# New developments in ultrasound in rheumatology: innovative tools and promising applications

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**ABSTRACT**
*In the setting of rheumatology, the assessment of the involvement of joints and peri-articular structures was the first application of ultrasonography in the management of rheumatic diseases. In this field, the main novelties are related to the development of new technical tools to help overcome some of the limitations of conventional ultrasonographic assessment. In the meantime, there has been a growing interest in the application of ultrasound to extra-articular sites, relying on the definition of new indications. The present review aims to provide a critical analysis of the technical developments and new fields of application of ultrasonography in rheumatology.*

## Introduction

When ultrasonography made its way into rheumatology, in the same years of the evolution in the management of inflammatory arthropathies, the interest focused on the evaluation of joints and peri-articular structures. In the following years, significant and fast progression of technology allowed to achieve a greater definition of the images, and to develop Doppler techniques sensitive to the slow velocity flow of inflamed structures (1). Therefore, for many years the clinical applications of ultrasound to the articular involvement in rheumatic disease have been widely explored. In this setting, in which the application of ultrasound in supporting the diagnosis and follow-up of inflammatory arthropathies has been clearly defined, the interest has partially shifted towards the search for new technical developments to help overcome some of the limitations of ultrasonography. In fact, conventional ultrasound assessment can be in some sites limited by the available acoustic window, and while it can give detailed morphologic information, in some tissues a precise information on inflammatory changes cannot be obtained. Moreover, when assessing joints and tendons, the possibility to quantify the degree of abnormalities is limited.

In the meantime, growing interest in the application of ultrasonography in extra-articular sites has arisen (2). The main innovations in this field still relate to the validation of ultrasonography and to the full definition of clinical indication.

In this work, we aim to summarise the main novelties in ultrasound applied in rheumatology, with specific reference to new techniques meant to implement joint assessment and to new indications in the evaluation of extra-articular structures in rheumatic diseases.

## Technical developments in ultrasonography of joints and periarticular structures

The main technical novelties in musculoskeletal ultrasound and their features are summarised in Table I.

### *3D ultrasound*

One of the main drawbacks in ultrasonography, and musculoskeletal ultrasound makes no exception, is the operator-dependence.

The use of volumetric probes allows the evaluation of both grey-scale (GS) and colour or power Doppler (CDUS/PDUS) images in longitudinal, transverse and coronal planes, providing a multiplanar ultrasonographic evaluation. Several elementary lesions can be identified by 3D ultrasound, including synovitis, effusion and bone erosions. This technique requires the correct application of gel and probe and avoidance of movement during acquisition; however, even relatively unexperienced operators can acquire images. These characteristics have led to an

**Table I.** Main features of new ultrasonographic techniques to assess joints and peri-articular structures.

| Technique | Advantages over conventional ultrasonography | Disadvantages over conventional ultrasonography |
|---|---|---|
| 3D | Coronal plane<br>Image acquisition with limited experience<br>Shorter time of image acquisition<br>3D image reconstruction<br>Virtually unlimited viewing perspectives | Requires specific software<br>Static images only<br>Requires training to read 3D images with specific software |
| CEUS | Increase sensitivity to synovial flow in both superficial and deep structures | Requires contrast medium and intra-venous injection<br>Time consuming<br>Higher overall cost |
| Sonoelastography | Allows quantitative evaluation | Evidence on the application to tendons, no evidence on the joints<br>Prospective research missing |
| SMI | Increased sensitivity to synovial flow | Currently evidence mostly for small joints |
| Fusion | More structures can be visualised by image superimposition | Time consuming<br>Requires previous MRI/CT<br>Higher overall cost |
| Very high frequency probes (>20 MHz) | Detailed visualisation of superficial structures | Limited visualisation of deeper structures<br>Higher cost |

3D: 3-dimensional ultrasonography; CEUS: contras-enhanced ultrasonography; SMI: super microvascular imaging; MRI: magnetic resonance imaging; CT: computed tomography.

interest in the study of joints with 3D ultrasound, which also allows the image to be recorded and sent for central reading by an experienced operator.

In 2009 Filippucci *et al*. compared 2D and 3D ultrasound, looking for the ability to detect rheumatoid arthritis (RA) erosions and synovitis at the wrist and metacarpophalangeal joints. They reported a good-to-excellent inter-reader agreement between a centralised reader and each sonographer. These findings were subsequently confirmed by other authors (3-5).

The value of 3D ultrasound to follow-up RA patients receiving biological disease-modifying anti-rheumatic drugs (DMARDs) was also tested, demonstrating a high intra-reader agreement in detecting erosions, synovitis and synovial power Doppler (PD). The longitudinal assessment by 3D PDUS was in agreement with the results obtained with linear probes, but 3D scans had the advantage to minimise biases due to the operator's skills (6).

The value of 3D ultrasound in terms of prognosis was investigated by Sreerangaiah *et al*., who tried to create mathematical models to estimate the probability of bone damage progression in early RA biologic-naïve patients over 12 months of follow-up, depending on baseline synovial vascularity (5).

The applications of 3D PDUS are not limited to the field of RA, since its value has also been tested in the assessment of Achilles tendon involvement in spondyloarthritis (SpA) (7). In this setting, the agreement between 2D and 3D ultrasound ranged from good to excellent in assessing both inflammatory lesions and signs of damage.

In order to implement and standardise 3D ultrasound in rheumatic diseases, the application of an automated breast volume scanner (ABVM), developed to create 3D images of breast, has recently been tested to image the joints. ABVM does not imply expertise by the sonographer, since the examined joint is placed into water and the probe does not have contact with the skin, thus avoiding compression. However, the application of this technique might not be suitable to assess the joints, since a slightly reduced ability to detect synovitis, erosions and tenosynovitis compared to conventional US was demonstrated in preliminary studies (8).

Although an increasing amount of evidence from clinical research supports the value of 3D ultrasound, its implementation in clinical practice is far from common. This might be also due to the need of specific software for image acquisition, as well as to the training required for image interpretation. Besides, the acquired and processed 3D images are static, and their interpretation cannot be assumed to be made in real time.

*Contrast enhancement US*

Growing research has addressed the application of contrast-enhanced (CEUS) ultrasound in rheumatic diseases, a technique that uses microbubble-based contrast agents to intensify Doppler signal in small vessels and help identify synovitis; the administered contrast media do not leak outside the vascular bed into the extra-synovial compartments. This technique tries to overcome some limitations in the sensitivity of CDUS and PDUS, which can detect only vessels of a diameter >100 μm (9) and can provide false negative results in large joints.

A study on a rabbit model of experimental arthritis (10) evaluated the value of CEUS and PDUS in detecting synovial vascularisation confirmed histologically. The authors found that CEUS enhanced only the synovial membrane with a pattern correlated with both microvessel density and synovitis score better than PDUS, supporting the validity of this technique, with no side effects.

The majority of studies on human subjects compare CEUS and Doppler ultrasound, considering as reference standard to diagnose synovitis DCE-MRI (Dynamic Contrast-Enhanced MRI), or compare the techniques to the vascularisation of histological samples. Otherwise, other studies compare the techniques to the vascularisation of histological samples.

One of the first papers applying CEUS in RA (11) found that this technique had various advantages compared to CDUS: the use of a contrast agent improved the detection of flow signals in a heterogeneous population of RA, including inactive, moderately active and active disease. In particular, CEUS allowed distinguishing patients with moderately active and very active joint inflammation, while standard ultrasound was unable to differentiate.

These results were confirmed in a comparative study of RA patients with clinically active disease and remission: the patients underwent CEUS in water immersion of the hands and stabilisation of the probe. A high inter-observer agreement was shown, moreover, synovial enhancement was found only in patients with active disease, while PDUS was negative in a portion of those subjects (12).

The utility of CEUS was also assessed in psoriatic arthritis (PsA) (13), showing the prolongation of the contrast-refilling time and the positive association of peak of contrast intensity to the histological presence of growing vascularisation (CD31+ and CD105+ vessels). In a subsequent study, the authors created a pixel-based CEUS assessment that could accurately quantify synovial inflammation in PsA (14).

While, in general, recent high-end ultrasound equipment has an adequate performance in detecting flow in the small and superficial joints, Doppler techniques often lack of sensitivity in large and deep joints. At the level of hips and shoulders, CEUS demonstrated a better sensitivity than PDUS to detect disease activity in inflammatory arthritis (15-17), although still lower compared to contrast-enhanced MRI (16). A further possible application of CEUS might be in the field of inflammatory back pain. In fact, CEUS assessment of the sacroiliac joints exhibited a high negative predictive value for active sacroiliitis (17).

Despite the interest in the diagnostic application of CEUS, longitudinal studies on this technique are still lacking. Moreover, its use implies a greater effort in performing ultrasound and increased costs, which might be regarded as obstacles for its extensive application.

*Doppler enrichment (Superb microvascular imaging)*

Superb microvascular imaging (SMI) is a technique that enhances low-flow signals, suppressing tissue motion artifacts by an algorithm incorporated into the ultrasound system.

One of the first studies assessing this technique compared SMI and PDUS, showing an improvement in detecting synovitis in RA patients, both with active disease and clinical remission, with the new method (18).

Orlandi *et al.* evaluated PDUS and SMI in detecting synovitis, in treatment-naïve early RA patients and patients treated with rituximab (19). The inter-observer agreement was very high with both techniques, while a higher detection of synovial blood flow with SMI compared to PDUS was identified especially in early patients; both techniques demonstrated a significant correlation with disease activity parameters, showing concurrent validity.

In line with these results, subsequent studies found this technique useful in detecting with greater accuracy active synovitis in inflammatory arthritis, compared to PD, and similarly in clinical remission. They also described that SMI results can be correlated to serological inflammatory markers (20, 21).

Recently, SMI was applied to RA patients in stable remission and patients experiencing a flare in a subsequent two-year follow-up (22). Patients with a flare had higher baseline SMI scores in both hands and feet, in particular the presence of a SMI score ≥1 in the wrist was an independent predictor of recurrence, while a GS-SMI combined score ≤4 in metacarpophalangeal joints 2-5 independently predicted prolonged remission.

While many studies examined the performance of SMI in small joints, the evidence on larger joints is more limited. A single study on a mixed population of inflammatory arthropathies compared SMI and PD in different joints, including the knee, and showed no difference between the two techniques (21). A very recent study examined the performance of SMI and PD in knee osteoarthritis (OA), correlating SMI findings with clinical features and MRI findings. SMI proved to lead to an increased detection rate of vascularisation, and this correlated with scores of clinical and MRI involvement (24).

Besides the application for the evaluation of the joints, SMI has also been tested to assess periarticular structures, showing increased vascularisation in arm extensor tendon pathology and carpal tunnel syndrome (23).

To date, no studies compare SMI to histologically-detected synovitis, providing the full validation of this method. Moreover, more studies on the assessment of large joints in larger populations of inflammatory arthropathies might help provide a greater insight into the potential of this technique.

*Sonoelastography*

Sonoelastography (SE) has been widely used in the last years to detect parenchymal fibrotic alteration in many conditions, including liver, breast and prostatic diseases. This technique is based on tissue response to compression and decompression external waves, allowing the measurement of tissue stiffness. SE include principally strain elastography (qualitative assessment that compare stiffness between one tissue and another) and shear wave elastography (quantitative assessment that estimate a value of tissue stiffness). More recently, this technique has been applied in the evaluation of tendon pathology. In fact, inflamed tendons contain higher amounts of fluid and inflammatory infiltrates, becoming softer.

Turan *et al.* in 2013 performed a case-control study on the Achilles tendons of patients with Ankylosing Spondylitis (AS): they described that AS patients had pathological alterations in the distal third of the tendon, while healthy controls (HCs) in the middle third, both in B-mode and in SE. These abnormalities were associated with clinical pain and

signs of enthesopathy such as tendon thickening (25). In AS patients treated with TNF-blocking agents in clinical remission, with negative PDUS and SMI, the stiffness of Achilles tendon assessed by SE was comparable to HCs, with the exception of an increased thickness in the middle third of the tendon (26).
SE has also been applied to assess carpal tunnel syndrome (CTS). Orman et al. observed that patients with CTS had stiffer median nerves than controls and, when correlating the tissue strain with electromyography, a decreased tissue strain in patients with more severe neuropathy, although without reaching statistical significance (27).
Similarly, Miyamoto *et al.* found that CTS patients had higher stiffness in both median nerve and intra-carpal tunnel content than controls, as well as a bigger transverse area of the nerve. They also demonstrated that corticosteroid injection decreased only the stiffness of carpal tunnel content and not of the nerve, despite reducing pain (28).
Shear wave elastography (SWE) (29) was also used to quantitatively assess cross-sectional areas and stiffness of the median nerve in patients and unaffected controls. Patients had bigger areas of the nerve at carpal tunnel inlet and estimated a cut-off of 9.5 $mm^2$ to diagnose CTS with 0.60 sensitivity and 0.92 specificity; the stiffness of the nerve was increased, with a diagnostic cut-off of 40.4 kPa (sensitivity 0.93, specificity 0.89 to diagnose CTS). Inter-observer agreement was excellent.
Although SE can be regarded as a promising method to assess nerve and tendon pathology, with particular reference to SpA in rheumatology, prospective studies assessing its sensitivity to change and value in the follow-up of tendon involvement are still missing.

*Fusion imaging*
In recent years, in several fields the application of fusion imaging (FI) techniques has supported a better anatomical definition of the structures under investigation and drove imaging-guided procedures. FI implies the superimposition of images obtained by two different techniques. This allows, in the case of ultrasound, to combine images (and thus information) from CT or MRI and real-time US images. In this way, the advantages of both techniques can be exploited, with the detailed images of both superficial and deep structures, including the bone, provided by MRI and CT, and the real time information (including PD examination) that can be visualised through ultrasound.
So far, the only application of FI in rheumatology has been the comparison of patients with OA and RA with MRI/US FI, which found a great agreement in the assessment of OA osteophytes and RA bone erosions (30). Further potentialities of fusion imaging include the assessment of areas with poor acoustic window and deeper structures, in which only the most superficial layers are accessible by ultrasound. Moreover, information on bone damage, obtained by CT or MRI, can be added to the information on vascularisation provided by ultrasound Doppler imaging. The need of specific software and an increased complexity might be regarded as the main obstacles against its diffusion.

## New applications of ultrasound to extra-articular targets

The main advantages and limitations of the novel applications of ultrasound to extra-articular sites are reported in Table II.

*Vasculitis*
The main application of ultrasound in vasculitis are large-vessel vasculitis (LVV), while minimal data are present about ultrasound in small-vessel vasculitis, because of the impossibility to assess smaller vessels. LVV include giant cell arteritis (GCA) and Takayasu's arteritis (TAK). In this context, EULAR recommends early imaging, especially ultrasound, for diagnostic purposes (31).
In GCA, ultrasound is useful in detecting the "halo sign" in the temporal arteries and in the visualisation of temporal, axillary and abdominal aorta, however EULAR recommendations have a poorer agreement on its role in visualising thoracic aorta and in monitoring long-term structural damage.
Because of the risk of vision loss in GCA, many studies focalised on creating a probability score in fast-track clinics, including ultrasound (32-34), to achieve a quick diagnosis. The minimum standard for the ultrasonographic assessment of GCA includes CDUS of temporal and axillary arteries (35). Nevertheless, diagnostic accuracy has not been largely evaluated and no clear data are available on ultrasound in the follow up and monitoring of GCA patients (31). The main limit is the poor assessment in extra-cranial arteries. Attention must be paid in differentiating inflammatory wall thickening and atherosclerosis in ultrasound examination. Usually they differ considerably, but, as described by De Miguel *et al.,* atherosclerosis may mimic intima-media thickening and halo sign in large vessels (36).
Recently Dasgupta *et al.* (37) described the "slope sign" at the axillary arteries, a smooth, long transition from increased to normal intima-media thickness in vasculitis, whereas in atherosclerosis the transition is short, localised and distinct (38). The authors postulate that it may be used in differentiating vasculitis from atherosclerosis (38). Recently a "halo score" was proposed to quantify the extent of vascular inflammation, in order to stratify GCA patients to individuate patients at high risk for ocular ischaemia (39).
In TAK, limited data are available. Nevertheless, ultrasound could detect vasculitic wall thickening, stenosis, aneurysms and other vessel abnormalities (33, 40). Recently, Svensson *et al.* (41) proposed ultrasound in evaluating the inflammatory changes in carotid vessel, monitoring the intima-media thickness and its echogenicity. They scanned 25 TAK patients and proposed the "Takayasu ultrasound index", where intima-media thickness from different vessels are scored. The score was higher in active compared with treated disease, suggesting a role of ultrasound to monitor inflammatory changes. Furthermore, ultrasound in TAK is useful in detecting the "Macaroni sign" (42), a homogeneous and circumferential wall-thickening, together with stenosis detectable at the common and internal carotid, vertebral, and brachial arteries.
Since 2014, CEUS was proposed in TAK since at the carotid arteries it could reveal vascular wall neovascu-

**Table II.** Main advantages and limitations of novel applications of ultrasound in the assessment of extra-articular structures in rheumatic diseases.

| Disease | Advantages | Limitations |
|---|---|---|
| Large-vessel vasculitis | Easily accessible compared to biopsy<br>Immediate application in fast-track outpatient clinics | Unable to assess thoracic aorta and cranial vessels<br>Possible difficulties in differential diagnosis with atherosclerosis<br>Limited information on Takayasu arteritis |
| Systemic sclerosis | Allows reliable assessment of skin involvement | Often requires specific equipment, with limited current availability<br>No clear data on the best sites of ultrasound image scan |
| Inflammatory myopathies | Easily accessible compared to biopsy<br>Allows ultrasound-guided biopsies, thus avoiding open biopsies | Limited number of studies |
| Interstitial lung disease | Absence of ionising radiation<br>Possible screening tool before considering CT | Poor standardisation<br>Impossibility to assess deeper areas |
| Primary Sjögren's syndrome | Non-invasive assessment of major salivary glands for diagnosis and follow-up | Possible false negatives |

CT: computed tomography.

larisation, a potential marker of disease activity (43). In 2017, Germanò *et al.* demonstrated correlation between carotid CEUS and vascularisation grade showed by 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) in LVV (44). More recently, Li *et al.* compared CEUS with FDG-PET in detecting carotid active lesions in TAK, confirming the value of CEUS (45).

In the setting of vasculitis, therefore, the use of ultrasound has already successfully faced the stage of initial validation. In this field, we can expect a significant evolution in the next years and an increased diffusion of this application.

*Systemic sclerosis*

Ultrasound is known to be useful in systemic sclerosis (SSc) to identify joint and tendon involvement and subcutaneous calcifications. More recently, it has been proposed for the evaluation of skin features, given the unsatisfactory reliability of the modified Rodnan skin score (mRSS) (46). High frequency ultrasound and SE can be applied in visualising skin thickness and elasticity, although the available studies are heterogeneous in terms of equipment, location and sites (47-49).

High frequency ultrasound (HFU) (≥15–18 MHz) is used to describe skin thickness in SSc patients. Li *et al.* (50) recruited 31 SSc patients and HCs and evaluated the mRSS and ultrasonographic skin thickness and echogenicity. Like in previous reports (47), ultrasonographic skin thickness correlated positively with mRSS and disease duration, but negatively with skin echogenity. This may be explained by the presence of skin oedema in early disease, suggesting that ultrasound may help distinguish early oedematous disease from early fibrosis and subclinical thickening.

Hesselstrand *et al.* (51) followed SSc patients for one year, evaluating skin HFU and clinical changes: ultrasonographic skin thickness showed a positive correlation with clinical assessment (mRSS) and questionnaire (HAMIS test). Hughes *et al.* (52) proposed HFU to assess digital ulcers. HFU was feasible, well tolerated and the images allowed measurement of width and depth of the ulcer.

A recent study by Naredo *et al.* (53) assessed the performance of ultra-high-frequency ultrasound (UHF-US) (>50 MHz probe) to evaluate skin thickness evaluation and discriminate between SSc and HCs. UHF-US allowed a precise measurement, demonstrating a higher dermal thickness in SSc compared with HCs. Early disease involved particularly hypodermis layer, sparing the dermal layer.

SE can also be applied in SSc to assess skin elasticity. Di Geso *et al.* (48) applied SE on the second finger in the dominant hand and found a correlation with GS. They proved that SE can improve the reliability in skin thickness measurement, especially at fingers, helping identify the dermis/hypodermis interface. Nevertheless, Iagnocco *et al.* (49) reported SE variability in digital evaluation, suggesting that the phalanx bone profile could interfere, while results obtained at the forearm were confirmed in subsequent studies (54).

SWE was also recently applied to SSc (55), demonstrating a difference between elastic modulus values in 60 SSc compared to HCs, at fingers and forearm. The intra and inter-observer reliability were good. This study demonstrated also a correlation between mRSS and skin stiffness and thickness.

The assessment of macro and microvascularisation in SSc has been recently studied (56). PDUS was used in evaluating resistivity index (RI), finger pulp blood flow and periungual vascularisation, while nailfold video-capillaroscopy to assess capillaries apex. Iloprost administration caused an acute effect on PDUS, but no chronic effects. A further study (57) hypothesised that macro and microvascular involvement in SSc patients are distinct processes and develop in different time.

The application of ultrasound to assess skin and ulcers in SSc might gain relevance in particular for the follow-up of cutaneous involvement, due to the limitations in the assessment by clinical means.

*Polymyositis and dermatomyositis*

Only a few studies assessing muscle changes in polymyositis/dermatomyositis (PM/DM) are available: ultrasound may be useful in detecting isoechoic appearance, muscle oedema (in acute disease) and atrophy (in chronic disease) (58, 59).

Because echogenicity has been linked to histological features (60), ultrasound-guided muscle biopsy might allow the avoidance of open surgical biopsy (61, 62). The performance of surgical and ultrasound-guided muscle biopsy seemed comparable in terms of diagnosis and safety (61).

CEUS was also proposed for diagnostic purposes (63), whereas PD may be useful in detecting the response to treatment (64).

Ultrasound was proposed to discriminate inclusion body myositis and PM/DM: high echoic signals in the medial gastrocnemius (compared to the soleo) were seen in inclusion body myositis, but not in DM/PM and controls (65). A similar differentiation was already described in the forearm by Noto *et al.* (66).

Machine learning is probably the future evolution: texture analysis (by mathematical analysis) of ultrasound images may distinguish muscle disease (inclusion body myositis, myotonic dystrophy type 1, PM/DM) (65).

*Interstitial lung disease in rheumatic diseases*

In the last 2 decades, many studies were conducted to demonstrate the usefulness of ultrasound assessment in lung disease. On this wave, lung ultrasound has been considered in early diagnosis of interstitial lung disease (ILD) in connective tissue diseases and ANCA-related vasculitis.

The detection of B-line correlates well with the high-resolution computed tomography (HRCT) score, as described by Cogliati *et al.* (67), leading to the idea that lung ultrasound may be a new technique in detecting ILD in rheumatologic disease.

An interesting review by Gutierrez *et al.* (68) proposed lung ultrasound as a screening tool in the management and evaluation of ILD, especially in connective tissue disease. Recently, Hai Qin Xie *et al.* (69) performed a systematic review of the literature on lung ultrasound in connective tissue disease, finding no evidence and standardisation in the evaluation, so far. Based on the available evidence, the evaluation of 14 lung intercostal spaces in bilateral anterior and posterior location may be the best compromise between diagnostic performance and time-consumption, allowing high sensitivity and specificity. Even if HRCT is considered the gold standard in ILD evaluation, lung ultrasound may play a role as screening tool in preclinical and early stages of the disease, due to the absence of ionising radiation and simple execution (70).

Lung ultrasound was also tested in the ANCA-associated vasculitis (71). The detected lesions were heterogenous: nodules, infiltrations, alveolar haemorrhages, caves and fibrosis. The sensitivity of lung ultrasound compared with HRCT was 79% (71), the main limitation is the difficulty in the detection of lesions not adjacent to the pleural line (72).

Due to a limited acoustic window and the difficulties in differentiating active inflammation from damage, the possible placement of ultrasound in the management of rheumatic disease is probably complementary to other imaging, in particular CT.

## Sjögren's syndrome

In primary Sjögren's syndrome (pSS), ultrasound emerged as a useful technique in the assessment of major salivary glands for diagnostic purpose (73), evaluation of response to treatment (74) and follow-up. The creation of a score was firstly proposed by De Vita *et al.* in 1992 (75), and many studies identified echostructural abnormalities characteristic of pSS (76-78). In 2019, OMERACT developed an agreement in the definition of normal salivary gland ultrasound appearance and pSS salivary gland abnormalities (79). They proposed to score pSS lesions only in greyscale and described a better reliability when evaluating anechoic/hypoechoic areas (in a semiquantitative matter or, if not possible, qualitatively) and fatty or fibrous lesions.

Salaffi *et al.* (80) compared ultrasound with histological changes, showing that ultrasound is useful in evaluating salivary gland involvement in pSS. More recently, Mossel *et al.* (81) enrolled 103 patients with clinically suspected pSS, which underwent both salivary gland ultrasound and salivary gland biopsy. In this cohort, positive ultrasound may predict pSS diagnosis, whereas negative ultrasound does not exclude pSS diagnosis because it underestimates pSS in a subgroup of SSA-negative patients.

Ultrasound has been also used in monitoring disease damage (82): salivary impairment (measured by sialometry and VAS oral dryness) was compared with ultrasound gland lesions, suggesting that hyperechoic bands might be associated with pSS gland damage. Also, Inanc *et al.* associated salivary gland ultrasound to patient-reported severity (83).

The use of CDUS/PDUS of the salivary gland has been of interest in the early 2000, as a tool to monitor hypervascularisation, salivary gland size and Doppler waveform (84, 85), but no further studies have been conducted because of the complex vascularisation system of salivary glands, leading to a limited feasibility. Recently a reliability exercise by OMERACT was conducted by 9 sonographers on 9 pSS patients and reported a good to excellent inter and intra-reader reliability in the assessment of salivary gland vascularisation (86). Further studies are needed for determining clinical applicability in a larger population of pSS patients.

SE, first used in detecting malignancy in salivary glands (87, 88), was introduced primarily in pSS for discriminating pSS patients and HCs. Samier-Guerin *et al.* (89) detected higher shear wave velocity in pSS patients compared with HCs, suggesting that parotid but not submandibular SE may play a role in the detection of abnormal gland changes, contributing to the pSS diagnosis.

According to Gunes Tatar *et al.* (90), SE might also be useful in monitoring the progression of the disease. They reported that patients with long duration of pSS symptoms presented increased elasticity score of the parotid gland compared with newly diagnosed patients.

The European HarmonicSS project has recently proposed original developments (91) in salivary gland ultrasound: image segmentation, that should offer automatic evaluation of salivary gland images by computer analysis, and the development of a salivary gland damage score, evaluated by ultrasound that might be proposed to the patient much frequently (compared with salivary gland biopsy) to assess response to treatment. These data confirm the important role of ultrasound in the study of pSS in the future.

## Conclusions

Ultrasonography is now increasingly available to support clinical diagnosis and follow-up in rheumatic diseases. Several technical novelties targeting musculoskeletal involvement have been introduced, though, in some cases, a still limited validation, the need of specific training for some of these tools and, more in general, limited availability, impede their immediate introduction in clinical practice. Because of the currently limited diffusion of these tools, the correct placement of such techniques in the context of the management of rheumatic diseases is still to be fully defined. In the setting of connective tissue diseases and vasculitis, there is an increasing interest in the application of ultrasound in extra-articular sites, with good results especially in the field of vasculitis and pSS. Based on this consideration, we can expect that some of these tools might become part of the routine ultrasonographic evaluation on rheumatology in the near future.

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