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REVIEW ARTICLE

Limits and perspectives of ultrasound in the diagnosis and management of rheumatic diseases

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Abstract Musculoskeletal sonography (MSUS) has played a growing role in the diagnosis and management of rheumatic diseases, enabling the imaging of synovitis, bone erosion, and cartilage damage in the early phase of arthritis. "Dynamic" evaluation of tendons and help in guiding needle positioning in interventional manoeuvres are some of the other reasons for its success. MSUS, particularly when coupled with power Doppler (PD) examination, has recently been shown to be an efficient tool for monitoring disease activity and progression in rheumatoid arthritis, spondyloarthritis, crystal-related arthropathy, and osteoarthritis, with general consensus on its interesting results. More specifically, the PD signal has proved to be a simple and promising tool for short-term monitoring of synovial vascularity changes induced by steroids or biological agents in RA patients. MSUS has some limits, because of the physical properties of US and the quality of the equipment; it is, moreover, an operator-related imaging technique, with few standardized protocols. Future goals should be standardization of the examining approach in grey scale and Doppler ultrasound (US), including use of new equipment (3D US), extensive use in other fields (i.e. connective tissue diseases and vasculitis), and possible new applications (e.g. thoracic US).

Keywords Ultrasound · Rheumatic diseases · Therapy · Arthritis · Tenosynovitis

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Introduction

In recent years, musculoskeletal sonography (MSUS) has played a growing role in the diagnosis and management of rheumatic diseases. Even if traditionally, and still in some countries, i.e. USA, MSUS is performed mainly by radiologists, for a great number of rheumatologists this imaging technique has become a fundamental tool in their daily clinical practice [1]. The possibility of imaging synovitis, bone erosion, and cartilage damage in the early phase of the disease, dynamic evaluation of tendons, and fundamental help in guiding the needle positioning in interventional manoeuvres [2, 3] are some of the reasons for the success of MSUS compared with more invasive (or expensive) imaging techniques. MSUS, particularly when coupled with power Doppler (PD) examination, has recently been shown to be an efficient tool for monitoring disease activity and progression [4–21], helping the rheumatologist to assess the effects of therapy. Moreover, as is already known, ultrasound (US) examination is safe, with no radiation exposure, widely available, non-invasive, well-accepted by patients, low cost, and allows multiregional assessment.

Musculoskeletal sonography: what can we assess?

MSUS allows accurate evaluation of soft tissues and bone profile. Typical patterns are described for all the anatomical structures which can be visualized [22–28], both in healthy subjects (Table 1) and patients (Table 2). Rheumatologists' attention has always been focussed on joints, tendons, and bursae, but interest in other structures, such as nerves and vessels, is growing.

Table 1 MSUS patterns in healthy subjects

Joint	An hypoechoic intra-articular fat pad can be present (i.e. in metacarpophalangeal joints it appears as an inverted triangular area with homogeneous echogenicity). The joint capsule profile can be usually visualised indirectly by dynamic assessment (active or passive movement of the joint). Articular surfaces are visualized as sharp, continuous, and hyperechoic lines generating acoustic shadows
Tendon	In longitudinal scans normal tendons are characterized by a typical "fibrillar" pattern (tightly packed echoic bands with thin parallel linear echoes separated by fine anechoic lines) generated by the tight arrangement of parallel collagen fibres, while in transverse scans they appear as oval-to-round structures characterized by tightly packed echoic dots with homogeneous distribution (corresponding to the intra-tendinous connective fibres). If present, a tendon sheath may be visualizes as a thin hyperechoic line which does not follow the movements of the collagen fibres
Cartilage	Homogeneous anechoic layer with sharply defined hyperechoic outer and inner margins. The superficial chondro-synovial margin (interface between synovial fluid and cartilage surface) is a hyperechoic layer usually thinner than the deeper one (interface between cartilage and bone)
Bone	Continuous sharp hyper-echoic line which generates an acoustic shadow
Nerves	In longitudinal scan, present a typical "fascicular" pattern due to a discontinuous cluster of linear echoes. These echoes are generated by intra-neural connective fibres and are clearly detectable on a hypoechoic background delimited by a hyper-echoic margin. The distribution of connective tissue along the nerve is not as regular and homogeneous as in tendons. Thus, the morpho-structural pattern of the nerve may show considerable variation

Table 2 MSUS patterns in pathological conditions

Joint effusion	Anechoic or hypoechoic, compressible, homogeneous joint space widening
Synovitis	Homogeneous, non-compressible, echoic joint space widening indicating synovial proliferation appearing as irregular clusters of soft echoes (bushy and villous appearance) and/or homogeneous synovial thickening
Bone erosion	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes
Tenosynovitis	Tendon sheath widening, visible in longitudinal and transverse planes, resulting from effusion (anechoic pattern), proliferative synovitis (echoic pattern), or both (mixed pattern), and which may exhibit Doppler signal
Tendonitis	Focal or diffuse thickening of the tendon, which is associated with alteration in echogenicity which varies according to the duration of the process, its location, and the anatomical characteristics of the tendon. Tendon thickening is a typical feature of chronic tendonitis and is almost invariably associated with various intra-substance changes that include loss of fibrillar echotexture and patchy hypoechogenicity
Tendinosis	An extended and heterogeneous change of echogenicity is the main sonographic feature of definite tendinosis and is also a key finding in patients with familial hypercholesterolaemia
Tendon rupture	Discontinuity of the tendon visualised with the ultrasound beam exactly perpendicular to the tendon, appearing as fragmentation of small groups of contiguous fibrils, which determines a characteristic loss of the normal fibrillar echotexture of the tendon
Osteophytes	Appear as single or multiple characteristic irregularities of the bone profile, located at the edges of the joint surfaces

Joints

Effusion, synovitis, cartilage damage, and bone erosion are assessed by MSUS with high sensitivity (Fig. 1). Synovial proliferation and effusion are accurately distinguished and synovitis is visualized in some joints (e.g. finger joints) with higher sensitivity than MRI [29].

Structural damage of articular cartilage (thinning, loss of homogenicity and sharpness of the cartilage margins) are also imaged [30, 31].

Bone

MSUS is more sensitive than conventional radiography in the detection of joint erosion, which can be clearly visualized in rheumatoid arthritis (RA), spondyloarthritis (SpA), or crystal-related arthropathies, even in the early stage of the disease (Fig. 1) [32–34]. Even minimal interruptions or irregularities of the bone cortex due to fracture are depicted as clear breaks in the hyperechoic line of the cortical bone, often surrounded by hypo-echoic haematoma within the soft tissues.

Tendons

The typical "fibrillar" pattern of tendons is well-detected by US which is now considered the "gold standard" for their evaluation, because of the possibility of dynamic assessment. A wide spectrum of pathological changes such as essudative or proliferative tenosynovitis, swelling, tears (Fig. 1), tendinosis, dislocation, fibrosis, and crystal deposits are clearly detected [22–28, 34–36]. Kane et al. [37] reported that US is superior to MRI for detection of longitudinal split tendon tear, subluxed tendon, and snapping tendon.

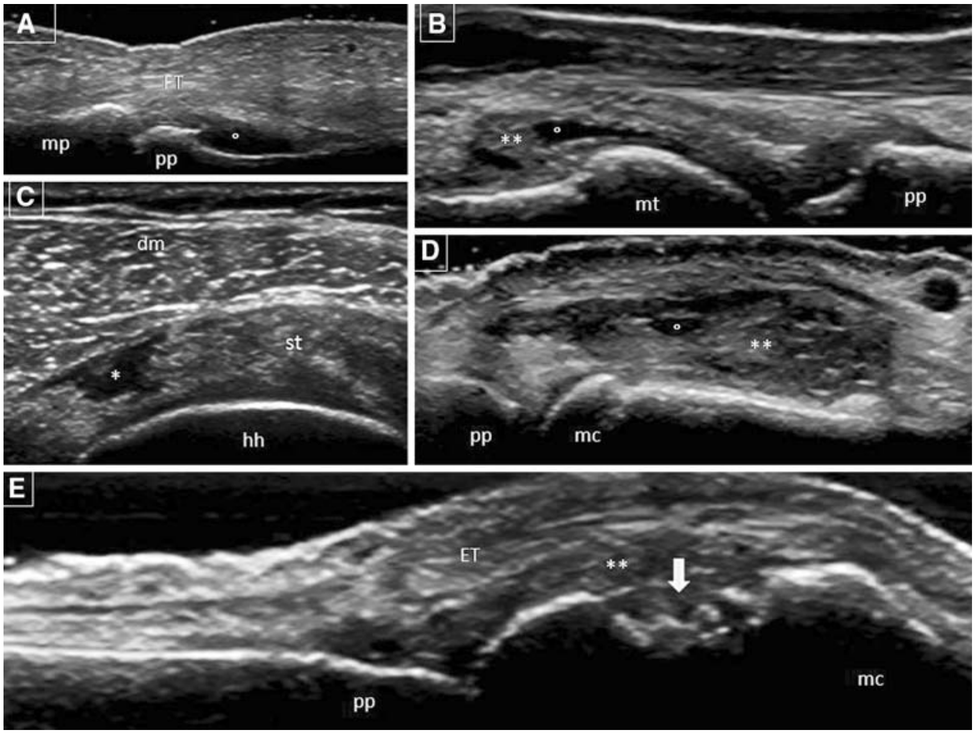

Fig. 1 (**a**) Rheumatoid arthritis. Volar longitudinal scan. Synovitis of the proximal interphalangeal joint. Joint cavity widening due to effusion (*open circle*). *pp*, proximal phalanx; *mp*, medium phalanx. (**b**) Rheumatoid arthritis. Dorsal longitudinal scan. Proliferative synovitis of the first metatarsophalangeal joint. Joint cavity widening due to synovial proliferation (*double asterisks*) and effusion (*open circle*). *mt*, metatarsal head; *pp*, proximal phalanx. (**c**) Shoulder pain. Transverse scan. Partial tendon tear (*single asterisk*) of the supraspinatus tendon. *hh*, humeral head; *st*, supraspinatus tendon; *dm*, deltoid muscle. (**d**) Rheumatoid arthritis. Volar longitudinal scan. Proliferative synovitis of the metacarpophalangeal joint. Marked joint cavity widening mainly due to synovial proliferation (*double asterisks*). *Open circle*, effusion; *mc*, metacarpal head; *pp*, proximal phalanx. (**e**) Rheumatoid arthritis. Volar longitudinal scan. Erosive synovitis of the second metacarpophalangeal joint. *Double asterisks*, synovial proliferation; *open circle*, effusion; *mc*, metacarpal head; *pp*, proximal phalanx; the *arrow* indicates bone erosion. All images represent grey scale US using a Logiq 9 (General Electrics Medical System, Milwaukee, WI, USA) with a 9–14 MHz linear probe

Nerves

Nerves appear with a typical fascicular pattern in US [28]. According to Kane et al. [37], US should be regarded as better than MRI and computed tomography in the assessment of nerves. The most clinically relevant application for US is in the evaluation of peripheral nerve entrapment. Several recent reports have proposed criteria for diagnosing carpal tunnel syndrome (CTS), the most important being a mean cross-sectional area of >10 mm^2 at the proximal entrance to the carpal tunnel, at the level of the pisiform bone [38]. US can also identify secondary causes of CTS (e.g. tenosynovitis of the finger flexor tendons, synovitis of the radio-carpal and/or inter-carpal joints, urate and amyloidosis deposits, aberrant muscles within the tunnel, arthrogenic cysts, post-surgical connective adhesion band).

Musculoskeletal sonography and therapy monitoring

Evaluation of rheumatic disease activity and response to therapy has been largely based on clinical assessment findings (tender and/or swollen joint count) and on the determination of serological markers of inflammation. However, the lack of validated and largely accepted tools for clinical assessment makes it difficult to monitor the efficacy of therapy. By MSUS we can image the changes in morphology and, if coupled with power and colour flow Doppler (CD), also in the degree of perfusion of articular and periarticular tissues in the course of therapy. MSUS associated with PD and CD examination is highly efficient in the follow-up and monitoring of therapy in RA [7–10, 13–19], early RA [11, 12], PsA [7, 9, 17], SpA [20], and gout [21].

Compared with MRI, arthroscopy, and histological examination, the PD signal in the assessment of synovial inflammation is highly sensitive [39–41].

More specifically, the PD signal has proved to be a simple and promising tool for short-term monitoring of synovial vascularity changes induced by steroids [4] or biological agents in RA patients, and, more specifically, in patients treated with infliximab [10–14], etanercept [15–18], and adalimumab [19].

The use of contrast media (intravenous microbubble), although hardly widespread, increases the sensitivity of the PD technique in the characterization of minimal flow [39]. Studies with longer follow-up are needed in order to provide further information concerning the persistence of significant reduction in PD signal score and its correlation with disease activity score, trying to provide information concerning the predictive value of rapid PD signal reduction for sustained remission of the disease at the small joint level.

Musculoskeletal sonography: limits

Application of MSUS in rheumatic diseases is limited by:

– the physical properties of ultrasound, which prevent its use in some conditions;
– the high-quality equipment required;
– the reputation of MSUS as one of the most operator-dependant imaging techniques; and
– lack of standardized scanning protocols.

1. The ultrasonic beam does not penetrate bone or metallic prostheses, so a restricted number of acoustic windows are available, limiting the possibilities of this imaging technique in some anatomic sites (e.g. the shoulder). Moreover, while bone profile is accurately defined, no data can be obtained about the features of deeper bone (i.e. it is impossible to detect bone edema).
2. MSUS certainly requires high-quality equipment [40] including transducers with different frequencies for examination of superficial and deep anatomic structures. Modern US machines, usually, allow good imaging, even if high-quality/frequency equipment is mandatory for the study of small and superficial joints (i.e. finger and toe joints). If it is true that grey-scale imaging is essential, it is now accepted that Doppler techniques also should be considered as an integral part of the basic armamentarium for MSUS [41]. For their technical features, great advances are expected from the introduction of 3D imaging.
3. It is well-established that operator experience and expertise may strongly influence the final results of US examination so that the perception that this technique is unproven and unreliable may arise. US still remains an operator-dependant imaging technique that needs a skilled sonographer; however, relevant basic findings (e.g. synovitis, bursitis and gross tendon pathology) are relatively easy to obtain by a rheumatologist with basic US training [42], as demonstrated also by Filippucci et al. [43]. Guidelines for appropriate training in US of rheumatologists have not been introduced and different approaches to overcoming the steep learning curve have been reported [42, 43]. To date, the MSUS learning curve of the rheumatologist is considered practically endless and, even if many different MSUS courses are now available all around the world, training with a more experienced sonographer remains of fundamental importance.
4. The lack of widely accepted scanning protocols to achieve good intra and inter-operator correlations is among the most important limits of US which creates great difficulties in the interpretation and comparison of studies. The OMERACT special interest group on US, which brings together experts in MSUS from all over Europe, was formed to highlight the main problems in application of US to rheumatic disorders [44–49]. Intra and inter-observer reliability, the most studied areas, were assessed in inflammatory and non-inflammatory diseases by a restricted and, in a second phase, by a larger number of rheumatologists who are experts in musculoskeletal US. The reliability was generally good with variability due to different joints and the type of disease. The emerging point was that while the OMERACT definitions [50] appeared to work well, differences occurred with regard to grading of pathologies and the technique of acquiring images. The principal differences in scanning methods and diagnostic criteria between experts were related to the use of dynamic examinations, definition of tendon lesions and pathological versus physiological fluid within joints, tendon sheaths, and bursae [46]. The same group also focussed the attention on synovitis of small joints in RA patients. The resulting intra and inter-reader reliability for detecting grey scale and PD synovitis on static images was very good, but when semiquantitative scores were required, lower values were noted. Evaluation of both acquisition and interpretation of images revealed variable intra and inter-reader reliability that was too high for regular use across centres in trials [47]. In order to reach an international consensus, the OMERACT special interest group on US is currently developing a comprehensive approach for scoring both synovitis and bone erosion in small joints of patients with RA. However a reliable method for scoring synovitis in large joints also is still lacking. Recently a preliminary scoring system was proposed for hand osteoarthritis (OA) involvement [51]. The OMERACT ultrasound special interest group first proposed, in 2005, a consensus on US definitions for the common pathological lesions seen in patients with inflammatory arthritis [50]. The lack of quantification of US pathology abnormalities is a problem which prevents advances in the application of MSUS in rheumatology.

Future developments in musculoskeletal sonography

Ultrasound is an imaging technique with a great number of potential benefits which need development. The list of future goals for this imaging technique includes:

- standardization of scanning protocols in grey scale and Doppler US;
- extensive use in more rheumatic disorders, for example connective tissue diseases and vasculitis;
- new applications (i.e. thoracic US in systemic sclerosis); and
- use of more advanced equipment (3D/4D US).

1. The OMERACT special interest group on US is continuing to refine and validate the scoring system proposed for synovitis and bone erosion in small joints of patients with RA [52] A scoring system has been proposed also for hand OA, but largely accepted scanning protocols and scoring systems are necessary for practically all rheumatic diseases. Furthermore, testing inter-machine reliability will be particularly interesting in view of multicentre clinical trials. Data are emerging also on the role of MSUS in longitudinal clinical trials [11, 12], but great efforts to better define this problem are needed. MSUS is a time-consuming technique and this is troublesome both for patients and physicians. A "practical" approach to making MSUS less time-consuming, with improvement in both physician and patient compliance, has recently been suggested by Naredo et al., showing that a targeted approach to US joint examination is comparable to a more comprehensive protocol [53].
2. MSUS have been widely used in "classic" arthritis (i.e. RA, SpA) whereas in other rheumatic chronic diseases (e.g. connective tissue diseases or vasculitis) it has not been used or has been poorly applied. The role of US in SLE has been reported by two studies which show the high frequency of subclinical joint involvement [54, 55]. Also preliminary studies on the evaluation of knee and hands in Sjögren syndrome gave promising results [56, 57]. Finally, MSUS, by enabling visualization of muscle fibre fine details and the presence of interstitial edema, can disclose the typical inflammation signs of myositis, even if with less sensitivity than MRI, and guide the needle for muscular biopsy [58–60]. In the field of vasculitis, US can assess the involvement of vessels, e.g. in temporal arteritis use of Doppler techniques is highly sensitive (95–100%) [61, 62]. Other intriguing applications are in Takayasu's arteritis and Raynaud's phenomenon [63, 64]. As already known, US can be used to measure skin thickness. Using a high frequencies probe (20 MHz or more) [65–68], it is possible to distinguish dermis from subcutaneous fat (enabling precise measurement of skin thickness) and to assess skin features (presence of edema or induration), so its application has been extended to the evaluation of patients affected by systemic sclerosis. A 17-point dermal US scoring method (approximating to those of the modified Rodnan skin score) has been proposed [65] and, recently, quantitative US has been used to study the effect of photochemotherapy in systemic sclerosis [66], so US could be an objective tool for study of disease progression and therapy monitoring, also in clinical trials.
3. A completely new US approach for disclosure of interstitial lung fibrosis is now under study and validation [69–71]. This method of examination could replace, or limit, the use of high resolution computed tomography in the follow-up of rheumatic disease patients with lung involvement.
4. The pursuit of more innovative approaches to US acquisition will probably be extremely important in the future. The most promising method is 3D US, which uses a volumetric probe providing automatic acquisition of a volume of echoes (representing a virtually infinite number of scanning planes lying under the footprint) with a single placement of the probe over the targeted region [72]. This innovative imaging is particularly interesting not only because of the high-quality images obtained but also because of its substantial operator-independence. Moreover, by use of this imaging technique evaluation of synovial perfusion using the PD [23, 24, 73] is simplified. In fact, computer-aided assessment of the volumetric pixel area of the synovial vessels could be a method of real objective quantitative estimation of the PD signal [1, 74].

Conclusions

Clinical applications of US in rheumatology are growing rapidly and an increasing number of rheumatologists are interested in such imaging techniques. Some questions are still to be addressed and will almost certainly form the basis of future research, mostly on the role of MSUS examination in therapy monitoring and in formal assessment of the extent and severity of several important rheumatic diseases. Future developments involving US applications in rheumatic disorders are keenly awaited by rheumatologists.

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