

## Ultrasound imaging for the rheumatologist VII. Ultrasound imaging in rheumatoid arthritis

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### ABSTRACT

*The present review provides an update of the available data and discusses research issues of ultrasound (US) imaging in rheumatoid arthritis (RA).*

*Currently the principal indications for using US in the assessment of patients with RA include: detection of sub-clinical synovitis, demonstration of bone erosion undetected by conventional radiography, detailed assessment of tendon pathology and guided injection and aspiration of joints and soft tissues. Future potential applications are likely to include short and long term therapy monitoring and early detection of cartilaginous changes in RA.*

*The main priorities requiring the attention of investigators include: addressing validity issues, especially those related to criterion and discriminator validity, development of international consensus on scoring systems, evaluation of the role of power Doppler in the assessment of disease activity, development of a specific training programme for rheumatologists performing US and investigation of the potential of 3D US using a volumetric probe.*

### Introduction

Over the last decade, there has been an explosion of research in the field of the management of patients with rheumatoid arthritis (RA). Refining diagnostic accuracy in early disease, intensive monitoring of disease activity and the search for the ideal therapy leading to remission have been the key targets of these investigations (1-3).

Ultrasound (US) is rapidly becoming one of the standard tools within the rheumatologist's armamentarium in the assessment of patients with RA.

Despite the enormous advances of the last decade, US imaging continues to evolve both in terms of technological

advancement and the ever increasing number of applications in rheumatology (4-7). Over the last five years, there has been exponential growth within the literature, centring upon the US assessment of patients with RA (8-18).

This review provides an update of the available data and discusses research issues of US imaging in RA.

### Clinical applications

Currently the principal indications for using US in the assessment of patients with RA include: detection of sub-clinical synovitis, demonstration of bone erosion undetected by conventional radiography, detailed assessment of tendon pathology and guided injection and aspiration of joints and soft tissues (19-23). These applications have been collated by an international panel of experts in US, both rheumatologists and radiologists, and represent part of the core knowledge and skills required for competency in musculoskeletal US (20).

Future potential applications are likely to include short and long term therapy monitoring and early detection of cartilaginous changes in RA.

Greyscale US with high quality equipment permits quick and accurate differentiation between synovial effusion and synovial proliferation (19, 24). Power Doppler provides information on the perfusional status of the synovial tissue which reflects the activity of the inflammatory process (25-27).

Moreover, US is helpful in identifying pathologic changes responsible for regional pain syndromes in patients with RA e.g., shoulder pain, carpal tunnel syndrome, knee pain (28-31).

The use of high frequency US to guide needle positioning within inflamed small joints of the hand, has been shown to provide greater accuracy than

the palpation guided approach (96% v 59%) (32).

Similarly, using US guidance the risk of damaging tendons, nerves, blood vessels and cartilage is significantly reduced (33-35).

### Sonographic findings

The main pathological features detected by US in patients with RA are those related to synovial tissue inflammation and joint damage (Table I) (Fig. 1).

Joint effusion and synovial proliferation result in joint cavity widening of various extent. Preliminary definitions of both synovial fluid and synovial proliferation have been recently provided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group for musculoskeletal US in Rheumatology (36). Real time examination is the most reliable method of scanning to distinguish between synovial fluid and proliferation. Synovial fluid is compressible and displaceable whereas synovial tissue is not. Further differentiation is provided by power Doppler signal whose detection within the joint cavity indicates blood flow at synovial tissue level. Power Doppler signal usually has a patchy distribution within the joint cavity. Some studies have reported that the areas of synovial proliferation closer to bone erosions and disruptions in cartilage are those most likely to show power Doppler signal (37), whilst others suggest there is no increased blood flow at the areas of pannus invading the bone (38).

In a recent study, Naredo *et al.* presented the US criteria for effusion/synovitis for the main joints of the body along with the necessary information for probe and calliper placement to take the correspond measurements (13).

Bone erosions appear as interruptions of the bone profile that must be documented on at least two perpendicular scanning planes (36). Their size is currently estimated measuring the largest diameter between the free edges of the crater. The sonographic features of the synovial tissue filling the bone erosion is important for distinguishing between "hot" and "cold" erosions. The former show hypoechoic and hyperperfused

**Table I.** Pathologic conditions and corresponding US findings.

Pathologic condition	US findings
Joint effusion	Anechoic homogeneous joint space widening (4). An intra-articular black, anechoic area (8). A compressible anechoic intra-capsular area (10). A hypoechoic or anechoic compressible intra-articular material, within synovial recesses (13). The presence of an abnormally anechoic space within the joint, which was compressible (21). Anechoic joint space widening (28).
Synovitis	Homogeneous echoic joint space widening indicating synovial proliferation appearing as irregular clusters of soft echoes (4). A thickening of the synovial membrane (synovial proliferation) was visualised by US as hypo- or hyperechoic structures within the region affected by effusion (8). A non-compressible hypoechoic intracapsular area (10). An echogenic non-compressible intra-articular tissue, within synovial recesses (13). The presence of an abnormally hypoechoic joint space reflecting synovial hypertrophy, distinct from the intra-articular fat pad and non-compressible with the transducer (21). Joint space widening with clusters of soft echoes (bushy and villous appearance) and/or homogeneous synovial thickening (28).
Bone erosion	An interruption of the bone surface visible in two planes (8). Change in the bone surface of the area adjacent to the joint (10). A cortical defect seen in two or more scanning planes (21). An intra-articular discontinuity of the bone surface that is visible in 2 perpendicular planes (36). A cortical "break" or defect with an irregular floor seen in longitudinal and transverse planes (41). An interruption of the bone margin (42).
Tenosynovitis	Tendon sheath widening resulting from effusion (anechoic pattern), proliferative synovitis (echoic pattern) or both (mixed pattern) (4, 22). Abnormally hypoechoic area around tendon seen in longitudinal and transverse planes (21). Homogeneous hypo- or anechoic tendon sheath wideing (exudative tenosynovitis) (30). Tendon sheath widening due to an irregular thickening of the synovial tissue (proliferative tenosynovitis) (30). Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath, which is seen in 2 perpendicular planes and which may exhibit Doppler signal (36). Presence of fluid within the tendon sheath, thickening of the tendon sheath, thickening of the tendon (43).
Tendon rupture	Discontinuity of the tendon visualised with the ultrasound beam exactly perpendicular to the tendon (22). Tendon tears appear as fragmentation of small groups of contiguous fibrils, which determines a characteristic loss of the normal fibrillar echotexture of the tendon (30).

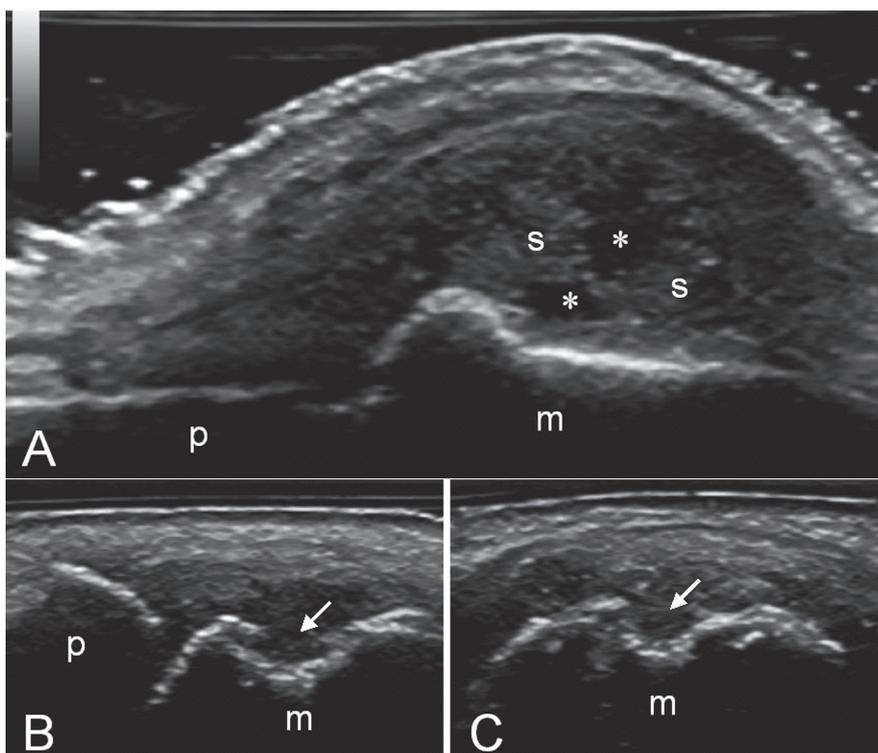
synovial tissue lying within the erosive cavity whilst the latter are filled with fibrotic pannus which is more echogenic on greyscale and does not exhibit power Doppler signal.

Tendon sheath widening is the hallmark of tenosynovitis. A variable degree of tendon thickening can be detected in patients with tendinopathy. Thickening is often associated with reduction of the tendon echogenicity and intratendinous power Doppler signal identifies the areas with increased perfusion. A tendon tear can be partial or complete and

appears as a disturbance in the continuity of the tendon fibrils which must be confirmed in at least two perpendicular scanning planes with the US beam perpendicular to the tendon direction (22).

### Literature review

Validity issues have been recently reviewed by Ostergaard *et al.* (39). Whilst US was found to be a promising tool for use in clinical trials further investigation is needed to confirm its diagnostic value, sensitivity to change and predictive value.



**Fig. 1.** Rheumatoid arthritis. Second metacarpophalangeal joint. Proliferative synovitis with a bone erosion on the radial aspect of the metacarpal head (arrows) documented on two perpendicular scanning planes. Dorsal longitudinal (A) and lateral longitudinal (B) and transverse (C) views. **m** = metacarpal bone; **p** = proximal phalanx; \* = synovial fluid; **s** = synovial proliferation. Images taken with a Logiq 9 (General Electric Medical Systems, Milwaukee, WI) using a volumetric probe (4D16L). For further ultrasound images, please go to [www.clinexprheumatol.org](http://www.clinexprheumatol.org)

More recently further evidence has emerged in support of the role of US in early RA and therapy monitoring. US is a sensitive imaging tool for the detection of synovitis and bone erosions especially in the early phases of the disease (40). Recent studies have shown that US is more sensitive than clinical examination in the detection of joint inflammation both in patients with early undifferentiated arthritis (21) and in patients with established RA (9, 13, 17).

In a cohort of 80 patients with early (< 12 months) oligoarthritis (< 5 joints with clinical synovitis), US found evidence of sub-clinical disease in 51 patients (64%) and led to reclassification as polyarthritis in 29 patients (36%) (21).

US has also been compared to clinical examination in the detection of synovitis in 60 joints of 94 consecutive RA patients with a mean disease duration of 69.3 months. US found a significantly higher number of joints with effusion (mean 15.2) and synovitis (mean 14.6)

than joint swelling detected by clinical examination (mean 11.5) (13).

Similar results have been demonstrated in the detection of synovitis at metacarpophalangeal and proximal interphalangeal joints of 40 RA patients with a median disease duration of 5 years. Of the 480 joints assessed, 194 (40.4%) were found inflamed by US and 121 (25.2%) by clinical examination (9).

The sensitivity of US in the detection of bone erosions is dependant upon the resolution power of the US equipment and upon the width of the acoustic window. Several studies have demonstrated that US is more sensitive than conventional radiography in the detection of bone erosions in the small joints of hands and feet (8, 9, 17, 41, 42). Most of these studies used magnetic resonance imaging (MRI) as the gold standard to confirm that the US findings corresponded to bone erosions. In a recent cross-sectional study, computer tomography (CT) was used as the gold standard method to compare the sensitivity, specificity and accuracy of

US, MRI and conventional radiography in the detection of bone erosions at the 2<sup>nd</sup> to 5<sup>th</sup> metacarpophalangeal (MCP) joints in 17 patients with RA. This showed that bone erosions detected by both MRI and US, invisible on conventional radiography, correspond to true erosions on CT. US detected 23% more erosions than conventional radiography and was especially sensitive at the 2<sup>nd</sup> and the 5<sup>th</sup> MCP joints because of the accessibility of the bone surfaces of those joints. At least one bone erosion was detected in all 17 patients by CT and MRI, in 15 patients by US and in 8 patients by conventional radiography (23).

Data from several studies support the evidence that US provides the highest sensitivity in detecting bone erosions at the II MCP joint, especially in early RA (9, 23, 41, 42). Such impressive sensitivity could not be obtained at IV MCP and wrist joints where the acoustic windows for exploring the intra-articular bone surfaces are narrow (41, 43).

Short-term monitoring with US has shown significant changes in joint inflammation after the administration of glucocorticoids and tumor necrosis factor  $\alpha$  antagonists. Significant reduction of intra-articular power Doppler signal (up to 100%) has been demonstrated with intra-articular and intravenous corticosteroid therapy (44-49). Very short-term follow up (mean 52 hours) can demonstrate dramatic changes in synovial perfusion as assessed with quantitative power Doppler in a study conducted in 13 patients with active RA treated with 1000 mg intravenous methylprednisolone in the small joints of the hand. The therapeutic effect of injection therapy with glucocorticoid has been demonstrated after 2 weeks of therapy with sustained reduction in power Doppler signal (49).

There is an increasing number of studies investigating US in biologic therapy monitoring (12, 50-56). Most of the studies show a significant reduction of intra-articular power Doppler signal at the small joints of the hands and wrists 2-3 weeks after commencing biologic therapy. US has recently been used to attempt to discriminate between two treatment regimes; infliximab plus meth-

otrexate and methotrexate monotherapy in patients with early arthritis (12). The results of that study demonstrated that US assessment of synovial proliferation and intra-articular perfusion could discriminate between the two groups after 18 weeks of treatment, with higher sensitivity than conventional clinical and laboratory evaluation including the numbers of tender and swollen joints together with ESR (12).

A recent study highlighted the sensitivity of imaging modalities, including US and MRI, in the detection of synovitis at MCP and wrist joints of the dominant hand in 107 RA patients with disease-modifying antirheumatic drug-induced clinical remission (16). Grey-scale US found evidence of synovial proliferation in 84.9% of the patients and power Doppler detected intra-articular signal in 60.4% of the patients.

### Research agenda

The main priorities requiring the attention of investigators are listed in Table II.

Over the last few years, several scoring systems have been proposed for assessing joint inflammation and bone erosions in patients with RA. The differences between these scoring systems rely on the following aspects:

- the US equipment used (two-dimensional US, three-dimensional US with volumetric probe or with hands-free acquisition);
- the technique adopted (B-mode or power Doppler mode or contrast agents);
- the scanning protocol followed (single standard scan or multiplanar examination);
- the US material assessed (static images or video clips);
- the method used to interpret the US findings: qualitative (presence or absence) or quantitative (using a software counting the coloured pixels located within a region of interest) or semiquantitative (3 or 4 degrees).

In order to reach an international consensus, the OMERACT special interest group on US is currently developing a comprehensive approach for scoring both synovitis and bone erosions in small joints of patients with RA.

**Table II.** US imaging in RA: research agenda.

To address validity issues, especially to obtain data on criterion and discriminator validity
To develop international consensus on scoring systems for assessing synovitis, tenosynovitis and bone erosions
To evaluate the role of US with power Doppler in the assessment of disease activity
To develop a specific training programme for rheumatologists performing US examination of patients with RA
To investigate the potential of 3D US with the volumetric probe.

One of the advantages of US is the potential for multiple joint examination but such an approach is time consuming and challenges both physicians and patients compliance. Which specific joints to examine with US remains a critical issue to address. There is some evidence to suggest that a targeted approach to US joint examination is comparable to a more comprehensive protocol (14).

Despite US is the most operator dependent modality and the learning curve has been defined steep and virtual infinite, a training programme specifically designed to acquire the specific competency required to assess patients with RA can speed up the process and put a group of motivated rheumatologists in a position to scan RA patients according to a specific scanning protocol in the clinical setting of the early arthritis clinics and/or clinical trials.

It seems likely that the pursuit of more innovative approaches to US acquisition will be the subject of considerable interest in the future. The most promising method is 3D US using a volumetric probe which provides automatic acquisition of a virtually infinite number of scanning planes lying under the footprint.

This US imaging approach has the potential to rectify the operator dependence of US, simplifying both acquisition and interpretation of US findings especially in the assessment of synovial perfusion using the power Doppler (5, 30, 60).

### Link

For further ultrasound images, go to [www.clinexprheumatol.org/ultrasound](http://www.clinexprheumatol.org/ultrasound)

### References

1. EMERY P: Treatment of rheumatoid arthritis. *BMJ* 2006; 332: 152-5.
2. SMOLEN JS, ALETAHA D: Challenges of pre-

dicting treatment response in patients with rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2005; 1: 62-3.

3. WELLS G, BOERS M, TUGWELL P: Low disease activity state in rheumatoid arthritis: concepts and derivation of minimal disease activity. *Clin Exp Rheumatol* 2006; 24: S052-9.
4. GRASSI W, CERVINI C: Ultrasonography in rheumatology: an evolving technique. *Ann Rheum Dis* 1998; 57: 268-71.
5. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al.*: Ultrasound imaging for the rheumatologist. *Clin Exp Rheumatol* 2006; 24: 1-5.
6. MEENAGH G, FILIPPUCCI E, KANE D, TAGGART A, GRASSI W: Ultrasonography in rheumatology: developing its potential in clinical practice and research. *Rheumatology* 2007; 46: 3-5.
7. GRASSI W, FILIPPUCCI E: Ultrasonography and the rheumatologist. *Curr Opin Rheumatol* 2007; 19: 55-60.
8. SCHEEL AK, HERMANN KG, OHRNDORF S *et al.*: Prospective 7 year follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis finger joints. *Ann Rheum Dis* 2006; 65: 595-600.
9. SZKUDLAREK M, KLARLUND M, NARVESTAD E *et al.*: Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination. *Arthritis Res Ther* 2006; 8: R52.
10. SZKUDLAREK M, COURT-PAYEN M, JACOBSEN S, KLARLUND M, THOMSEN HS, OSTERGAARD M: Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 955-62.
11. TERSLEV L, TORP-PEDERSEN S, SAVNIK *et al.*: Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum* 2003; 48: 2434-41.
12. TAYLOR PC, STEUER A, GRUBER J *et al.*: Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 1107-16.
13. 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 ultrasonogra-

- phy. *Ann Rheum Dis* 2005; 64: 375-81.
14. 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 Rheumatol* 2005; 23: 881-4.
  15. SCHEEL AK, HERMANN KG, KAHLER E *et al.*: A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 733-43.
  16. BROWN AK, QUINN MA, KARIM Z *et al.*: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: Evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; 54: 3761-73.
  17. 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* 2004; 50: 2103-12.
  18. OSTERGAARD M, EJBBERG B, SZKUDLAREK M: Imaging in early rheumatoid arthritis: roles of magnetic resonance imaging, ultrasonography, conventional radiography and computed tomography. *Best Pract Res Clin Rheumatol* 2005; 19: 91-116.
  19. KANE D, GRASSI W, STURROCK R, BALINT PV: Musculoskeletal ultrasound--a state of the art review in rheumatology. Part 2: Clinical indications for musculoskeletal ultrasound in rheumatology. *Rheumatology* 2004; 43: 829-38.
  20. BROWN AK, O'CONNOR PJ, ROBERTS TE, WAKEFIELD RJ, KARIM Z, EMERY P: Ultrasonography for rheumatologists: the development of specific competency based educational outcomes. *Ann Rheum Dis* 2006; 65: 629-36.
  21. WAKEFIELD RJ, GREEN MJ, MARZO-ORTEGA H *et al.*: Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of sub-clinical disease. *Ann Rheum Dis* 2004; 63: 382-5.
  22. GRASSI W, FILIPPUCCI E, FARINA A, CERVINI C: Sonographic imaging of tendons. *Arthritis Rheum* 2000; 43: 969-76.
  23. DOHN UM, EJBBERG BJ, COURT-PAYEN M *et al.*: Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. *Arthritis Res Ther* 2006; 8: R110.
  24. GRASSI W, SALAFFI F, FILIPPUCCI E: Ultrasound in rheumatology. *Best Pract Res Clin Rheumatol* 2005; 19: 467-85.
  25. WAKEFIELD RJ, BROWN AK, O'CONNOR PJ, EMERY P: Power Doppler sonography: improving disease activity assessment in inflammatory musculoskeletal disease. *Arthritis Rheum* 2003; 48: 285-8.
  26. GRASSI W, FILIPPUCCI E: Is power Doppler sonography the new frontier in therapy monitoring? *Clin Exp Rheumatol* 2003; 21: 424-8.
  27. SCHMIDT WA: Technology Insight: the role of color and power Doppler ultrasonography in rheumatology. *Nat Clin Pract Rheumatol* 2007; 3: 35-42.
  28. GRASSI W, FILIPPUCCI E, CAROTTI M, SALAFFI F: Imaging modalities for identifying the origin of regional musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2003; 17: 17-32.
  29. IAGNOCCO A, FILIPPUCCI E, MEENAGH G *et al.*: Ultrasound imaging for the rheumatologist I. Ultrasonography of the shoulder. *Clin Exp Rheumatol* 2006; 24: 6-11.
  30. FILIPPUCCI E, IAGNOCCO A, MEENAGH G *et al.*: Ultrasound imaging for the rheumatologist II. Ultrasonography of the hand and wrist. *Clin Exp Rheumatol* 2006; 24: 118-22.
  31. MEENAGH G, IAGNOCCO A, FILIPPUCCI E *et al.*: Ultrasound imaging for the rheumatologist IV. Ultrasonography of the knee. *Clin Exp Rheumatol* 2006; 24: 357-60.
  32. RAZAK, LEE CY, PILLING D *et al.*: Ultrasound guidance allows accurate needle placement and aspiration from small joints in patients with early inflammatory arthritis. *Rheumatology* 2003; 42: 976-9.
  33. GRASSI W, FARINA A, FILIPPUCCI E, CERVINI C: Sonographically guided procedures in rheumatology. *Semin Arthritis Rheum* 2001; 30: 347-53.
  34. KOSKI JM, HERMUNEN HS, KILPONEN VM, SAARAKKALA SJ, HAKULINEN UK, HEIKKINEN JO: Verification of palpation-guided intra-articular injections using glucocorticoid-air-saline mixture and ultrasound imaging (GAS-graphy). *Clin Exp Rheumatol* 2006; 24: 247-52.
  35. GRASSI W, FARINA A, FILIPPUCCI E, CERVINI C: Intralesional therapy in carpal tunnel syndrome: a sonographic-guided approach. *Clin Exp Rheumatol* 2002; 20: 73-6.
  36. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al.*: OMERACT 7 Special Interest Group. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32: 2485-7.
  37. STEUER A, BLOMLEY M, COSGROVE D, MAINI RN, TAYLOR PC: Combined power color Doppler and greyscale ultrasound demonstrate an association between vascularity and erosions in rheumatoid arthritis [abstract]. *Arthritis Rheum* 2000; 43: S292.
  38. 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* 2001; 60: 690-3.
  39. OSTERGAARD M, SZKUDLAREK M: Ultrasonography: a valid method for assessing rheumatoid arthritis? *Arthritis Rheum* 2005; 52: 681-6.
  40. WAKEFIELD RJ, KONG KO, CONAGHAN PG, BROWN AK, O'CONNOR PJ, EMERY P: The role of ultrasonography and magnetic resonance imaging in early rheumatoid arthritis. *Clin Exp Rheumatol* 2003; 21: S42-9.
  41. WAKEFIELD RJ, GIBBON WW, CONAGHAN PG *et al.*: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum* 2000; 43: 2762-70.
  42. GRASSI W, FILIPPUCCI E, FARINA A, SALAFFI F, CERVINI C: Ultrasonography in the evaluation of bone erosions. *Ann Rheum Dis* 2001; 60: 98-103.
  43. HOVING JL, 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* 2004; 31: 663-75.
  44. NEWMAN JS, LAING TJ, MCCARTHY CJ, ADLER RS: Power Doppler sonography of synovitis: assessment of therapeutic response - preliminary observations. *Radiology* 1996; 198: 582-4.
  45. STONE M, BERGIN D, WHELAN B, MAHER M, MURRAY J, MCCARTHY C: Power Doppler ultrasound assessment of rheumatoid hand synovitis. *J Rheumatol* 2001; 28: 1979-82.
  46. TERSLEV L, TORP-PEDERSEN S, QVISTGAARD E, DANNESKIOLD-SAMSOE B, BLIDDAL H: E stimulation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 1049-53.
  47. D'AGOSTINO MA, AYRAL X, BARON G, RAVAUD P, BREBAN M, DOUGADOS M: Impact of ultrasound imaging on local corticosteroid injections of symptomatic ankle, hind-, and mid-foot in chronic inflammatory diseases. *Arthritis Rheum* 2005; 53: 284-92.
  48. 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* 2004; 63: 740-3.
  49. TEH J, STEVENS K, WILLIAMSON L, LEUNG J, MCNALLY EG: Power Doppler ultrasound of rheumatoid synovitis: quantification of therapeutic response. *Br J Radiol* 2003; 76: 875-9.
  50. FILIPPUCCI E, IAGNOCCO A, SALAFFI F, CERIONI A, VALESINI G, GRASSI W: Power Doppler sonography monitoring of synovial perfusion at the wrist joints in patients with rheumatoid arthritis treated with adalimumab. *Ann Rheum Dis* 2006; 65: 1433-7.
  51. TERSLEV L, TORP-PEDERSEN S, QVISTGAARD E *et al.*: Effects of treatment with etanercept (Enbrel, TNRF:Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. *Ann Rheum Dis* 2003; 62: 178-81.
  52. HAU M, KNEITZ C, TONY HP *et al.*: High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor a receptor (etanercept). *Ann Rheum Dis* 2002; 61: 55-8.
  53. RIBBENS C, ANDRE B, MARCELIS S *et al.*: Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor-alpha treatment: pilot study. *Radiology* 2003; 229: 562-9.
  54. 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* 2005; 64: 899-905.
  55. TAYLOR PC, STEUER A, GRUBER J *et al.*:

- Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 47-53.
56. HAU M, KNEITZ C, TONY HP, KEBERLE M, JAHNS R, JENETT M: High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor alpha receptor (etanercept). *Ann Rheum Dis* 2002; 61: 55-8.
57. IAGNOCCO A, PERELLA C, CECCARELLI F *et al.*: Ultrasonographic assessment of the response to Etanercept treatment in patients with rheumatoid arthritis. *Reumatismo* 2006; 58: 233-8.
58. BLIDDAL H, TERSLEV L, QVISTGAARD E *et al.*: Safety of intra-articular injection of etanercept in small-joint arthritis: an uncontrolled, pilot-study with independent imaging assessment. *Joint Bone Spine* 2006; 73: 714-7.
59. SHIO K, HOMMA F, KANNO Y *et al.*: Doppler sonographic comparative study on usefulness of synovial vascularity between knee and metacarpophalangeal joints for evaluation of articular inflammation in patients with rheumatoid arthritis treated by infliximab. *Mod Rheumatol* 2006; 16: 220-5.
60. STRUNK J, LANGE U: Three-dimensional power Doppler sonographic visualization of synovial angiogenesis in rheumatoid arthritis. *J Rheumatol* 2004; 31: 1004-6.