Ultrasound in assessing disease severity and therapeutic response in rheumatoid arthritis

Helen I Keen†, Richard J Wakefield & Philip G Conaghan

†Author for correspondence
Chapel Allerton Hospital, Academic Unit of Musculoskeletal Disease, 2nd Floor, Chapeltown Road, Leeds, LS7 4SA, UK
Tel.: +44 0113 392 4884; Fax: +44 0113 392 4991; h.i.keen@leeds.ac.uk

The management of rheumatoid arthritis has become increasingly aggressive in recent years, resulting in improved disease control and better outcomes for patients. Outcome-directed management has driven the development of novel tools to aid in understanding disease severity and therapeutic response. Ultrasonography (US) is an ideal tool for assessing rheumatoid arthritis. It is relatively inexpensive, portable and does not involve radiation, making it ideal to use repeatedly in the outpatient clinic. There is a growing body of evidence to demonstrate the validity of US in determining pathological changes of rheumatoid arthritis, including synovitis, bone erosions and tenosynovitis. In addition, there is increasing evidence to demonstrate that the ability of US to determine true inflammatory disease activity is better than conventional clinical assessments. The current focus of research into US remains on understanding its clinical utility, particularly with regard to determining disease severity, prognostic evaluation and monitoring response to therapy.

Recent years have seen a dramatic improvement in the management of rheumatoid arthritis (RA). While this is partly due to improved drug therapies, it is also due to the recognition that early aggressive therapy and outcome-directed management decisions result in qualitatively and quantitatively better outcomes for RA patients [1–3]. These advances have driven the development of novel tools to aid in the assessment of disease severity and therapeutic response in this disease.

Ultrasonography (US) is an ideal tool to be utilized in the management of a primarily synovial disease such as RA. It is relatively quick to perform and portable, so it can be used in the clinic to produce real-time, dynamic images. It is relatively inexpensive compared with other imaging techniques, such as magnetic resonance imaging (MRI), and does not involve ionizing radiation, in contrast to conventional radiographs (CR) and computed tomography (CT), and thus it can be used in a temporal fashion to monitor disease progression. Therefore US is a clinical tool likely to be in widespread use in the future to assess disease severity and monitor response to therapy in rheumatology clinics.

Keywords: colour Doppler, disease severity, erosions, power Doppler, rheumatoid arthritis, synovitis, tenosynovitis, therapeutic response, ultrasonography

future medicine

How does US work?

US utilizes properties of sound such as absorption and reflection to image tissue. Sound is emitted from a probe and travels through tissue, being reflected when it meets a surface interface. The interface of tissues with very different compositions is most reflective; for example, the interface between soft tissue and bone is highly reflective. The reflected soundwaves (echoes) are recognized by the probe, and the intensity of the reflected echo is displayed in shades of gray (gray scale [GS] US). The addition of the Doppler technique to GS enables the identification of movement, and thus the flow in blood vessels can be studied and the vascularity of tissues assessed. This relies on the principle that sound hitting a moving object is reflected as an echo with an altered frequency. Power Doppler (PD) is the most common technique applied to musculoskeletal US. The amplitude of the flow is displayed as a color spectrum, allowing very small amounts of flow to be detected (e.g., small vessels in inflamed synovium). Colour Doppler (CD) displays information about velocity and direction as a color spectrum. Flow velocity and direction are generally of lesser importance in musculoskeletal imaging than detecting the presence of flow in small synovial vessels. Recently, there has been some investigation of the role of contrast agents, which may aid the detection of vascular flow in inflamed tissues [4].

Detecting pathology in RA

While the traditional metric properties of this tool in rheumatology remain under investigation, there is currently increasing information in RA about its validity, reliability, sensitivity to change and clinical utility. International interest groups have been formed under the auspices of the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) and the European League Against Rheumatism (EULAR) in order to address some of these issues. Recently, the

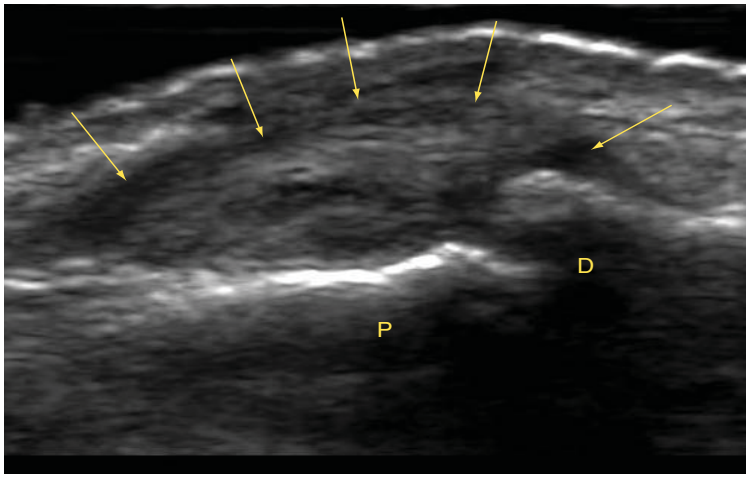
Table 1. Outcome Measures in Rheumatoid Arthritis Clinical Trials group definitions of pathology in inflammatory arthritis.

Feature	Definition
Synovial fluid	Abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible, but does not exhibit power Doppler signal
Synovial hypertrophy	Abnormal hypoechoic or anechoic intra-articular material that is nondisplaceable and poorly compressible and may exhibit power Doppler signal
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in two perpendicular planes and that may exhibit Doppler signal
Erosion	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes

OMERACT group published preliminary definitions of pathologies in inflammatory arthritis, including bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis and enthesopathy (Table 1) [5].

Clinical synovitis may be considered to be a composite measure of synovial fluid and synovial hypertrophy. US has repeatedly been demonstrated to be more sensitive, in both large and small joints, to the presence of synovitis than clinical examination in RA (Figure 1) [6–12]. The ability of US to detect synovitis has been compared against arthroscopy and MRI, with good correlation [10–13]. The addition of PD to GS US can enhance the detection of synovitis by allowing assessment of vascularity of the synovium (Figure 2). In the hip and knee joints, PD signal has been shown to correlate with histological evidence of synovial vascularity [14,15]. Studies comparing PD or CD flow with post-contrast synovial enhancement on MRI have also shown good sensitivity and excellent specificity [7,16].

Figure 1. Gray-scale synovitis in a proximal interphalangeal joint synovitis (longitudinal dorsal image).

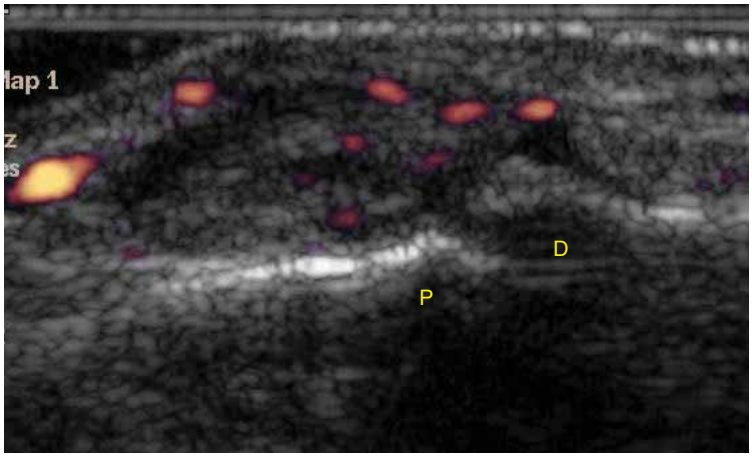


Arrows indicate areas of synovitis.
D: Distal phalanx; P: Proximal phalanx.

Quantifying GS synovitis and PD signal is usually performed in order to provide outcomes for clinical trials and remains a tedious and problematic task that is not currently amenable to clinical practice. Current methods of scoring include semiquantitative scores on a dichotomous (normal/abnormal) or 0–3 scale, which have been applied to both GS synovitis and PD signal. Scoring can be done at the time of scanning as a global joint score, or delayed scoring on saved images; delayed scoring is reliant on the technical skills of the image acquirer. Some recent work has been undertaken to address the interobserver reliability of US scanning and scoring, with encouraging results in terms of both interpretation of images acquired by the scorer and scoring of preacquired dynamic images [17]. Other scoring systems include computer-derived programs that analyze, including pixel counting, regions of interest. These programs are generally considered to be more objective than semiquantitative scoring systems, but are still dependent on the image acquired, and delineation of the region of interest by the technician/physician.

Some caution should be used when assessing studies comparing tenosynovitis detected by US and MRI [11,18], as US and MRI may differ in their planes and sites of image acquisition. Commonly used MRI sequences focus on the joint, whereas US can be used dynamically to image the tendon in multiple planes and during motion. In addition, studies have used different definitions of tenosynovitis. In general, US has been shown to detect tenosynovitis in hands with reasonable sensitivity compared with MRI in RA [11,18]; however, for example, a study which subcategorized tenosynovitis found that

Figure 2. Power Doppler signal in the same proximal interphalangeal joint synovitis (longitudinal dorsal image).



D: Distal phalanx; P: Proximal phalanx.

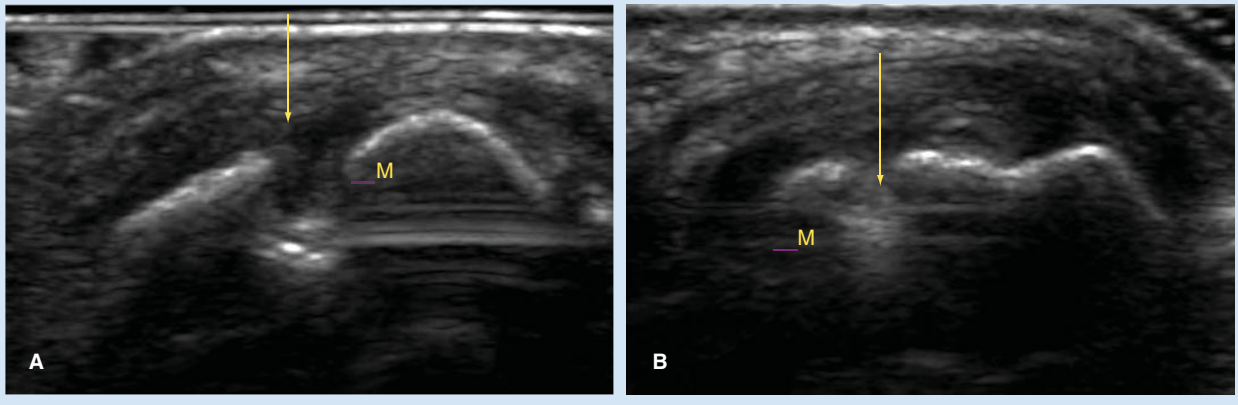
US detected more tendon sheath effusions, but MRI detected more tendon sheath thickening [18]. In the hand, there are difficulties in the ability of both MRI and US to adequately visualize the extensor tendons due to their size and lack of distinct sheath; hence a study comparing imaging findings by US and MRI to direct visualization of extensor tendons at surgery found that neither imaging technique was reliable at detecting extensor tendon tears [19].

The ability of US to detect bony erosions has been compared with CR, MRI and CT (Figure 3) [11,20,21]. The ability of US to detect erosions (with greater sensitivity than CR) depends on the technology utilized and which joints are imaged. US generally detects more erosions in RA fingers and toes than CR, and a similar number to MRI [20–22]. CR and MRI tend to be superior in regions where visualization is difficult with the ultrasound probe, such as between metacarpophalangeal joints or carpal bones [11,18]. In the regions easily accessible to the ultrasound probe, such as the second and fifth metacarpophalangeal joints and the ulna styloid, US performs well compared with both MRI and CR [21], due to its multiplanar nature and high resolution, enabling small lesions to be detected.

Assessing RA severity

Current assessment of disease severity in RA relies mainly on the use of composite tools such as the Disease Activity Score (DAS) and the American College of Rheumatology (ACR) response criteria. These are well-validated outcome measures derived largely from patient and physician subjective assessments and only a single objective, but nonspecific, laboratory measure (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) [23,24]. These outcome measures are at least partially subjective and it has been suggested that they are not specific for inflammation, limiting their value in assessing true inflammatory disease severity [24]. Radiographs are also used to assess prognosis and severity of disease, largely by identifying bone damage (erosions), rather than the primary site of disease pathology (the synovium). The role of US in assessing disease severity is under investigation and appears promising.

Figure 3. Erosion in metacarpophalangeal joint.



(A) Longitudinal view **(B)** Transverse view.
M: Metacarpal.
Arrow indictates area of erosion.

At the individual joint level, several studies have investigated the relationship between clinical synovitis and imaging-detected (US and MRI) synovitis [6–11]. In these studies, significant numbers of joints deemed to be actively inflamed by US and MRI were not detected clinically. In addition, joints felt to be inflamed clinically did not appear to be so when imaged. If MRI is to be considered the gold standard, the better correlation between US and MRI than either with clinical examination suggests that US may be more sensitive and specific to the presence of inflammation than clinical examination [7,14–16].

It is likely that PD determination of synovial vascularity will have implications for assessing disease severity. This is because GS synovial hypertrophy may be due to active hypervascular inflammatory synovitis or fibrosis or both [25]. The distinction is important, as it has been shown that the burden of active synovitis as detected by MRI correlates with future erosive disease [26], and that baseline US PD levels have been shown to correlate with progression of Sharpe scores in a RA cohort treated with methotrexate for 48 weeks [27].

A study examining CD US in the single joint (determined by the patient as the most inflamed joint in the hand) was found to correlate with ESR, but, again, not with the patient and physician global visual analog scale (which may not be specific for inflammation) [28]. This was a small number study, and other attempts to relate imaging of single joints to systemic disease activity have not been successful. It seems unlikely that imaging a single predetermined joint will reliably reflect systemic burden of inflammation.

However, at the systemic level, US is likely to be a more objective tool than traditional swollen and tender joint counts in assessing the extent of disease. In a study using US to define the extent of joint involvement in 80 patients presenting with early (<3 months of symptoms) oligoarthritis, subclinical synovitis was found in 64% of patients, with 23% actually meeting criteria for polyarthritis (more than five joints) based on US findings [29]. Synovitis was demonstrated on US in 33% of joints reported as painful by the patient, but felt to be normal by the two examining rheumatologists [29]. This clearly has implications in assessing the extent of joint involvement in inflammatory arthritides. Furthermore, not all joints felt to be swollen clinically were demonstrated to have synovitis by US, and in approximately a third of these joints, the clinical findings were actually attributable to overlying tenosynovitis.

Studies in RA are in keeping with these findings. A recent publication compared a 60 joint count performed clinically with that done by US in 90 RA patients [30]. US identified a significantly greater number of inflamed joints than clinical examination. In addition, US correlated with ESR and CRP better than clinical examination did. US did not correlate well with patient-reported measures, such as tender joint count or health assessment questionnaire. Whilst extensive US examination may be more sensitive and specific to the presence of joint inflammation, imaging 60 joints is not feasible in clinical practice. A reduced US assessment of 12 joints in this cohort correlated well with the extended US joint count (60 joints), and demonstrated similar relationships with clinical and laboratory parameters as the extended US joint count [31].

When considering disease severity, bone damage/erosions may be considered a measure of cumulative rather than current disease activity, but the presence of erosions has prognostic importance. The ability of US to detect erosions has previously been addressed; however, a major advantage of US over CR is that US is more sensitive than CR to erosions in early disease [21], which has implications for the timely identification of those with a poorer prognosis or perhaps those with more severe disease in the current climate of treating disease early.

Assessing response to therapy in RA

Several studies have demonstrated short-term reductions in both GS synovitis and Doppler flow after intra-articular steroid therapy to the inflamed joint [32–36]. Studies examining response to therapy with TNF inhibitors in RA have demonstrated a decrease in Doppler flow as early as 2 weeks and sustained to 12 weeks with continued therapy [37–39]. In these studies, there was some correlation between reduction in US synovitis and a fall in clinical assessment of disease activity. The strongest correlation between a decrease in clinical disease activity and US disease activity was seen in the study that imaged the greatest number of joints. These studies were small and not controlled.

To date, perhaps the best indicator of the ability of US to assess response to therapy was a trial of 24 patients with RA randomized to either methotrexate and placebo or methotrexate and infliximab [27]. At 18 weeks, US assessment of metacarpophalangeal joint synovitis by both GS and PD was more sensitive to differences between therapeutic groups than clinical assessment with the DAS 28.

Conclusion

US is increasingly being utilized in rheumatology outpatient clinics. US may provide improved predictive and prognostic utility, by virtue of its increased sensitivity and reliability when compared with clinical examination. Given the current focus on aggressive, expensive therapies with the increasingly achievable aim of achieving true, imaging-diagnosed remission, sensitive yet feasible techniques are needed to assess disease activity and response to therapy. The ability of US to perform this role requires further investigation.

Future perspective

The use of US in rheumatology is continually increasing on a worldwide scale. The role of GS and Doppler must be further validated, particularly focusing on algorithms of joint counts to make routine use in clinics more feasible. As technology improves, sensitivity and resolution will also improve. Contrast agents are likely to undergo further validation, although the net benefits over improved GS and Doppler technology may not outweigh the risks and added cost.

Current scoring techniques have largely been designed with clinical trials in mind, and more clinician-friendly assessment systems are required; software to devise more objective measures of synovitis may help this. More machines now have 3D capability, which should further reduce acquisition error and enable the possibility of examining a block of tissue rather than a single slice. This will be increasingly supplemented by the capability for 4D imaging (3D with real-time video).

On a more practical note, the ability of US to guide management decisions and improve outcomes for patients has still be to fully established, and increasing work is expected on useful clinical algorithms. In addition, the cost–effectiveness of using US must be established using such algorithms before widespread use is adopted.

Executive summary

- Ultrasonography (US) is increasingly being utilized in rheumatology.
- Outcome measures in rheumatoid arthritis (RA) clinical trials have recently published definitions for US pathology in RA that should improve interstudy comparisons.
- US is more sensitive to the presence of synovitis than clinical examination.
- Doppler flow can provide information above synovial vascularity, which is thought to suggest active inflammation.
- Gray scale and power Doppler US have been validated against magnetic resonance imaging and histopathology.
- US can demonstrate erosions in early RA better than conventional radiography.
- Since US can detect subclinical synovitis, it should provide a better estimate of disease burden than clinical examination.
- US can demonstrate reductions in synovitis in response to therapy.
- Further work is needed to determine optimal clinical utility in RA.

Bibliography

1. Klareskog L, van der Heijde D, de Jager JP *et al.*: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363(9410), 675–681 (2004).
2. Grigor C, Capell H, Stirling A *et al.*: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study), a single-blind randomised controlled trial. *Lancet* 364(9430), 263–269 (2004).
3. Korpela M, Laasonen L, Hannonen P *et al.*: Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum.* 50(7), 2072–2081 (2004).
4. Klauser A, Demharter J, De Marchi A *et al.*: Contrast enhanced gray-scale sonography in assessment of joint vascularity in rheumatoid arthritis: results from the IACUS study group. *Eur. Radiol.* 15(12), 2404–2410 (2005).
5. Wakefield RJ, Balint PV, Szkudlarek M *et al.*: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J. Rheumatol.* 32(12), 2485–2487 (2005).
   •• Details a working definition of pathology demonstrable by ultrasonography (US). Allows standardization of definitions for the purpose of clinical trials.
6. Luukkainen R, Sanila MT, Saltyshev M, Huhtala H, Koski JM: Relationship between clinically detected joint swelling and effusion diagnosed by ultrasonography in elbow joints in patients with rheumatoid arthritis. *Clin. Rheumatol.* 24(3), 228–231 (2005).
7. Terslev L, Torp-Pedersen S, Savnik A *et al.*: Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum.* 48(9), 2434–2441 (2003).
   • Validates US against magnetic resonance imgaing (MRI) in rheumatoid arthritis in the hand.

8. Kane D, Balint P, Sturrock R: Ultrasonography is superior to clinical examination inthe detection and localization of knee joint effusion in rheumatoid arthritis. *J. Rheumatol.* 30, 966–971 (2003).
• Demonstrates that US is superior to clinical examination in detecting synovitis in the knee joint.
9. van Holsbeeck M, van Holsbeeck K, Gevers G *et al.*: Staging and follow-up of rheumatoid arthritis of the knee. Comparison of sonography, thermography, and clinical assessment. *J. Ultrasound Med.* 7(10),561–566 (1988).
10. Karim Z, Wakefield R, Quinn M *et al.*: Validation and reproducibility of ultrasonography in the detection of synovitis in the knee: a comparison with arthroscopy and clinical examination. *Arthritis Rheum.* 50(2), 387–394 (2004).
• Comprehensive validation of US against other imaging techniques and histopathology.
11. Backhaus M, Kamradt T, Sandrock D *et al.*: Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum.* 42(6), 1232–1245 (1999).
•• Comprehensive validation of US against other imaging techniques with regards to inflammatory arthritis of the finger joints.
12. Conaghan P, Wakefield R, Ostergaard M *et al.*: MCPJ assessment in early RA: a comparison between x-ray, MRI, high resolution ultrasouns and clinical examination. *Arthritis Rheum.* 41, S246 (1998).
13. Szkudlarek M, Narvestad E, Klarlund M, Court-Payen M, Thomsen HS, Ostergaard M: Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. *Arthritis Rheum.* 50(7), 2103–2112 (2004).
• Comprehensive validation of US against other imaging techniques in the toe joints of patients with rheumatoid arthritis.
14. Walther M, Harms H, Krenn V, Radke S, Faehndrich TP, Gohlke F: Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum.* 44(2), 331–338 (2001).
15. Walther M, Harms H, Krenn V, Radke S, Kirschner S, Gohlke F: Synovial tissue of the hip at power Doppler US: correlation between vascularity and power Doppler US signal. *Radiology* 225(1), 225–231 (2002).
16. Szkudlarek M, Court-Payen M, Strandberg C, Klarlund M, Klausen T, Ostergaard M: Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. *Arthritis Rheum.* 44(9), 2018–2023 (2001).
17. Koski JM, Saarakkala S, Helle M *et al.*: Assessing the intra- and inter-reader reliability of dynamic ultrasound images in power Doppler ultrasonography. *Ann. Rheum. Dis.* (2006) (Epub ahead of print).
18. Hoving J, Buchbinder R, Hall S *et al.*: A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J. Rheumatol.* 31(4), 663–675 (2004).
19. Swen WA, Jacobs JW, Hubach PC, Klasens JH, Algra PR, Bijlsma JW: Comparison of sonography and magnetic resonance imaging for the diagnosis of partial tears of finger extensor tendons in rheumatoid arthritis. *Rheumatology* 39(1), 55–62 (2000).
20. Klocke R, Glew D, Cox N, Blake D. Sonographic erosions of the rheumatoid little toe. *Ann. Rheum. Dis.* 60(9), 896–897 (2001).
21. Wakefield R, Gibbon W, Conaghan P *et al.*: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum.* 43(12), 2762–2770 (2000).
22. Grassi W, Filippucci E, Farina A, Salaffi F, Cervini C: Ultrasonography in the evaluation of bone erosions. *Ann. Rheum. Dis.* 60(2), 98–103 (2001).
23. van der Heijde DM, van´t Hof MA, van Riel PL *et al.*: Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann. Rheum. Dis.* 49(11), 916–920 (1990).
24. Felson DT, Anderson JJ, Boers M *et al.*: The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum.* 36(6), 729–740 (1993).
25. Schmidt WA, Volker L, Zacher J, Schlafke M, Ruhnke M, Gromnica-Ihle E: Colour Doppler ultrasonography to detect pannus in knee joint synovitis. *Clin. Experimental Rheumatol.* 18(4), 439–444 (2000).
26. Ostergaard M, Hansen M, Stoltenberg M *et al.*: Magnetic resonance imaging-determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. *Arthritis Rheum.* 42(5), 918–929 (1999).
27. Taylor P, Steue A, Gruber D *et al.*: Comparison of ultrasonographic evaluation in a randomized placebo-controlled study of inlfiximab therapy in early rheumatoid arthritis. *Arthritis Rheum.* 50, 1107–1116 (2004).
•• Compares two groups treated with either DMARDs or antitumor necrosis factor therapy. US is better than clinical findings at differentiating between therapy with biologics than DMARDs. The first study demonstrating that US findings at baseline can predict findings at follow-up.
28. Qvistgaard E, Rogind H, Torp-Pedersen S, Terslev L, Danneskiold-Samsoe B, Bliddal H: Quantitative ultrasonography in rheumatoid arthritis: evaluation of inflammation by Doppler technique. *Ann. Rheum. Dis.* 60(7), 690–693 (2001).
29. Wakefield RJ, Green MJ, Marzo-Ortega H *et al.*: Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann. Rheum. Dis.* 63(4), 382–385 (2004).
•• Demonstrates that US can detect subclinical synovitis. In patients classified as oligartyhritis, many have synovitis in joints, which would result in reclassification if demonstratable clinically. This has important implications for classification of disease and management decisions.
30. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A: Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann. Rheum. Dis.* 64(3), 375–381 (2005).

•• Demostrates that US joint counts (60 joints) correlate better with biochemical markers of inflammation than clinically derived measures. In recent times, clinical trial outcomes, such as the DAS, have been criticized as being nonspecific to inflammation. Whilst routine use of a 60 joint count is not practical, US may be shown to be more specific to inflammation and potentially a better measure of disease activity than current outcome measures.

31. Naredo E, Gamero F, Bonilla G, Uson J, Carmona L, Laffon A: Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: comparison of extended versus reduced joint evaluation. *Clin. Exp. Rheum.* 23(6), 881–884 (2005).

•• Builds on [30], demonstrating that a 12-joint count by US correlates with a 60-joint count, and also with biochemical markers of inflammation. Limited joint counts may be a reasonable reflection of inflammatory burden, both systemically and in the joints.

32. Salaffi F, Carotti M, Manganelli P, Filippucci E, Giuseppetti GM, Grassi W: Contrast-enhanced power Doppler sonography of knee synovitis in rheumatoid arthritis: assessment of therapeutic response. *Clin. Rheumatol.* 23(4), 285–290 (2004).

33. Strunk J, Strube K, Muller-Ladner U, Lange U: Three dimensional power Doppler ultrasonography confirms early reduction of synovial perfusion after intra-articular steroid injection. *Ann. Rheum. Dis.* 65(3), 411–412 (2006).

34. Newman J, Laing T, McCarthy C, Adler R: Power Doppler sonography of synovitis: assessment of therapeutic response – preliminary observations. *Radiology* 198(2), 582–584 (1996).

35. Carotti M, Salaffi F, Manganelli P, Salera D, Simonetti B, Grassi W: Power Doppler sonography in the assessment of synovial tissue of the knee joint in rheumatoid arthritis: a preliminary experience. *Ann. Rheum. Dis.* 61(10), 877–882 (2002).

36. Filippucci E, Farina A, Carotti M, Salaffi F, Grassi W: Grey scale and power Doppler sonographic changes induced by intra-articular steroid injection treatment. *Ann. Rheum. Dis.* 63(6), 740–743 (2004).

37. Filippucci E, Iagnocco A, Meenagh G *et al.*: Power Doppler sonography monitoring of synovial perfusion at wrist joint in rheumatoid patients treated with adalimumab. *Ann. Rheum. Dis.* (2006) (Epub ahead of print).

38. Ribbens C, Andre B, Marcelis S *et al.*: Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor-α treatment: pilot study. *Radiology* 229(2), 562–569 (2003).

39. Fiocco U, Ferro F, Vezzu M *et al.*: Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. *Ann. Rheum. Dis.* 64(6), 899–905 (2005).

Affiliations

- *Helen I Keen*
  Chapel Allerton Hospital, Academic Unit of Musculoskeletal Disease, 2nd Floor, Chapeltown Road, Leeds, LS7 4SA, UK
  Tel.: +44 0113 392 4884;
  Fax: +44 0113 392 4991;
  h.i.keen@leeds.ac.uk
- *Richard J Wakefield*
  Chapel Allerton Hospital, Academic Unit of Musculoskeletal Disease, 2nd Floor, Chapeltown Road, Leeds, LS7 4SA, UK
  Tel.: +44 0113 392 4884;
  Fax: +44 0113 392 4991;
  r.j.wakefield@leeds.ac.uk
- *Philip G Conaghan*
  Chapel Allerton Hospital, Academic Unit of Musculoskeletal Disease, 2nd Floor, Chapeltown Road, Leeds, LS7 4SA, UK
  Tel.: +44 0113 392 4884;
  Fax: +44 0113 392 4991;
  p.conaghan@leeds.ac.uk