett CC, Rout J, O'Dwyer JL, Emery P, Pitzalis C, et al. Effect of rituximab on a salivary gland ultrasound score in primary Sjögren's syndrome: results of the TRACTiSS randomised double-blind multicentre substudy. Ann Rheum Dis. 2018;77:412–6.
77. Jonsson MV, Baldini C. Major salivary gland ultrasonography in the diagnosis of Sjogren's syndrome: a place in the diagnostic criteria? Rheum Dis Clin North Am. 2016;42:501–17.
78. De Vita S, Lorenzon G, Rossi G, Sabella M, Fossaluzza V. Salivary gland echography in primary and secondary Sjögren's syndrome. Clin Exp Rheumatol. 1992;10:351–6.
79. Theander E, Mandl T. Primary Sjögren's syndrome: diagnostic and prognostic value of salivary gland ultrasonography using a simplified scoring system. Arthritis Care Res (Hoboken). 2014;66:1102–7.
80. Jousse-Joulin S, D'Agostino MA, Nicolas C, Naredo E, Ohrndorf S, Backhaus M, et al. Video clip assessment of a salivary gland ultrasound scoring system in Sjögren's syndrome using consensual definitions: an OMERACT ultrasound working group reliability exercise. Ann Rheum Dis. 2019;78:967–73.
81. Nieto-González JC, Monteagudo I, Bello N, Martínez-Estupiñan L, Naredo E, Carreño L. Salivary gland ultrasound in children: a useful tool in the diagnosis of juvenile Sjögren's syndrome. Clin Exp Rheumatol. 2014;32:578–80.
82. Guissa VR, Martinelli EL, Brandão LMKR, Garcia LD, Provenza JR, Mendonça JA. Sonographic evaluation of salivary glands in juvenile Sjögren's syndrome. Acta Rheumatol Port. 2018;43:61–5.
83. García CJ, Flores PA, Arce JD, Chuaqui B, Schwartz DS. Ultrasonography in the study of salivary gland lesions in children. Pediatr Radiol. 1998;28:418–25.
84. Taljanovic MS, Gimber LH, Becker GW, Latt LD, Klauser AS, Melville DM, et al. Shear-wave elastography: basic physics and musculoskeletal applications. Radiographics. 2017;37:855–70.
85. Berko NS, Hay A, Sterba Y, Wahezi D, Levin TL. Efficacy of ultrasound elastography in detecting active myositis in children: can it replace MRI? Pediatr Radiol. 2015;45:1522–8.
86. Alfuraih AM, O'Connor P, Tan AL, Hensor EMA, Ladas A, Emery P, et al. Muscle shear wave elastography in idiopathic inflammatory myopathies: a case–control study with MRI correlation. Skeletal Radiol. 2019;48:1209–19.
87. Wang L, Yan F, Yang Y, Xiang X, Qiu L. Quantitative assessment of skin stiffness in localized scleroderma using ultrasound shear-wave elastography. Ultrasound Med Biol. 2017;43:1339–47.
88. Yang Y, Qiu L, Wang L, Xiang X, Tang Y, Li H, et al. Quantitative assessment of skin stiffness using ultrasound shear wave elastography in systemic sclerosis. Ultrasound Med Biol. 2019;45:902–12.
89. Hofauer B, Mansour N, Heiser C, Gahleitner C, Thuermel K, Bas M, et al. Sonoelastographic modalities in the evaluation of salivary gland characteristics in Sjogren's syndrome. Ultrasound Med Biol. 2016;42:2130–9.
90. Ooi CC, Richards PJ, Maffulli N, Ede D, Schneider ME, Connell D, et al. A soft patellar tendon on ultrasound elastography is associated with pain and functional deficit in volleyball players. J Sci Med Sport. 2016;19:373–8.
91. Wilson SR, Greenbaum LD, Goldberg BB. Contrast-enhanced ultrasound: what is the evidence and what are the obstacles? AJR Am J Roentgenol. 2009;193:55–60.
92. Chang KV, Lew HL, Wang TG, Chen WS. Use of contrast-enhanced ultrasonography in musculoskeletal medicine. Am J Phys Med Rehabil. 2012;91:449–57.
93. Zhao CY, Jiang YX, Li JC, Xu ZH, Zhang Q, Su N, et al. Role of contrast-enhanced ultrasound in the evaluation of inflammatory arthritis. Chin Med J (Engl). 2017;130:1722–30.
94. Czihal M, Lottspeich C, Hoffmann U. Ultrasound imaging in the diagnosis of large vessel vasculitis. Vasa. 2017;46:241–53.
95. Ma LY, Li CL, Ma LL, Cui XM, Dai XM, Sun Y, et al. Value of contrast-enhanced ultrasonography of the carotid artery for evaluating disease activity in Takayasu arteritis. Arthritis Res Ther. 2019;21:24.
96. Li Z, Zheng Z, Ding J, Li X, Zhao Y, Kang F, et al. Contrast-enhanced ultrasonography for monitoring arterial inflammation in Takayasu arteritis. J Rheumatol. 2019;46:616–22.
97. Deshpande N, Lutz AM, Ren Y, Foygel K, Tian L, Schneider M, et al. Quantification and monitoring of inflammation in murine inflammatory bowel disease with targeted contrast-enhanced US. Radiology. 2012;262:172–80.