A brief history of ultrasound in rheumatology: where we are now

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ABSTRACT

Ultrasound is gradually becoming established as an indispensable tool within the rheumatology clinical setting. Falling costs, improved educational opportunities, standardisation and developments in therapeutics have all led to the greater acceptability of the technique. This review will highlight how far ultrasound has come in a relatively short period of time by providing an overview of how it is being applied in rheumatology today.

Introduction

If ultrasound were a person, they might be considered at a transition point in life – not yet a mature adult but growing in strength and confidence and looking for a way ahead and meaning in life. Looking back, they would be proud of the achievements made in a relatively short time and be excited about the future. To the rheumatologist, ultrasound has now become an important and some might argue essential adjunct to clinical assessment. It is already a required core skill for rheumatology trainees in some countries with others likely to follow; in addition, there is increasing interest from nursing and allied health professionals to learn as well. One major driving force has been the need for improved methods of the assessment of inflammatory arthritis particularly with respect to diagnosis, prediction of outcome and disease activity (1). As availability of the tool has increased, new applications have developed in areas such as vasculitis and the connective tissue diseases.

This review will highlight how far ultrasound has evolved by describing the current ways in which ultrasound is being applied in rheumatological practice. However, beforehand is important to highlight the important role that EULAR and OMERACT have played and continue to play in this development.

As interest in ultrasound grew in the 1990s, it became clear that there was a need to provide a standardised process for the assessment of musculoskeletal structures, particularly as it was still considered to be an operator-dependent tool. In response to this, in 2001, a newly-formed EULAR Working Group for Musculoskeletal Ultrasound published the first guideline for equipment specifications, scanning methods and standards for image acquisition in rheumatology ultrasound (2). However, there remained a lack of consensus regarding the interpretation of images. It followed that in 2004, a special interest group under the auspices of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group was formed to develop a research agenda towards the testing and development of standardised US measures. To this end, the first consensus derived ultrasound definitions for common pathological lesions were published (3). In the same year, the first inter-disciplinary consensus of recommendations for what rheumatologists should be scanning was also published (4).

The OMERACT group (which was later named the OMERACT/EULAR Ultrasound Task Force) initially focused on the testing of reliability of synovitis definitions in the MCPJ of patients with RA. It was determined by D'Agostino that whilst an OMERACT definition of synovitis improved reliability when scoring static images, there remained wide variation when trying to acquire and score images simultaneously (5). This led to work aimed at standardising the process of scanning and the development of a scoring system (6). Following work on synovitis, attention was directed towards tenosynovitis (7-9) and more recently enthesitis (10). Although most work has been focused on RA to date, work has also been directed towards different disease groups such as OA, spondy-

loarthropathy and gout (11) as well as paediatrics (12).

Alongside the standardisation of the imaging techniques, the need for ultrasound courses has permeated across all world continents, with the incorporation of ultrasound into national training programmes in some countries. In Europe, the first consensus based educational guidelines for the content and conduct of EULAR ultrasound courses was developed (13) to provide recommendations for national and local ultrasound training programmes. These have been embraced by many national ultrasound courses run in Europe. As a result of the popularity of US and the difficult of delivering centralised US training for all, EULAR introduced the first on-line Introductory Ultrasound Course in 2012 which incorporates an on-line assessment. The awarding of hands-on scanning competency however still poses a challenge although this has recently been addressed by EFSUMB (14).

We will next discuss the way in which ultrasound is currently applied in rheumatology in order to highlight its range of uses.

Rheumatoid arthritis

Rheumatoid arthritis is the disease where most attention has been focussed. The development of grey-scale and Doppler techniques allowed the earlier detection of synovitis and a method of quantification. Ultrasound unlike MRI has allowed the rapid assessment of multiple joints and particularly those that are known to be early targets of inflammatory change. Early studies highlighted the presence of subclinical inflammation in RA and that reliance on clinical examination alone may lead to misclassification of disease as well as an under-estimation of disease activity (15). US was also shown to be more sensitive than radiography for the detection of bone erosions (16, 17).

With this additional information about synovitis and bone erosion, the earlier fulfilment of diagnostic criteria for RA has been made possible (18). The presence of increased Doppler in the small joints of sero-negative patients with inflammatory symptoms has been shown to predict disease persistence and likely progression to RA (19, 20). The role of US in disease monitoring in RA is uncertain; whilst ultrasound has been shown to be more reliable than clinical examination for synovitis in in the context of clinical trials and able however to demonstrate changes with DMARD therapy, the added value over standard clinical measures of disease response, *e.g.* DAS28, are unproven (21). Where US probably has a role is as a treatment endpoint with respect to knowing when to stop escalating treatment or even when to reduce it. It has been shown that the current composite measures of disease remission assessment are inaccurate for defining true remission in that ultrasound and MRI detected inflammation is found commonly in the joints of patients thought to be clinical remission (22-24) which is independent of the criteria used (25). It has been shown that this inflammation especially that associated by the presence of power Doppler (PD) signal is associated with an increased risk of future bone damage (26). The presence of PD has also been correlated with the risk of clinical relapse. New EULAR guidelines support the use of imaging like US for the assessment of RA (ACR criteria) (27) however controversy remains with respect to which joints should be assessed and whether true imaging remission is possible especially in the context of concomitant degenerative joint disease. The use of US for the prospective evaluation of erosions has been hampered by the development of a standardised scoring system but work on this is underway.

Spondyloarthroapathies

As with RA, the SpAs have attracted interest due to their inflammatory nature and the development of new therapeutic agents. The accurate clinical assessment of enthesitis has always been problematic since it is based on the presence of tenderness and swelling at an affected site which often would lead to either over- or under-estimation of true disease. An ability to directly visualise the enthesis would therefore be an advantage. Initial ultrasound studies showed better sensitivity over clinical examination in detecting entheseal abnormalities (28) (29) and indeed as with RA, subclinical disease appeared common. Later studies in psoriatic and enteropathic arthritis patients, noted entheseal abnormalities in patients with no joint symptoms (30, 31). However, caution needs to be taken as to how enthesitis is defined since there are a number of potential ultrasound findings associated the lesion but some are more specific than others. For example, enthesophytes are commonly seen in SpA patients on US but that are also seen in commonly in asymptomatic normal controls (32). In contrast, other findings such as the presence of Doppler close to the insertion appears to offer greater specificity for inflammatory mediated disease (33). A recent literature review conducted through the OMERACT network has highlighted the lack of consensus on defining enthesitis (10). This prompted a recent OMERACT Delphi exercise which highlighted entheseal thickening, hypo-echogenicity and the presence of Doppler as markers of active inflammation whilst bone erosion at the insertion was indicative of damage (34). Several attempts have been made to quantify entheseal abnormalities using different ultrasound scoring systems (35, 36) but these remain largely untested in prospective studies.

Crystal diseases

Ultrasound has been shown to offer interesting insights into the diagnosis of crystalline arthropathies (37, 38). In gout, aggregated crystals may be seen as hyperechocic lines or dots with sparkling reflectivity on the hyaline cartilage surface whilst in CPPD, the deposits are more commonly seen within the cartilage itself (39). In both cases, these deposits are often not seen on radiographs thus offering the chance of an earlier diagnosis. The term "double contour" was coined to describe appearance of MSU crystals deposited on the articular cartilage surface paralleling the bone cortex (40). Recent studies have suggested that the double contour sign and tophi may diminish with urate lowering therapies (41, 42).

Osteoarthritis

Osteoarthritis (OA), although the most common arthropathy seen in rheuma-

tology is relatively less studied than rheumatoid arthritis (43). Ultrasound has played an important role in demonstrating the high prevalence of synovitis in patients with knee OA (44). It followed that synovitis was found to be common in hand OA and that increased Doppler may be found in these joints as well (45). This means that the diagnosis of inflammation can be problematic in situations where inflammatory and degenerative conditions co-exist and that complete reliance should not be placed on the presence of Doppler to differentiate the two. Ultrasound has been shown to be more sensitive than x-ray for the detection of osteophytes (46) with good reproducibility although the detection of joint space narrowing remains problematic. The development of higher frequency transducers, has allowed the better depiction of hyaline cartilage with loss of thickness, homogeneity and sharpness (47-51). However, in this respect the technique is limited by the need for an acoustic window and therefore full coverage of the joint is not as comprehensive as with MRI.

Temporal arteritis and polymyalgia rheumatica

An early significant report by Schmidt in 1995 described a dark hypoechoic circumferential wall thickening known as a hypoechoic halo in patients with temporal arteritis (52). This characteristic sign was suggested to be sufficiently specific to obviate the need for temporal artery biopsy (53). The diagnostic value of the hypoechoic halo was further supported by other studies reported in the 2000s (54, 55). Currently, studies are underway to determine the added value and feasibility of ultrasound in clinical practice. In polymyalgia rheumatic, the presence of US detected bursitis has been shown to be a frequent finding and as such has been acknowledged in the new ACR/EULAR classification criteria (56).

Connective tissue diseases

Ultrasound has emerged as a promising tool for the assessment of connective tissue disorders including Sjögren syndrome, lupus and scleroderma. Ultrasound was first suggested as a diagnostic imaging modality for Sjögren syndrome in the late 1980s (57, 58). In the 2000, the diagnostic accuracy of US-detected qualitative salivary gland abnormalities was first compared with minor salivary gland biopsy (59). The study showed excellent correlation giving the prospect that US could replace more invasive diagnostic method such as sialography or salivary scintigraphy as a means of diagnosis. More recently, an US grading system was shown to compare well with MRI and MR sialography of the parotid gland (60). Recently, it was published that ultrasound findings of the major salivary glands could replace sialo-scintigraphy in the modified American-European classification criteria (AEC) for primary Sjögren's syndrome (61). Thus, at present, ultrasound is regarded as promising modality capable of replacing invasive test for the diagnosis of Sjögren's syndrome.

In systemic lupus erythematosus, US has been shown to detect subclinical inflammatory changes in the hand and feet with the demonstration of synovitis, bone erosion and tendon disease (62, 63). More recently, the frequency of foot involvement has been highlighted (64). In scleroderma, US has been shown be able to measure skin thickness (65), as well as exciting prospects as a means of assessing the elasticity of the skin through the technique of elastography (66). This, alongside techniques such as optical coherence tomography, is beginning to offer more accurate and objective methods of disease assessment (67).

In conclusion, the use and range of applications of ultrasound in rheumatology continues to increase and evolve. This has been facilitated by improvements in technology, standardisation and education. Indeed, new techniques offer even more exciting possibilities for future disease assessment. Within a relatively short time, rheumatologists have become empowered to take control of disease assessment; ultrasound has allowed better informed decision making thereby improving both clinician and patient satisfaction and patient outcomes. It is likely that as evidence grows and ultrasound is incorporated into disease management guidelines, *e.g.* diagnostic criteria for RA, then every unit will be required to train personnel. There are many questions however still to answer and given the limited resources of rheumatology departments, future work needs to be directed to the clinical added value and cost effectiveness of the technique.

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