Musculoskeletal Ultrasound in the Diagnosis of Rheumatic Disease

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Abstract
The use of musculoskeletal ultrasound (MSKUS) in rheumatology practice and research has increased steadily over the last decade. An ever-growing body of literature shows parity and even superiority of MSKUS when compared to physical examination, plain radiography, and more expensive and static imaging modalities such as MRI. While many use the modality for procedure guidance, investigators continue to demonstrate its ability to impact diagnoses in a variety of rheumatic diseases. Initial efforts focused on establishing MSKUS as a helpful tool for rheumatoid arthritis (RA), especially in the detection of synovitis and joint erosions, but numerous studies are validating the use of MSKUS as a helpful diagnostic tool for the spondyloarthropathies, crystal diseases, osteoarthritis, and other rheumatic diseases. Advances in ultrasound technology are translating into more sensitive and accurate studies. Within the research community, current efforts aim at maximizing the direct clinical impact of MSKUS by developing global or patient-level assessments and simplified joint scoring systems, with improvements in intra- and inter-reader reproducibility.

Musculoskeletal ultrasound (MSKUS) emerged as a key diagnostic tool among European rheumatologists more than 20 years ago, but only recently has become more attractive to rheumatologists in the United States. Few would dispute that ultrasound is less expensive than MRI, yet other advantages of MSKUS over various imaging modalities have eluded much of the rheumatology community. MSKUS is painless, avoids the contraindications of metal implants or claustrophobia, allows dynamic images (to include moving views of anatomic structures), and enables physicians to view contralateral or additional anatomic locations immediately and spontaneously.1,2 Recently, there has been a surge of interest in MSKUS in the U.S., with numerous weekend training courses (some are ACR sponsored) for fellows and practicing physicians. In addition, a group of dedicated American rheumatologists (USSONAR, Ultrasound School of North American Rheumatologists) is assisting in the educational effort with many fellowship trainees nationwide and administering a competency exam. Research in this discipline within rheumatology has also gradually increased, as evidenced by the number of published manuscripts and abstracts at meetings over the last decade.

While many physicians focus their sonographic efforts on procedural guidance to improve accuracy, MSKUS serves as a diagnostic tool for a variety of rheumatologic diseases, and usage is, thus, increasing in both research and clinical practice. While this began with gray-scale imaging (based on the visible contrast from structures appearing shades of black, gray, and white), power Doppler also plays a key role in providing clearer and more visible evidence of acute inflammation.3 In this review, we focus on the major areas in which ultrasound has improved our diagnostic abilities in the rheumatic diseases (Table 1).

Rheumatoid Arthritis
Of all rheumatologic diagnoses, rheumatoid arthritis (RA) has garnered the most attention and support with regard to the utility of MSKUS. In this disease, sonographers have shown that MSKUS facilitates (early) detection of synovitis and erosions beyond the capability of plain radiographs.
and the clinical exam. By focusing mostly on these two sonographic features, researchers have demonstrated its utility as a clinical guide regarding disease progression and treatment response.

**Synovitis**
Assessment of inflammation within joints is vital to the management of RA. Gray-scale images often identify hypertrophy (gray to white) and adjacent fluid (black) (Fig. 1A), or either alone, as markers of pathologic synovium in inflammatory arthritis,4 and add quantitative data by allowing measurement of synovial thickness and the size of effusions.5 Evaluation has been enhanced on most all machines with the power Doppler setting, which depicts the increased vascularity of hypertrophied synovium by demonstrating microvascular flow (as opposed to color Doppler commonly used in radiology, which detects directional flow of large vessels). Doppler technology has increased the sensitivity for detection of early disease and may be more suited to show changes in established disease where there is chronically thickened synovium.5 Doppler has also correlated well with histopathology6 in the detection of synovitis. As Doppler sensitivity in machines is increasing, efforts are being made to define appropriate cutoff values to separate out normal vascularization in healthy joints7,8 and improve the technique’s specificity. While MSKUS allows us to detect synovitis not visible by plain radiography, multiple studies have shown sonography to be superior to clinical exam9,10 and at least on par (if not superior) to MRI11,12 in the identification of early synovitis. In RA, MSKUS has been similarly helpful with evaluation of tenosynovitis. Some investigators have suggested MSKUS be considered the gold standard of tenosynovial evaluation.13 Wakefield and colleagues showed that gray-scale imaging could diagnose tenosynovitis with marked specificity and positive predictive value when compared to MRI.14

**Erosions**
Particularly in early RA, conventional radiography is not a sensitive marker for detecting cortical bone erosions, which can be important in making a diagnosis of inflammatory arthritis and monitoring disease activity and damage to guide therapy.5 Wakefield and coworkers15 first showed that, compared to radiography, MSKUS identifies 6.5-fold more erosions in “early” (under 12 months) RA patients versus 3.4-fold in those with “late” (more than 12 months) RA, using MRI as the gold standard. Additional studies support the superiority of MSKUS over radiography in the detection of erosions.16-18 Ultrasonographers can also identify erosions nearly as well as MRI,19,20 and notably with lower cost and more efficiency.

**Clinical Utility**
Articular and peri-articular findings on MSKUS have the potential to impact clinical practice, especially in RA patients. Numerous studies have demonstrated the ability to follow disease progression and remission with treatment, as well as the confirmation of synovitis and erosions in the challenging patient.5 Brown, a leading European sonographer, has addressed the importance of MSKUS in longitudinal assessment, even when the patient is asymptomatic on treatment.21 His group described the presence of synovial hypertrophy and increased Doppler signal in 85% and 60%, respectively, in a cohort of 107 RA patients deemed to be in clinical remission while on non-biologic disease-modifying anti-rheumatic drugs (DMARDs). In a 12-month follow-up,22 the investigators showed that both synovial hypertrophy and Doppler activity at baseline correlated significantly with radiographic progression, by as much as a 12-fold risk. MSKUS also correlates with clinical markers of disease activity on longitudinal follow-up. Naredo and associates23 studied 367 RA patients starting a TNF-inhibitor and followed them for 12 months, finding that serial Doppler results correlated well with DAS 28 measurements (p < 0.0005), while also predicting radiographic progression.

Use of MSKUS in the challenging patient was exemplified by Freeston and colleagues,24 who showed that MSKUS helped predict which of the seronegative RA patients with early hand symptoms later developed inflammatory arthritis. On the daily practice level, Karim and coworkers,25 in 2001,

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<th>Table 1 Key Sonographic Findings</th>
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<td>Rheumatoid arthritis</td>
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<td>Gout</td>
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<td>Giant cell arthritis</td>
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*Seen with gray-scale or power Doppler images; †At tendon insertion sites; ‡Effusion, altered color Doppler flow in the posterior SI joint; §Hyper-echoic (bright) linear signal in middle of articular and fibrocartilage. Note: Also many other findings with soft tissue pathology (i.e., rotator cuff tears, nerve entrapments).
showed that in 100 outpatients in a clinic setting, the management plan was altered in 53% as a consequence of MSKUS. We surmise that as MSKUS technology has improved over the past decade and will continue to improve, its potential to impact daily practice will grow as well.

While diagnostic abilities have increased with MSKUS, it is important for clinicians and researchers to determine if and how they can rely on this technology. Inherent concerns about any newer imaging modality are always raised, and these have been addressed in MSKUS, with the RA literature reporting a wide range of inter- and intra-observer correlation measures. A recent analysis of 35 RA studies showed fair to excellent inter- and intra-observer reliability in evaluating synovitis with images already acquired. However, reliability and variability for the actual acquisition of images was worse and, at times, poor.

Use of MSKUS to assess polyarticular activity on the global level (as opposed to the single joint) level has also been explored, specifically in RA. While Dougados and associates found, overall, little difference in reliability, validity, and sensitivity to change between scoring systems of 20, 28, and 38 joints among RA patients receiving anti-TNF therapy, others have made similar efforts to simplify MSKUS evaluation. Naredo and colleagues showed a highly significant correlation (p < 0.0005) between a synovitis scoring system in a 12-joint exam, compared to a more comprehensive 44-joint exam in a group of RA patients on biologic therapy (decreasing the mean exam time from 84 to 22 minutes). Backhaus and coworkers recent work suggested a further simplification to seven joints (wrist; metacarpophalangeal joints, MCP2 and MCP3; proximal interphalangeal joints, PIP2 and PIP3; and metatarsophalangeal joints, MTP2 and MTP5 on the clinically dominant side, performed in 10 to 20 minutes, including documentation), with their scores correlating well with DAS28 changes at 3 and 6 months, and patients on DMARD, biologic, and combination therapy.

**Figure 1**

Meanwhile, an ultrasound task force within the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) continues to work on the development of a Global OMERACT Sonography Scoring (GLOSS) system for RA.

**Spondyloarthritis**

There is also increasing evidence supporting the use of MSKUS in SpA, including psoriatic arthritis. In large part, the main use of MSKUS in SpA is for the detection of peripheral joint pathology, similar to RA, with synovial effusions, hypertrophy, and increased Doppler signal. The other major indication for MSKUS in SpA peripheral pathology is to look for enthesitis at locations such as the Achilles tendon. MSKUS findings include enthesial calcifications, enthesophytes, bony erosions at the insertion sites, increased fascia and tendon thickness, decreased tendon echogenicity (gray-scale signal) reflecting tendon edema, and abnormally increased Doppler signal. MSKUS has been shown to be significantly superior to clinical examination in the detection of enthesitis. In a cohort of SpA patients examined by D’Agostino and associates, the vast majority (98%) had evidence of enthesitis on MSKUS, not replicated in RA or mechanical back pain cohorts. At least one study suggested that MSKUS was superior to MRI in detecting enthesitis.

Older scoring systems, such as the GUESS (Glasgow Ultrasound Enthesitis Index Scoring System) and the Sonographic Enthesitis Index (SEI), used gray-scale techniques, but more recent research efforts have tried to incorporate power Doppler. While experts have yet to agree on a standard SpA sonographic scoring system, multiple studies have shown enthesitis assessment with MSKUS to be reliable and reproducible. In addition, an increased power Doppler ultrasonography (PDUS) signal may help separate inflammatory from non-inflammatory (i.e., mechanical) enthesitis.

While rheumatologists have traditionally considered MSKUS to be of limited value in assessing the axial skeleton because of insufficient windows to capture axial structures, recent reports suggest otherwise with respect to the sacroiliac joint (SIJ). Investigators have used gray-scale images to view SI effusions and color Doppler to estimate arterial flow within SIJ and paravertebral areas, the latter detecting differences between ankylosing spondylitis patients and controls at both baseline as well as serial assessment of the former on biologic therapy. A recent contrast-enhanced study by Klauser and colleagues revealed SIJ enhancement in SpA patients, with 100% sensitivity and specificity compared to the clinical exam.

**Crystal Disease**

**Gout**

MSKUS has become a helpful diagnostic tool with the crystal arthropathies, particularly gout. While some investigators have suggested non-specific articular and peri-articular sonographic findings in acute gout attacks, the hallmark features focus on evidence of chronic disease: tophi (Fig. 1B), erosions, and urate deposition in articular cartilage.

Thiele and Schlesinger described findings in multiple joints and articular cartilage sites in patients with chronic gout in comparison with controls. A tophus, characterized as a nonhomogeneous gray and white area surrounded by a small black rim, was found in 100% of the clinically affected MCPs and MTPs in the gout group (23 patients, 37 joints) but in none of the controls (23 patients, 33 joints) with other rheumatic diseases. Perez-Ruiz and coworkers showed that MSKUS: 1. correlated well with MRI in the detection of tophi, 2. concurred with microscopic analysis for urate crystals after arthrocentesis in a majority (10/12) of suspected tophi, and 3. detected decreases in tophus size in 9 of 12 patients after urate lowering therapy. In addition, several investigators have described the utility of ultrasound when trying to distinguish between polyarticular tophaceous gout and RA with rheumatoid nodules when the initial diagnosis is not clear. In such cases, the sonographic appearance of tophi (heterogeneous and calcified-white) differs from a rheumatoid nodule, which is more homogeneous and gray, often with a sharply demarcated necrotic darker-appearing center.

Similar to erosions in RA, gout-induced erosions are more easily detected by MSKUS than by radiography. Wright and associates found this significant margin to be 67% versus 28% in 78 first MTPs of 39 chronic gout patients, with this cohort’s erosions correlating significantly with disease duration as well as the presence of tophi. MSKUS also surpassed radiography in detecting erosions in clinically silent MTPs (45% vs 28%).

A characteristic MSKUS finding in gout is the “double contour sign” (Fig. 1C), a white (hyperechoic) irregular band on the surface as seen in gout. The sonographic appearance of urate crystals differs from that seen in calcium pyrophosphate deposition (CPPD), which can lead to pseudogout attacks. In CPPD, the white (hyperechoic) crystals form a band within the black-appearing femoral articular cartilage (Fig. 1D), rather than on the surface as seen in gout. Intra-cartilaginous hyper-echoic enhancement correlated with CPPD crystal-proven
arthropathy with a sensitivity of 69% and specificity of 98% in a recent knee study.\(^5\)

In addition, medial and lateral knee views in patients with CPPD often demonstrate white inclusions in the menisci, correlating with tibiofemoral joint calcifications on plain radiographs, while medial wrist views can reveal calcifications of the triangular fibrocartilage, also seen on radiographs.\(^48\)

**Osteoarthritis**

MSKUS has traditionally attracted far less attention with osteoarthritis (OA), the most common type of arthritis, compared with the other diagnoses discussed above. Radiography, the standard for OA imaging, has inherent limitations, as it only allows indirect evaluation of articular cartilage damage (using joint space narrowing as a surrogate) and precludes visualization of other soft tissues. Sonographic evaluation overcomes these obstacles, albeit with poor windows, limiting views of some of the hyaline articular cartilage; in addition, sonographic waves cannot penetrate the cortex to identify key OA features of subchondral sclerosis, cysts, or bone marrow lesions. However, with recent efforts focusing on OA of the knee, hip, and hand, MSKUS has become more useful for OA diagnosis in both research and practice.

Osteophytes are easily identified by MSKUS in many anatomic locations, appearing as white (hyperechoic) elevated structures close to joint spaces such as the medial-lateral knee (Fig. 1E), the interphalangeal (IP) joints of the hands, and the femoral-acetabular space. Studies have shown good sonographic correlation with radiographs,\(^5\) if not superiority,\(^12\) while one investigator suggests that MSKUS is more sensitive than radiography at detecting both osteophytes and erosions in the erosive OA subset.\(^53\) Even in hip OA, which requires sonographic penetration to visualize deep structures, studies have demonstrated good inter- and intra-reader reliability in diagnosing and scoring the disease,\(^52\) primarily with anterior femoral-acetabular views.

Even more compelling are the ways in which MSKUS provides soft tissue information in OA that is unobtainable with radiography. In addition to the identification of popliteal Baker’s cysts, meniscal extrusion, and bursitis (i.e., anserine), MSKUS can identify and quantify articular cartilage damage (i.e., femoral condyle and IP joints). Multiple investigators\(^55-57\) describe similar changes of early distortion of cartilage margins, followed by a loss of homogeneity of the layer, and, finally, frank thinning of the cartilage (Fig. 1F). In addition, MSKUS can help identify synovial thickening, which has emerged as an important contributor to OA, previously viewed as more of a chronic degenerative disease without a significant inflammatory component.\(^58\)

Other investigators\(^59,60\) have reported the frequent identification of synovitis in various OA joints by MSKUS, with similar findings to the RA section described above on both gray-scale and power Doppler images.

While sonographic identification of synovial effusions is an important diagnostic tool in many rheumatic diseases, in knee OA it may provide prognostic information as well. Conaghan and colleagues\(^61\) recently reported that in a multicenter study of 600 knee OA patients, those with a suprapatellar effusion of at least 4 mm were 2.6-times as likely to have a total knee replacement within 4 years [hazard ratio (HR) = 2.63, \(p < 0.0001\)]. In addition, two separate reports found that patients with MSKUS-identified inflammatory changes (synovitis, effusions) may be less likely to benefit from steroid injections.\(^62,63\)

Despite the descriptive progress in sonographic imaging of OA, some investigators over the last 2 years have shared sentiments of tempered enthusiasm. While a number of studies have introduced and proposed validation of semi-quantitative scoring systems for OA in the knee, hand, and hip joints,\(^54,64,65\) there is caution in that these have not been vetted with as much assurance as in MSKUS of RA. After reviewing 47 studies involving MSKUS in OA, Keen and coworkers\(^66\) concluded that scoring systems and data quality were too heterogeneous, and that researchers were generally at fault for automatically adapting RA sonographic criteria and definitions to OA without sufficient proof that this was applicable. Thus, before rheumatologists can use ultrasound to assess the benefit of disease modifying drugs in OA, the modality needs to be better validated as a reliable tool specific to this disease. Such efforts appear to be underway, in addition to those by the current OMERACT ultrasound task force subcommittee for OA.\(^30\)

**Other Diseases**

In addition to the above arthritides, a number of other rheumatic disorders have been studied with regard to diagnostic sonographic findings. Many investigators have shown that MSKUS can demonstrate even mild carpal tunnel syndrome (CTS) by an increased cross-sectional area of the median nerve at the level of the carpal inlet, signifying compression distal to this site.\(^67,68\) While investigators continue to debate a valid cutoff value in order to reliably make a diagnosis and, thus, spare patients painful electromyography and nerve conduction study (EMG-NCS) procedures, they generally agree that painless sonography can diagnose CTS with comparable sensitivity to the more invasive technique.\(^59,70\) In addition, ultrasound can also be used to assess local anatomy, with possible elucidation of alternative pathology causing the symptoms, such as a space-occupying lesion, amyloid deposition, erosions, or synovitis.

A growing literature exists describing MSKUS findings in systemic lupus erythematosus (SLE). Wright and associates\(^71\) described synovial hypertrophy and effusions, in addition to erosions and tenosynovitis in the hands of 17 patients, while Demirkaya and colleagues\(^72\) noted synovitis and tenosynovitis in the upper and lower extremities in 30 juvenile SLE patients. Torrente-Segarra and coworkers\(^73\) described improvement in synovitis assessed by power Doppler in a patient receiving rituximab for SLE nephritis.
Utility of ultrasound in the rheumatic diseases is not limited to articular or peri-articular imaging. A recent study reported that submandibular gland sonography had similar diagnostic ability for Sjogren’s syndrome as invasive sialography. Ultrasound findings that non-invasively confirm a diagnosis of giant cell arteritis (GCA) were first described by Schmidt and associates more than a decade ago, and many groups since have studied this approach. In addition to temporal artery stenosis and occlusion, a hallmark feature is dark hypoechoic wall thickening around the circumference of the artery, also known as the “halo” sign. A meta-analysis of 23 sonography studies involving more than 2000 patients showed a sensitivity of 87% and a specificity of 96% for GCA, when compared to the ACR diagnostic criteria.

While our review focuses on the diagnostic uses of MSKUS, many investigators have accumulated data suggesting that MSKUS may be helpful with procedure guidance. Most dramatic has been the introduction of office-based aspirations and injections of the hip, by visualizing the key bony landmarks and avoiding neurovascular structures with the needles. A recent study by Cunnington and colleagues demonstrated improved accuracy of MSKUS-guided injections, performed by a trainee rheumatologist, in a variety of joints (glenohumeral, elbow, wrist, knee, ankle) in 184 patients, when compared to non-guided injections, performed by a senior rheumatologist (83% vs 66%, p = 0.01). However, we still lack conclusive data to show whether this accuracy translates to better patient outcomes.

Conclusion
Ultrasound has emerged as a helpful tool in musculoskeletal medicine in recent years, with an abundance of applications in rheumatology. We have reviewed the current literature, showing how MSKUS helps physicians diagnose a wide variety of rheumatic diseases, assess treatment response, and guide clinical management. Importantly, MSKUS does the above in a relatively inexpensive and non-invasive manner and can be used in real-time at the bedside, where results can be interpreted both rapidly and conveniently. Much of the current research in MSKUS focuses on continued improvement in sensitivity, specificity, validity, and reproducibility of sonographic findings.

Disclosure Statement
The authors have no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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