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Review Article

Ultrasonography in the diagnosis and management of patients with inflammatory arthritides

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ABSTRACT

In primary care and internal medicine settings clinicians are often reluctant to take advantage of the resources that ultrasonography (US) offers as a diagnostic tool in the initial management of patients with inflammatory arthritis, despite the recognised importance of an accurate and timely diagnosis of rheumatoid arthritis (RA) and of early referral to ensure optimal patient management. Both grey-scale (GS) and power Doppler (PD) imaging have been extensively used in early detection of synovitis and bone erosions in patients with inflammatory arthritides. We reviewed the main data on the clinical use of US in the initial management of patients with inflammatory arthritis, focusing on RA diagnosis in patients with undifferentiated arthritis, prediction of disease severity, differential diagnoses and assessment of synovitis in children with juvenile idiopathic arthritis (JIA). The role of US in assessing treatment response and monitoring disease activity in clinical remission was also briefly evaluated. The reliability of US as a diagnostic tool in rheumatological diseases has greatly advanced in the last years and the use of this imaging technique, in association with conventional assessments such as physical examination and serological tests, should be considered more often also in primary care settings.

1. Introduction

The use of ultrasonography (US) in patients with inflammatory arthritides has increased dramatically over the last decade and most rheumatologists have adopted this technique as an integral part of routine diagnosis and management of musculoskeletal diseases. However, in primary care or internal medicine settings the advantages that ultrasound imaging might offer as a diagnostic tool and for referral guidance are not always given due consideration. An increasing number of publications support the use of US in a variety of musculoskeletal conditions, both in clinical studies and routine practice, particularly as a tool for the detection and monitoring of inflammation in joints and soft tissues, as well as bone erosive damage, in patients with known or suspected rheumatoid arthritis (RA). US has been demonstrated to be more sensitive than clinical assessment in detecting joint swelling, thus helping identify patients with subclinical synovitis [1–4]. While conventional radiography has been until recently the imaging technique of choice in patients with suspected inflammatory arthropathies, it is relatively insensitive to soft-tissue changes and detects bone erosions with a considerable delay up to 12 months compared with US or magnetic resonance imaging (MRI) [5,6]. US is a safe, painless and non invasive technique that offers clear advantages over other imaging modalities

Abbreviations: CCP, Cyclic citrullinated peptide; CI, Confidence intervals; CRP, C reactive protein; CT, Computed tomography; DAS28, Disease Activity Score-28 joints; DMARDs, Disease-modifying antirheumatic drugs; ESR, Erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; GS/GSUS, Grey-scale/grey-scale ultrasonography; JIA, Juvenile idiopathic arthritis; MCP, Metacarpophalangeal; MRI, Magnetic resonance imaging; MSU, Monosodium urate; MTP, Metatarsophalangeal; MTX, Methotrexate; OMERACT, Outcome Measurement Rheumatoid Arthritis Clinical Trial; OR, Odds ratio; PD/PDUS, Power Doppler/Power Doppler ultrasonography; PIP, Proximal interphalangeal; RA, Rheumatoid arthritis; RF, Rheumatoid factor; ROC-AUC, Area under the receiver operating characteristic curve; SpA, Spondyloarthritis; SDD, Smallest detectable difference; TNF-α, Tumour necrosis factor-α; US, Ultrasonography.

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such as MRI or computed tomography (CT), including ease of use at the patient's bedside, lack of exposure to ionizing radiation, reduced costs, lack of contraindications from claustrophobia or metal implants, and ability to provide dynamic images. One aspect of US which is especially relevant in primary care settings, where patients with undiagnosed arthritis often undergo their first evaluation, is its ability, in conjunction with clinical assessment and laboratory testing, to identify early RA, thus enabling a timely referral of such patients for appropriate management of the disease. If untreated, RA leads to irreversible joint damage and progressive disability, with extra-articular manifestations and important comorbidities (i.e. cardiovascular) related to chronic systemic inflammation [7,8]. Treatment with conventional or biologic disease-modifying antirheumatic drugs (DMARDs) has been proven effective in blocking inflammation and preventing structural deterioration, and it is now well accepted that starting these therapies during the initial phase of RA can improve clinical and functional outcome. Indeed, some investigators have identified a therapeutic 'window of opportunity', corresponding to approximately 3 months after symptom onset, during which phase aggressive treatment of RA is more likely to succeed compared with the same treatment instituted later in the course of disease [9–11]. According to the 2007 European League Against Rheumatism (EULAR) guidelines for the management of early arthritis, patients with arthritis of more than one joint should be referred early to a rheumatologist, ideally within 6 weeks after symptom onset [12]. However, there is evidence that in routine practice times to referral (and, consequently, to appropriate treatment initiation) are often suboptimal. Data from the UK indicate that patients are often referred to rheumatologist 6–10 months after symptom onset, while a mean time to access to specialist care of 76 days was reported for early arthritis patients in a cohort study from France, which also found that less than half the cohort (46%) consulted a rheumatologist within the EULAR-recommended time frame of 6 weeks [7,8]. It should also be noted that the decision to recur to radiographic assessment was found to significantly lengthen the period from presentation to referral in a study from the UK [13]. Among the various factors that contribute to delayed referral, the difficulties experienced by primary care physicians in identifying patients with early RA (or in predicting those who will develop persistent arthritis) because of a misleading or incomplete clinical presentation are perceived as one of the main drawbacks to a timely access to specialist care. US might greatly facilitate the diagnostic process in this context, identifying the patients who will most benefit from early referral.

In this paper we review the main evidence supporting the use of US as a diagnostic tool in the initial management of inflammatory arthritides. The role of US in the assessment of treatment response and monitoring of disease activity in remission will also be briefly evaluated.

2. Sonographic assessment of inflammatory and erosive changes in arthritis

Traditional grey-scale (GS) imaging has been used for many years for the detection of inflammatory soft tissue changes. More recently, Doppler US has been introduced for the assessment of blood flow. Of the two main types of Doppler techniques available, both characterised by a colour spectral map superimposed onto the GS image, colour flow Doppler reflects the velocity and direction of the red blood cells and is therefore better suited to the evaluation of high-velocity flows in large vessels, whereas Power Doppler (PD) relates to the volume of blood present and is used to evaluate low-velocity flows in small vessels. This latter technique, which is sensitive to changes in blood flow at the microvascular level, is particularly useful for identifying and measuring inflammatory changes in joints and surrounding soft tissue [14]. Both GSUS and PDUS have been used extensively in the assessment of inflammatory arthritides for early detection of soft tissue abnormalities, including synovial proliferation and joint effusions, and bone erosions. Although this review focuses on joint pathology, US is also used to detect abnormalities in extra-articular structures often associated with inflammatory arthritis, such as tenosynovitis, bursitis and enthesopathies. Tenosynovitis is a common feature of early RA, and, therefore, patients with early arthritis should be accurately examined for the presence of tendon disease, while the presence of enthesitis can help differentiate seronegative arthritides, such as psoriatic arthritis, from RA [5,15]. Standardised definitions of sonographic abnormalities in patients with inflammatory arthritis have been proposed at the 7th Outcome Measurement Rheumatoid Arthritis Clinical Trial (OMERACT) conference (Table 1) [16].

The synovium is the primary site of inflammation in RA, acting as a source of inflammatory cytokines that mediate neoangiogenesis. Synovial proliferation progressively leads to pannus development, subsequent disruption of the articular cartilage and appearance of erosions at the osteochondral junction [5]. Prospective studies have demonstrated a link between the presence of synovitis and subsequent structural joint damage [5,17]. An accurate and early diagnosis of synovitis is, therefore, crucial for improvement of RA outcomes. GS imaging can detect synovial hypertrophy and effusions, also allowing measurement of synovial thickness and size of effusions, while PD can reliably assess synovial hyperaemia (Figs. 1–2). Many studies have validated sonographic assessment of synovitis at multiple anatomic sites, including the small joints of the hands and feet, shoulder, wrist and knee [18]. US findings were found to correlate well with histopathological data and MRI findings, and some studies suggest that PDUS may indeed be more sensitive than MRI in the detection of synovitis [19–21]. Bone erosions are an important pathologic hallmark of RA and represent one of the 3 diagnostic criteria for this disease (combined with clinical and serological markers). Most erosions develop in the first 2 years of disease, and the presence of erosions within the first 6 months is an indicator of aggressive disease and poor prognosis [5]. Sonographically, erosions appear as a discontinuity of the bone surfaces that can be visualised in two perpendicular planes. Conventional radiography, the historical gold standard for the assessment of bone erosions, is not sufficiently sensitive in early disease. Numerous studies confirm the superiority of US over conventional radiography in the assessment of bone erosions [22]. In a study by Wakefield et al., US detected 6.5-fold more erosions than did radiographic assessment in patients with early RA (disease duration <12 months), and in a 7.5-fold higher number of patients [6]. A meta-analysis of studies comparing the efficacy of US vs MRI for the detection of bone erosions found the two imaging techniques to be comparable at both joint and patient levels, with no statistical differences between efficacies, although the

Table 1
Definitions of US pathology according to the 7th OMERACT Conference (adapted from Wakefield et al. [16]).

Synovial fluid	Abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal
Synovial hypertrophy	Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intra-articular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal
Bone erosions (RA)	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and which may exhibit Doppler signal
Enthesopathy	Abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit Doppler signal and/or bony changes including enthesophytes, erosions, or irregularity