
Optimising ultrasonography in rheumatology

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ABSTRACT

Ultrasonography is an imaging modality that has been utilised in clinical medicine since the 1950s. However, application to joints and rheumatic disease was delayed until appropriate advances in technology made it feasible. Since the 1990s, rheumatologists have embraced ultrasonography as a useful clinical tool and it has increasingly been applied in routine practice. Initial criticism correctly focused on a lack of validity data, recognition that this modality is highly user-dependent and that reliability was not established. In response, the rheumatological community identified relevant pathologies to study, starting with synovitis in rheumatoid arthritis, and set about defining the ultrasound abnormalities, followed by demonstrating the validity, reproducibility and responsiveness of these measures. Much work is now ongoing in the areas of enthesitis, gout and osteoarthritis. Additionally, the evidence base for ultrasonography in clinical practice is being investigated, in order to understand its appropriate place. Given the sensitivity of ultrasonography over clinical examination for detection of inflammation, this work will focus on its role in optimising diagnosis, directing therapy through accurate assessment of disease activity and understanding the optimal selection of joints for feasible disease monitoring. This review summarises the work undertaken to date, ongoing work and future challenges of optimising the role of ultrasonography in rheumatology.

Introduction

Ultrasonography exploits the physical properties of sound to provide information about the human body. Electrical energy is converted to high frequency sound by piezoelectric elements in a transducer (1), which in turn directs the sound waves through matter towards the anatomical feature of interest. The properties of both sound (frequency)

and tissue density (acoustic impedance) will affect how the waves travel through the body. Ultrasonography was first applied clinically in the 1950s and the first publication describing the ultrasonographic appearances of inflammatory arthritis appeared in the late 1970s (2). It was not until the 1990s that technology improved to allow reasonable quality imaging of superficial joints (3). The uptake of ultrasonography in rheumatology clinical practice was then relatively quick and widespread: a questionnaire of rheumatologists attending a European conference in 1999 found 40% of respondents were using ultrasound in their practice, with a further 45% expressing interest in using it (4).

Optimising outcome assessment

The utility of ultrasound as an outcome tool was initially hampered by the absence of validity data and its user-dependant nature (3). Scanning techniques and machine settings were not standardised. Definitions of pathologies were lacking, making interpretation and comparison of published studies difficult. Widely accepted quantification methods were not available, making change difficult to demonstrate.

The Outcome Measures in Rheumatology (OMERACT) ultrasound working group have, for over a decade, undertaken exercises and studies to establish the validity of ultrasonography as an outcome tool; this remains a work in progress. Work initially focused on consensus-driven definitions of ultrasound detectable pathologies (for synovial hypertrophy, effusion, rheumatoid erosions, enthesopathy and tenosynovitis) (5). These definitions are now widely used in the rheumatologic ultrasound literature. In terms of validity, ultrasound determined synovial pathology has been shown to correlate with arthroscopic (6-8) and MRI synovial hypertrophy (9-11, 13). Additionally, Doppler signal has been correlated with vascularity and histological features of inflammation in

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biopsy studies (14-16). Early reviews recognised a lack of reliability data, essential for a responsive outcome measure. Subsequent publications reported reliability data for ultrasound detected synovitis and effusions (12, 17), tendon lesions (12, 17, 18) tenosynovitis (17), enthesitis (12), erosions (12, 17).

In terms of quantification at the individual joint level, the OMERACT group have developed separate synovial hypertrophy and power Doppler signal scores each using a 4-point semi-quantitative scale (where 0 equates to a normal joint, and 3 indicates a very inflamed joint) (19) as well as a score combining both features. Subsequent work in RA has focused on quantifying the individual burden of pathology and identifying an optimal number of joints to reflect the burden of inflammation – an ultrasound-based scoring system should better reflect ‘true’ inflammation in joints (as compared to clinical examination), but the time constraints of imaging multiple joints should be considered (19). Several studies have investigated the performance of a variety of ultrasound-assessed joint counts (20, 21); responsiveness data exists for a number of these systems but the optimal combination of joints to scan remains unclear.

Recently, the ultrasound working group tested a ‘whole-body’ RA outcome tool (the ultrasound global synovitis score or GLOSS), imaging 22 joints in a clinical study. This was compared against other previously published systems (n=12 and 7 joints) with similar responsiveness (22). Such a global ultrasound tool must provide a balance of reflecting the burden of inflammation within an individual, while being responsive and feasible. This work is ongoing.

While ultrasound has demonstrated truth, discrimination and feasibility in imaging synovitis, the metrics of ultrasound in other RA pathologies, such as erosions or tenosynovitis, also require further work. A summary of the metric properties of US detected pathologies in a variety of common arthritides is presented in Table I.

Beyond rheumatoid arthritis

In rheumatic diseases other than RA,

Table I. Summary of the published metrics on ultrasound-detected pathologies in different arthritides.

Disease	Pathology	Validity	Reliability	Responsiveness
RA	Synovitis	+++	+++	+++
	Tenosynovitis	+	++	++
	Erosions	+++	+++	+
OA	Osteophytes	+++	+++	?
	Synovitis	++	++	+/?
	Cartilage	+	+/?	?
	Erosions	+	+	?
Seronegative arthritis	Synovitis	+	++	+/?
	Tenosynovitis	+	++	+
	Enthesitis	+	++	+
	Erosions	+	+	?
Gout	Synovitis	++	+	?
	Tenosynovitis	+	+	?
	Erosions	+	+	?
	Double contour	++	++	+/?
	Aggregates	+/?	+/?	?
	Tophi	++	++	+
Pseudogout	Synovitis	++	+	?
	Erosions	+	+	?
	Intra-cartilaginous deposition	++	+	?

This represents the authors’ opinions on the relevant literature and not the findings of a systematic literature review. For an individual pathology, we have not assumed the same metrics apply across diseases, though this may be true. For example, synovitis has been extensively studied in rheumatoid arthritis, but less work has been undertaken to confirm that US has similar performance characteristics in other diseases.

much more work is required to improve the utility of ultrasound (Table I). In *seronegative inflammatory arthritis*, enthesopathy and dactylitis require development as domains that ultrasound is suitably able to assess. A consensus definition of the normal enthesis has been published, and it has been agreed that the main elements of enthesitis that will be investigated in optimising the measurement of enthesitis will be tendon hypoechogenicity, increased thickness of the tendon insertion, calcifications, enthesophytes, erosions, and Doppler activity (23); initial reliability data was variable, indicating further work is required (23). A systematic review of ultrasound-detected lesions in *osteoarthritis* (OA) (24) described the pathologies that can be imaged, and identified a lack of consensus definitions, reliability and responsiveness data. Informed by a Delphi process, international experts in rheumatology and ultrasonography have agreed the main lesions to optimise in OA include cartilage, cortical bone (erosions, irregularities, osteophytes) and synovial fluid

and hypertrophy (25). Preliminary reliability data has shown excellent intra- and inter-reader reliability of cartilage lesions, and further work is underway with respect to the other lesions.

A systematic review of ultrasonography in *gout* identified that tophi, a double contour sign, erosions and inflammatory changes of joints and tendons are the relevant pathologies (26). Whilst synovitis is recognised as identifiable in gout, the systematic review did not reveal much on the validity or responsiveness of synovitis as detected by ultrasound in this disease. International experts have decided against redefining synovial hypertrophy specifically for gout, and believe that the definition presented for RA is applicable. It is uncertain, of course, whether the reproducibility and responsiveness as seen in RA will be mirrored in gout; the ability of ultrasound to demonstrate responsiveness may vary between diseases. Diseases with a high inflammatory burden, may demonstrate change with ultrasonography easily, whereas in a disease with lower inflammatory burden, ultra-

sound may be less able to discriminate change (27). The definition of RA erosions is less applicable to gout, because in RA it is specified that an erosion is an intra-articular lesion, whereas gouty erosions may occur in extra-articular sites. Additionally, the gout literature also features a variety of descriptions of lesions, often intra-articular or intra-synovial, that remain relatively poorly defined, such as of "hyperechoic cloudy areas", "aggregates" or "hyperechoic spots" (28-31). These lesions have been reported to be specific to gout in some studies, but seen in other diseases by other groups. Such descriptions may be a focus of confusion unless they can be defined. Work is therefore ongoing on defining, scoring and establishing reliability with regards to gouty lesions.

Challenges in clinical practice

Ultrasonography is now commonly used in clinical practice, and demonstrating its appropriate use and improved outcomes is now the challenge. This may be through optimising diagnostic certainty, aiding assessment of prognosis, or improving the effectiveness of therapy. Diagnostically, utilising ultrasonography may be of use in clinical practice. Ultrasound is able to alter the site specific and systemic diagnosis made by a clinician (32-34) and compared to utilising clinical examination alone, (particularly power Doppler signal) improves the sensitivity and specificity of the diagnosis of RA according to the 2010 ACR/EULAR classification criteria (35). Additionally, in the setting of anti-CCP-negative very early inflammatory arthritis, the presence of power Doppler signal predicts the development of a persistent inflammatory arthritis (36). In the setting of gout, ultrasonographically detected urate deposition either on cartilage (the double contour sign) or in joints and tendons may have diagnostic utility (29). However, whether ultrasonography can it improve clinical certainty in the differential diagnosis of gout, particularly in the early stages of disease, is as yet untested and is an example of how the use of ultrasound is yet to be optimised in the clinic setting. Prognostically, in RA studies, ultra-

sonography can predict those likely to demonstrate radiographic progression (37), those most likely to respond to therapy (38) and those patients with low disease activity likely to flare (39). This would be clinically useful information and may guide therapy, but in the busy clinical setting, regular and systematic imaging as is done in clinical studies is usually not feasible, so the challenge remains as to how to translate what is known about ultrasonography from the clinical study setting to the clinic. Much work is ongoing on how to optimise the use of ultrasonography in the clinic to improve the effectiveness of therapy. It is known that ultrasound-guided corticosteroid injections are more likely to be accurately localised (40, 41) and that accurately localised injections are generally more efficacious (42-44), however a meta-analysis has questioned the benefit of guided injections. The analysis included only 5 studies, and found a short term benefit of image guided injections, but reported that if trials with perceived methodological problems were excluded, then the difference was not significant (45). Clearly the accuracy of ultrasound in detecting 'true' inflamed joints (over traditional measures of tender and swollen joints) may have major effects on disease activity assessment, and both under and over-treating patients. The question of whether the information provided at joint level can inform therapeutic decisions in RA is underway. A large international study comparing a conventional treat-to-target approach against one in which ultrasonography informs the decision making is underway and will help address this issue. This is likely to provide valuable information about how ultrasonography can be optimised, however, once again, the challenge will be to translate serial time-consuming assessments to the clinic setting.

Conclusion

The rheumatology ultrasound community has responded responsibly to criticism and worked for over a decade to optimise ultrasound as useful outcome tool in rheumatologic disease, and demonstrate evidence of its validity, re-

liability, sensitivity to change and feasibility for a range of conditions. Work is ongoing but that done to date has ensured that ultrasound as both a research and clinical tool has an established role in the management of rheumatological conditions, though much work is still required for optimisation.

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