# Lessons Learned from Imaging on Rheumatoid Arthritis

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**ABSTRACT:** Over the last 15 years ultrasound has gained importance for the clinical management of patients with inflammatory rheumatic diseases, especially rheumatoid arthritis. This review summarizes the recent developments and achievements in the use of ultrasound in RA, as well as the unmet needs.

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**KEY WORDS:** ultrasound, rheumatoid arthritis (RA), diagnostic and therapeutic evaluation, remission

The clinical management of rheumatoid arthritis (RA) has changed dramatically due to the introduction of new imaging techniques such as ultrasound and magnetic resonance imaging (MRI), which are capable of visualizing both inflammation and structural damage. The potential use of ultrasound for the clinical management of RA has been recently outlined by the European League Against Rheumatisms (EULAR) recommendations on the use of imaging [1]. Compared to MRI, which is quite expensive and can be difficult to access, ultrasound plays an important role in the daily management of patients due to its safety, accessibility, and economy [2]. In addition to conventional methods such as radiography, clinical examination, and laboratory findings, ultrasound offers the advantage of a real-time, multi-joints assessment [2-3].

**Ultrasound has the advantage of being a dynamic imaging technique capable to visualizing both the morphology and the function (i.e., inflammatory activity) of the structure under evaluation**

Despite these advantages, and the use of this technique in many other medical fields, ultrasound in rheumatology is still perceived as one of the most operator-dependent techniques and therefore less used and trusted for clinical trials than conventional radiography or MRI. This situation is probably due to how the technology works. The clinical image is produced by the mechanical transmission and reflection of ultrasound waves through the body [4]. The anatomical structures are differentiated by the relative intensity of returned echoes and relative pixel brightness (from white to black) in the so called "B mode" or "grey-scale." The movement of blood flow (both velocity and direction) can be visualized by using the Doppler mode. Therefore, variations in the positioning of the probe, the quality of the ultrasound machines, and the experience and training of the operator, as well as in the protocol of acquisition may lead to differences in the interpretation of clinical findings. Several efforts have been implemented during the last 10 years to standardize the ultrasound application by the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group [5,6]. This worldwide group of experts has been working on the validation of ultrasound as an outcome measurement instrument. This consensus-based effort has resulted in describing and underlining the capability of the technique to reliably detect joint lesions whatever the disease [5,6].

In a recent publication, the role of ultrasound for the diagnostic workup, the monitoring of disease activity, and the defining/monitoring remission have been analyzed by a group of ultrasound experts [7]. The researchers analyzed the recent literature for proposing to clinicians a pragmatic approach for using ultrasound in different clinical scenarios. In case of lack of published evidence, the experts proposed a consensus-based approach and detailed a research agenda. They proposed five algorithms: the first two deal with the diagnosis of RA in symptomatic patients and in patients fulfilling the ACR (American College of Rheumatology)/EULAR classification criteria. The third concerns the monitoring of response to treatment in both patients treated by conventional synthetic and/or biological disease modifying anti-rheumatic drugs (bDMARDS). The fourth algorithm relates to patients with loss of treatment response and the fifth with patients in remission or stable low disease activity.

In daily practice, the combined use of clinical, laboratory, and ultrasound findings may improve the diagnostic management of RA. Ultrasound is able to detect minimal signs of synovitis and differentiate between intra-joint synovial inflammation and other causes of clinical swelling, such as tenosynovitis, bursitis, and other soft tissue lesions [2,3]. The use of ultrasound has also been envisaged by the ACR/EULAR classification criteria to help detect synovitis in clinically unaffected joints and evaluate an increase in the number of involved joints needed to fulfill the criteria [8]. In addition, several studies showed that patients undergoing an ultrasound evaluation are likely to fulfill these

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criteria at an earlier stage of their disease than those assessed using conventional tools [9,10].

In patients at risk for developing RA (i.e., patients with isolated arthralgia, rheumatoid factor, or anti-citrullinated peptide antibodies [ACPA] positivity, without clinical inflammation), ultrasound has shown to be a prognostic marker of RA development [11-14]. Both grey scale (GS) synovitis and Doppler signals seem to be predictive but at different levels. van de Stadt and colleagues [13] showed that the combination of GS synovitis and power Doppler abnormalities was the strongest predictor of arthritis at joint level, but not at the patient level. In contrast, Rakieh and co-authors [12] showed that only power Doppler signals were an independent predictive factor of arthritis development at patient level. The value of ultrasound in detecting sub-clinical synovitis has also been outlined in the EULAR recommendations for the management of early undifferentiated arthritis [14]. The use of ultrasound appears even more important in ACPA-negative patients with arthralgia, especially in the absence of clinical and biological inflammatory markers. In this case, ultrasound helps to confirm the presence of joint inflammation before the appearance of a definite RA [12]. In addition, the ultrasound detection of synovitis in both early and established RA is an important outcome in terms of radiographic progression and response to treatment [15-17].

Since the resolution of ultrasound equipment is continuously improving, it is important to define the threshold of ultrasound-detected inflammatory findings at the joint level, as well as the number and type of joints to scan routinely. Witt and colleagues [18] suggested that in established RA minimal GS findings are frequently observed in small joints, even in absence of active disease. Few studies reported the detection of Doppler and GS findings in healthy subjects [18,19] To try to address this discrepancy, a recent publication analyzed the prevalence of ultrasound inflammatory findings (i.e., effusion, synovial hypertrophy and Doppler signal) in the small joints of hands and feet of a large cohort of healthy subjects [20]. In that study Padovano and colleagues found at least one ultrasound abnormality in more than 80% of the subjects. When compared to the number of joints examined, the number that are involved is very low (less than 6% of the total number). The most frequently detected finding was effusion, detected at metatarsophalangeal (MTP) joints (especially the first and the second), followed by the wrist, which questions the relevance of effusion as isolated inflammatory sign, as well as the signification of isolated ultrasound abnormalities at MTP 1-2, and wrist for diagnostic purposes.

Ultrasound may play an important role for monitoring disease activity and treatment response. The sensitivity to change of ultrasound findings in RA treated patients has been shown in several papers [21-27]. Both GS and Doppler findings have been shown to be as sensitive as clinical examination and laboratory markers [27]. A recent study has shown that an ultrasound response can be seen after 1 week of treatment [25]. In addition, the detection of a decrease in Doppler inflammation at 3 months seems to be predictive of clinical response at 6 months [26]. This rapid response was observed independently of the number of joints scanned. This observation is very important as several reduced joint sets have been proposed for monitoring treatment response. At the moment, to the best of our knowledge, no consensus exists on the best-reduced number of joints to scan. The more comprehensive the ultrasound evaluation, the more sensitive it is in detecting change [22-24,26-28]. The inclusions of both small and large joints seem to ensure the best responsiveness [22-24,26-28]. Concerning the modality to use for grading synovial inflammation Doppler appears very sensitive, although very dependent on the quality of the machine used [28]; therefore, a combined score based on both GS and Doppler seems the more adapted to overcome the need of high quality Doppler modality [25]. Possibly one of the most important roles of ultrasound is to evaluate the presence of remission. Since sustained remission is the ultimate goal of the modern RA treatments, the definition of this state is of maximal importance. In fact, it has been shown that flares predict erosive progression over time and functional disability [29-31].

Recent studies have shown that in patients in remission determined either by a physician or by the use of various remission criteria, sub-clinical synovitis is present in both GS and Doppler in more than 30% of the patients despite the treatment methods (csDMARDs or bDMARDs) [32-34].

**Ultrasound has demonstrated high sensitivity to change for following patients under treatment and for predicting structural severity**

The presence of an ultrasound-detected synovitis in patients on csDMARDs seems to be related to the development of structural damage on CR at both joint and patient levels [35-40]. However, the role and the predictive value for the development of structural damage in patients under bDMARDs needs to be further explored, as this detection does not seem to be related to radiographic damage [38].

In RA patients in remission independent of the treatment, the presence of subclinical synovitis seems to predict flare. Saleem and colleagues [32] have shown that the presence of subclinical synovitis with a positive Doppler signal increases the risk of flare in 30% of the RA patients in remission [34,35,37], whereas the absence of Doppler signal is the best predictor for not experiencing it [37].

Patients with a high score of subclinical synovitis on both GS and Doppler seem to have more risk for relapse when stopping or tapering bDMARDs than patients with a low score [37,38].

What is the role of ultrasound in a treat to target (T2T) approach? Two recently published studies argue the added value of ultrasound for achieving a remission state in the context of a tight control in early RA [38,39].

Both studies showed that in an early population both the clinical and the ultrasound tight controls permit to achieve remission, without any superiority of an ultrasound approach. However, in both studies the ultrasound arm seemed to produce a better structural outcome with a lower percentage of radiographic progression as compared to the clinical arm. Further studies, in more established RA populations and with a blinded design are needed for answering this question [40].

## CONCLUSIONS

Ultrasound has the advantage of being a dynamic imaging technique capable to visualizing both the morphology and the function (i.e., inflammatory activity) of the structure under evaluation. The use of ultrasound in any step of the management of RA patients has gained importance over the last years. Ultrasound, alone or in combination with other imaging, as well as laboratory markers contributes to the improved management of RA. Increased evidence in the literature has demonstrated the added value of ultrasound for the management of RA over conventional tools. Its safety, inexpensive and holistic approach have contributed to a better understanding and of the clinical symptoms in patients with RA. Further studies, however are needed for investigating the exact role of ultrasound for helping in defining a patient type, in a T2T approach and as end point in clinical therapeutic trials.

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## Capsule

### GFRAL is the receptor for GDF15 and the ligand promotes weight loss in mice and non-human primates

Growth differentiation factor 15 (GDF15), a distant member of the transforming growth factor (TGF)-β family, is a secreted protein that circulates as a 25-kDa dimer. In humans, elevated GDF15 correlates with weight loss, and the administration of GDF15 to mice with obesity reduces body weight, at least in part, by decreasing food intake. The mechanisms through which GDF15 reduces body weight remain poorly understood because the cognate receptor for GDF15 is unknown. Mullican and colleagues showed that recombinant GDF15 induces weight loss in mice fed a high-fat diet and in non-human primates with spontaneous obesity. Furthermore, the authors found that GDF15 binds with high affinity to GDNF family receptor α–like (GFRAL), a distant relative of receptors for a distinct class of the TGF-β superfamily ligands. *Gfral* is expressed in neurons of the postrema area and nucleus of the solitary tract in mice and humans, and genetic deletion of the receptor abrogates the ability of GDF15 to decrease food intake and body weight in mice. In addition, diet-induced obesity and insulin resistance are exacerbated in GFRAL-deficient mice, suggesting a homeostatic role for this receptor in metabolism. Finally, the authors demonstrated that GDF15-induced cell signaling requires the interaction of GFRAL with the co-receptor RET. These data identify GFRAL as a new regulator of body weight and as the bona fide receptor mediating the metabolic effects of GDF15, enabling a more comprehensive assessment of GDF15 as a potential pharmacotherapy for the treatment of obesity.

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Eitan Israeli

## Capsule

### Fine-mapping inflammatory bowel disease loci to single-variant resolution

Inflammatory bowel diseases are chronic gastrointestinal inflammatory disorders that affect millions of people worldwide. Genome-wide association studies have identified 200 inflammatory bowel disease-associated loci, but few have been conclusively resolved to specific functional variants. Huang and colleagues reported fine-mapping of 94 inflammatory bowel disease loci using high-density genotyping in 67,852 individuals. The authors pinpointed 18 associations to a single causal variant with greater than 95% certainty, and an additional 27 associations to a single variant with greater than 50% certainty. These 45 variants are significantly enriched for protein-coding changes (n=13), direct disruption of transcription-factor binding sites (n=3), and tissue-specific epigenetic marks (n=10), with the last category showing enrichment in specific immune cells among associations stronger in Crohn's disease and in gut mucosa among associations stronger in ulcerative colitis. The results of this study suggest that high-resolution fine-mapping in large samples can convert many discoveries from genome-wide association studies into statistically convincing causal variants, providing a powerful substrate for experimental elucidation of disease mechanisms.

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