Supplementary file 1. Initial literature search

OBJECTIVES

1. To search for evidence of quality of reporting of ultrasound studies in Rheumatic and Musculoskeletal Diseases (RMDs)

METHODS:

a. Study selection criteria

We decided to focus the search to the use of ultrasound for evaluating synovitis in rheumatoid arthritis because this subject has been extensively studied with a wide range of study designs, number of patients and objective of measurement.

b. Search strategies

We used PubMed Clinical Queries and performed a broad search in the following categories: diagnosis, aetiology, prognosis, and therapy. The search was limited by language (English) but not by year of publication. Review articles were excluded. The search strategies are detailed in Tables 1 to 4.

c. Selection of studies and data collection

The searches were downloaded separately and a random sample of 20 studies was taken from each category (total 80 studies). The objectives and Methods sections were transposed into a table including the following headings: Objective (blue = abstract; red = intro) / Design (red = study design, blue = ethics) / Technical data (blue = machine, green = joints, red = operator, grey = time/place) / Measure / Outcome (blue = elementary lesions, red = score, green = reliability).

d. Data analysis

The tables were sent to each member of the taskforce who were required to identify, prior to the first face-to-face meeting, information that could be a source of bias or error in this area, and missing aspects that should be considered for inclusion in the guidelines.

Table 1. PubMed Clinical Queries strategy: diagnosis category (July 2016).

| 1 | #1 AND Filters: "humans"[MeSH Terms]; English[lang] NOT Filters Review[ptyp] | 143 |
Table 2. PubMed Clinical Queries strategy: aetiology category (July 2016).

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Table 3. PubMed Clinical Queries strategy: prognosis category (July 2016).

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Table 4. PubMed Clinical Queries strategy: therapy category (July 2016).

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**SUMMARY OF RESULTS**
### Table 5. Data collection of the randomly selected sample of articles in Diagnosis category.

<table>
<thead>
<tr>
<th>Title</th>
<th>Objective (blue = abstract ; red = intro)</th>
<th>Design (red = study design, blue = ethics)</th>
<th>Technical data (blue = machine, green = joints, red = operator, grey = time/place)</th>
<th>Measure / Outcome (blue = elementary lesions, red = score, green = reliability)</th>
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<tbody>
<tr>
<td>Amitai et al. - 2015 – [1] Comparison of Photo Optical Imaging with Musculoskeletal Ultrasound and Clinical Examination in the Assessment of Inflammatory Activity in Proximal Interphalangeal Joints in Rheumatoid Arthritis and Osteoarthritis</td>
<td>Abstract: NA Intro: The aim of our study was to compare the new photo optical imaging system POI (“Lightscan”) with US and CE in assessing inflammatory activity in PIP joints in a cohort of patients with RA and OA. Further, we defined the most useful cutoff by also including healthy subjects to distinguish between healthy and pathological conditions and a POI score for each joint, as well as a POI mean sum score of the PIP joints on both sides (n = 8 in each patient) to show the total average activity.</td>
<td>There were 87 subjects consecutively recruited from the Rheumatology Outpatient Clinic of the University Hospital Charité Berlin, Germany. Patients with the confirmed diagnosis of RA or OA who agreed to participate in our study were included. For inclusion, all participants had to sign consent forms after receiving written and oral information.</td>
<td>All included subjects were examined by musculoskeletal US using the Esaote Mylab Twice ultrasound machine (Esaote) with high resolution 8–18 MHz linear array transducer. The US examinations were carried out by an experienced ultrasonographer (SO) who assessed the PIP joints according to the EULAR guidelines, after OMERACT definitions and German standard scans each joint from the dorsal and from the palmar view. Clinical and imaging examinations (US and Lightscan) were done on the same day.</td>
<td>PIP joints 2-5 (n = 696) were evaluated semiquantitatively (grades 0–3) for synovitis in greyscale mode and synovial/tenosynovial vascularity in power Doppler mode. Tenosynovitis was scored for presence and absence (0–1) for a further characterization of the patient cohort (results are not included in our study). Each joint/joint region was considered separately for synovitis in GSUS and PDUS. Further, a semiquantitative sum score for the 8 PIP joints in palmar and dorsal view was calculated (range 0–24), as well as a sum score including all results for palmar and dorsal view (range 0–48) to create an US mean sum score for further comparison with the POI results.</td>
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<td>Beittinger et al. - 2013 – [2] The value of colour Doppler sonography of the knee joint: a useful tool to discriminate inflammatory from non-inflammatory disease?</td>
<td>Abstract : “To determine the diagnostic value of colour Doppler ultrasound (CDUS) in patients with inflammatory arthritis (IA) vs non-inflammatory disease (e.g. OA) of the knee joint.” Introduction : “the objective of the present study was to determine the value of CDUS in the assessment of inflammatory vs non-inflammatory disease of the knee joint”</td>
<td>A total of 111 knee joints in 106 patients (71 women and 35 men) were investigated in the study (OA: n = 72, IA: n = 39). The study was approved by the local ethics committee of the University of Regensburg</td>
<td>US was performed by two sonographers (W.H. and N.B.) with longstanding experience in musculoskeletal US within 24 h before arthrocentesis or knee surgery. The investigators were blinded to the result of the SF analyses. Logiq 7 equipment from GE (General Electric Healthcare, Chalfont St Giles, UK) with a linear multifrequency probe (M12L) with 514 MHz frequency and a field of view of 40 mm was used. The technical parameters of the examination included pulse repetition frequency of 700 Hz, colour Doppler frequency of 6.7 MHz, highest gain level without background noise and high colour persistence and a low wall filter. The knee was examined with the patient in the supine position in four different planes: the suprapatellar longitudinal scan, the</td>
<td>In each scan, colour Doppler activity was semi-quantitatively scored as follows: grade 0 = no intra-articular colour signal, grade 1 = up to three single colour signals or two single colour signals and one confluent colour signal representing only low flow, grade 2 = greater than grade 1 to ~50% of the intra-articular area filled with colour signals representing clear flow and grade 3 = &gt;50% of the intra-articular area filled with colour signal. Then a PDUS sum score (range 0-12) was calculated for each patient.</td>
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<td>Brown et al. - 2006 [3]</td>
<td>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</td>
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<td>Abstract: “The purpose of this study was to test the hypothesis that modern joint imaging improves the accuracy of remission measurement in RA.”</td>
<td>In this prospective controlled cohort study, 107 patients attending rheumatology outpatient clinics at Leeds General Infirmary were studied. Each patient underwent US assessment of the dominant hand and wrist joints, using gray-scale and power Doppler techniques. Eight joint regions were imaged with US: the second through the fifth metacarpophalangeal (MCP) joints and the radiocarpal, ulnar-carpal, distal radioulnar, and intercarpal compartments of the wrist. US was performed by a single experienced sonographer (ZK) who was blinded to all other study findings. An ATL HDI 3000 US machine (ATL, Bothell, WA) with a 10–5-MHz linear-array “hockey-stick” transducer was used, and the US examination was performed according to the European League Against Rheumatism (EULAR) guidelines (38). Each patient evaluation took 30 minutes, and representative images were archived.</td>
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<td>Introduction: “In the present study, we examined a large cohort of RA patients in clinical remission to test our hypothesis that objective evaluation of synovial inflammation using US and MRI may improve the accuracy of disease activity assessment”</td>
<td>The presence and location of any synovial hypertrophy and tenosynovitis was recorded with reference to the Outcome measures in Rheumatology (OMERACT) EULAR definitions of pathology (39). Synovial hypertrophy was graded on grayscale images, using a semiquantitative scoring method (the Leeds Score) (19,20), which consists of a 0–3 scale, where 0 no synovial hypertrophy, 1 mild hypertrophy, 2 moderate hypertrophy, and 3 severe hypertrophy. The maximal area of enhancement on power Doppler was recorded using a previously described semiquantitative technique (40), which consists of a 0–3 scale, where 0 normal/minimal vascularity, 1 mild hyperemia, 2 moderate hyperemia, and 3 marked hyperemia. Tenosynovitis was recorded as either present or absent. Interobserver reliability was determined by comparing the findings of 2 independent experienced rheumatologist ultrasonographers (ZK and AKB) who performed US examinations of 120 joint regions in a random subset of 15 patients. Each examiner performed the US assessments independently and sequentially while blinded to all other study data. Intraobserver reliability was assessed by blinded rescoring of the archived US images in the same subset 12 months after the original US assessment.</td>
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<td>Intro: The purpose of this cross-sectional study was to perform laser Doppler imaging and US of the hands of patients with known RA who were judged on clinical grounds to have pain and tenderness of the MCP joints and the skin temperature over the dorsum</td>
<td>Thirteen consecutive patients (10 women and three men; mean age, 48.8 years ± 14.1 [SD]; age range, 23–62 years) with known RA, on the basis of American Rheumatism Association criteria (14), were recruited for the study. All study participants were asked to avoid physical activity before the examination, and none had applied any cream to the hand or recently undergone physical therapy. The room temperature was monitored, as was the skin temperature over the dorsum.</td>
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<td>At grayscale US, anechoic metacarpal hyaline cartilage and the hyperechoic triangular dorsal fat pad were considered to be normal features. Other hypochoic and anechoic regions in the joint space were defined as synovitis without regard to the size of these lesions. Distinguishing</td>
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to establish whether elevated perfusion associated with MCP joints 2 and 3 was detectable.

This study was approved by the institutional ethics committee, and informed consent was obtained from each participant of the fourth finger.

Sagittal two-dimensional gray-scale and power Doppler images of the dorsal region of the MCP joint were obtained with a US machine (High Definition Imaging 3000; Advanced Technology Laboratories, Bothell, Wash) with a compact linear 10.5-MHz, 26-mm probe. The power Doppler zero level was established before the study. The power color gain was always adjusted to such a level that no power Doppler sign (red pixels in the active green box) appeared in the active state of the probe with air contact or after gel was applied to the surface of the probe. With this setup, there was no power Doppler sign when healthy MCP joints were imaged. A low wall filter and low flow optimum were chosen from the software. The pulse repetition frequency varied between 500 and 1,000 Hz. During the study, scans were obtained when stable red pixels were observed with no pixels present under cortical bone. In this way, we attempted to exclude the main disadvantages of the power Doppler technique, namely motion sensitivity and common flash artifacts. Quantification of the hyperemia was not possible with power Doppler imaging; we could observe only the presence or absence of the pixels in the region of interest.

We used a dorsal approach in this study because it was the plane used at laser Doppler imaging, and we wanted to avoid the relatively large pulsatile digital arteries, which lie laterally along the joints. For gray-scale US, the region of interest was centered across the MCP joint line, and its size was strictly dependent on the 26-mm footprint of the transducer. The region of interest at power Doppler US was necessarily smaller and was based on the fourth finger. Between hypoechoic or anechoic synovitis and effusion is not possible without joint aspiration; therefore, they could not be separated in our study. However, the presence of an inflammatory effusion is pathognomonic of synovitis in RA.
pathologic features but always included the whole joint. All the US images were stored on magneto-optical disks for off-line analysis. The laser Doppler imaging and US measurements were performed separately, one immediately after the other, by different operators (C.G.E. and P.V.B., respectively); the order was randomly varied in successive patients. Laser Doppler imaging and US measurements were analyzed independently by different investigators (W.R.F. and P.V.B., respectively) so that they were blinded to results of the other tests until the comparison stage of the study. For each imaging modality, the same person sized and placed the regions of interest in each case.


Power Doppler ultrasonography for assessment of rheumatoid synovitis: comparison with dynamic magnetic resonance imaging

Abstract: The aim of this study was to compare the effectiveness of power Doppler ultrasonography (PDUS) with that of dynamic magnetic resonance imaging (MRI) for detecting active synovitis in the hands of rheumatoid arthritis (RA) patients.

Intro: The purpose of the present study was to compare the effectiveness of PDUS with that of dynamic MRI for detecting active synovitis in the hands of the overall-grade RA patients.

The study was performed according to the Declaration of Helsinki. All patients provided written informed consent for the use of their data in this study. Ten patients with RA diagnosed according to the American College of Rheumatology (formerly, the American Rheumatism Association) criteria [18] were studied.

US was performed with a LOGIQ 7 unit (GE Healthcare Co., Milwaukee, WI, USA) and a 7- to 13-MHz linear transducer. The basic scanning technique followed the EULAR guidelines [19]. Gray-scale US was performed at the wrist joint, the first to fifth metacarpophalangeal (MCP) joints, the second to fifth proximal interphalangeal (PIP) joints, and the first interphalangeal joint of both hands to identify the affected joints. Subsequently, PDUS examination of all these joints was performed in the longitudinal plane. The velocity filter of the US unit was set for measurement of low velocity flow. Color gain was initially set at the level where noise artifacts appeared and then was gradually reduced until only a flow signal was left (if any).

Synovial blood flow was measured in each joint, and the synovial vascularity was categorized into four grades: 0 (none), 1 (low; one or a few blood flow signal), 2 (moderate; several blood flow signal clusters less than half of the visible synovium), and 3 (high; blood flow signals in more than half of the visible synovium).

US was performed by a radiologist (E.F.) who had more than 10 years of experience and expertise in musculoskeletal sonography and who was not informed of the assessment for disease activity of each
**Sonographic joint assessment in rheumatoid arthritis Associations With Clinical Joint Assessment During a State of Remission**

**Abstract:** “The present study was undertaken to compare clinically active joints with sonographically active joints in patients with RA, applying different sonographic definitions of an active joint.”

**Intro:** “To fully appreciate the potential added value of sonography over clinical joint assessment, we compared these 2 examination methods in the present study, taking into account the differences in quantification method (graded assessment by sonography and binary approach for clinical evaluation) and the impact of the findings on various aspects of the disease, especially physical function.”

| Participants in the study were consecutive RA patients (age 18 years) who regularly visited our outpatient clinic and whose diagnosis met the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) 2010 criteria for RA (29) The study was approved by the local ethics committee and conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants. | All sonographic assessments were performed using high-sensitivity ultrasound equipment (Logiq E9; General Electric), with an ML 6-15 transducer. Sonographic assessments were performed using a frequency range from 9 MHz to 15 MHz. When performing PD ultrasound evaluation, the pulse repetition frequency was set between 500 Hz and 800 Hz, and receiver gain settings were controlled to eliminate the appearance of artifacts. An experienced sonographer (GS) who had no access to the clinical and laboratory data and was unaware of the results of the clinical joint examination evaluated 11 joints of each hand (including the proximal interphalangeal [PIP] joints, the metacarpophalangeal [MCP] joints, and the wrists), using the method proposed by Filer et al (33) for both GS and intraarticular PD ultrasound signals. All included joints were scanned for GS and PD signals in the dorsal aspect, using longitudinal midline planes as well as transversal planes. The wrists were additionally examined using longitudinal dorsoradial and dorso-ulnar scans. | Synovitis was defined according to the published Outcome Measures in Rheumatoid Arthritis Clinical Trials definitions (14). GS and PD signals for signs of synovitis were graded using a 4-grade semiquantitative scoring system, on a scale of 0–3 (grade 0 none, grade 1 mild, grade 2 moderate, and grade 3 severe), according to the method developed by Szkudlarek et al (34). The highest GS and PD grade detected during the different scans was adopted as representative for each respective joint. In all analyses, the sonographic grades were stratified according to the level of “stringency” for defining an active joint; in this context, stringent was taken to indicate a GS and/or PD signal grade of 1, more stringent as a GS and/or PD signal grade of 2, and most stringent as a GS and/or PD grade of 3. The interobserver reliability (using sonographic examinations of identical joints in 10 patients performed by 2 experienced sonographers [GS and PM] independently on the same day) likewise revealed good agreement (ICC of 0.856 for all sonographic assessments, 0.837 for GS ultrasound, and 0.762 for PD ultrasound). These levels of reliability were very similar to those observed in recent evaluations of the metrologic properties of joint sonography (19,20). The intraobserver reliability of sonographic examinations (assessed by performing the evaluation twice in 10 patients on the same day) revealed a good intraclass correlation coefficient (ICC) of 0.978 (0.972 for GS ultrasound and 0.665 for PD ultrasound).
<table>
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<tr>
<th>Authors</th>
<th>Year</th>
<th>Title</th>
<th>Methods</th>
<th>Patients</th>
<th>Imaging Technique</th>
<th>Findings</th>
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<tr>
<td>Gullick et al.</td>
<td>2010</td>
<td>Linking power Doppler ultrasound to the presence of Th17 Cells in the Rheumatoid Arthritis Joint</td>
<td>“This study aimed to compare frequencies of Th17, Th1, IL-17+ IFNc+ and TNFa+ CD4+ T cells in PB from RA patients and healthy controls, and to assess if the relative proportions of these cells were increased in either RA SF or ST. Furthermore, we aimed to determine correlations between frequencies of these cells in PB or SF, and synovitis as defined by PDUS score.”</td>
<td>PB was obtained from patients with established RA according to the 1987 American College of Rheumatology criteria [21] attending for follow-up at Guy’s &amp; St Thomas’ Rheumatology Department. Healthy controls were recruited from hospital/university students and members of staff. Ethical approval was obtained from the Bromley and St Thomas’ NHS Research Ethics Committees, and all patients and controls gave written informed consent.</td>
<td>Ultrasound (US) scans were performed within 2 hours of clinical assessment in a darkened room using a Logiq 9 (GE Healthcare, Buckinghamshire, UK) with a matrix array transducer (5–12 MHz). Pulse repetition frequency was adjusted to the lowest permissible value to maximize sensitivity, with the gain set at the point where cortical PDUS signals disappeared. Synovial blood flow was evaluated by PDUS at the metacarpophalangeal (MCP) joints and both wrists (24 RA patients) and knee joints (20 patients, 22 knees) in longitudinal and transverse views. For the knee joint, longitudinal and transverse images were recorded of the suprapatellar pouch and the lateral and medial patella recesses. The ultrasonographer was blinded to clinical data at the time of the ultrasound examination, and ultrasound images were anonymised prior to scoring. PDUS signals as a percentage of synovial tissue were graded on a semi-quantitative scale from 0 to 3 (where 0 = no synovial flow; 1 = up to 25% synovial tissue signal; 2 = 25–50% signal; 3 = &gt;50% signal). Scores for the three areas of a single knee joint were used to calculate a mean knee Doppler score. If fluid was aspirated from both knee joints, then both knee joints were scored independently. The maximum semi-quantitative scores for MCP joints and both wrists (12 joints) were averaged to produce a “hand Doppler” score.</td>
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<td>Horikoshi et al.</td>
<td>2010</td>
<td>Comparison of low-field dedicated extremity magnetic resonance imaging with articular ultrasonography in patients with rheumatoid arthritis</td>
<td>“To compare magnetic resonance imaging (MRI) and ultrasoundography (US) in the detection of joint inflammation of rheumatoid arthritis (RA)”</td>
<td>Intro: “In the present study, we compared low-field MRI with grayscale US (GS-US) and power Doppler US (PD-US) in detecting joint inflammation and analyzed the correlation between the two techniques.”</td>
<td>Six RA patients underwent examination of the hands by US and MRI. Ultrasound (US) scans were performed using Aplio SSA-700A (Toshiba, Tokyo, Japan) with a 12-MHz linear array and a 12-MHz hockey-stick array transducer. Intercarpal joints, radioulnar joints, radiocarpal joints, all of PIP joints and MCP joints (total 156 joints) were assessed and scored (Fig. 1). GS-US and PD-US were examined by two experienced investigators (rheumatologists). Scoring by one of the two investigators was used for comparison with MRI. The rheumatologists who assessed the MRI and the US were informed of the correlation between the two techniques.</td>
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<td>Lagnoocco et al.</td>
<td>2015</td>
<td>Power Doppler ultrasound</td>
<td>“To monitor by power Doppler US (PDUS) the short-term response to anti-TNFa”</td>
<td>A total of 68 consecutive patients, who fulfilled the 2010 RA classification criteria [22]</td>
<td>A single rheumatologist, experienced in musculoskeletal US, who was blinded to the clinical and laboratory data, performed joint inflammation on GS-US was defined as hypoechoic intracapsular area, and on PD-US represented the presence of positive findings of flow signal. These findings on both GS-US and PD-US were scored 0–3 as described previously [18].</td>
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## Intro

“The objectives of the present study were to use PDUS to monitor the short-term response to anti-TNFa therapy in six target joints of RA patients and to correlate PDUS findings with clinical and laboratory indices of disease activity.”

## Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Comitato Etico Sapienza Università di Roma). Informed consent was obtained from all patients enrolled.

## PDUS Examination

We performed PDUS at seven time points during infliximab treatment (0 weeks, 2 weeks, 6 weeks, 14 weeks, 30 weeks, 38 weeks, 46 weeks, and 54 weeks) to assess the joints in patients with established RA. PDUS was carried out for each patient at each visit by operators (M.H., A.N.) with settings for PD: frequency 9.1 MHz, pulse repetition frequency 750 Hz, PDUS gain 50%, low filters. The US assessment and scanning technique included evaluation of the synovial sites in six target joints (wrist—radiocarpal, midcarpal, ulnocarpal joints; second MCP—dorsal side, palmar side; knee—suprapatellar recess, lateral parapatellar recess) as previously reported [16]. These joints and synovial sites were selected according to the previous study on the 6-joint score by Perricone et al. [16].

The PDUS examination at baseline and at 3 months follow-up, with a multiplanar GS and PD examination, using a MyLab 70 VXision Gold machine (Esaote, Genova, Italy) with a multifrequency linear array transducer (618 MHz, 13 MHz for the knee, 15 MHz for the wrist and 18 MHz for II MCP). Settings for PD were: frequency 9.1 MHz, pulse repetition frequency 750 Hz, PDUS gain 50%, low filters.

The US assessment and scanning technique included evaluation of the synovial sites in six target joints (wrist—radiocarpal, midcarpal, ulnocarpal joints; second MCP—dorsal side, palmar side; knee—suprapatellar recess, lateral parapatellar recess) as previously reported [16]. These joints and synovial sites were selected according to the previous study on the 6-joint score by Perricone et al. [16].

The US-Wrist, score of the knee US-Knee, US-PD score, range 0–18; a score for the single joint bilaterally (summing the scores for each one of the elementary lesions in all six joints: the sum of the scores for the six joints: USSE score, US-SH score; US-PD score, range 018); a score for the single joint bilaterally (summing the basic lesions for each joint; score of the II MCP joint: US-II MCP, score of the wrist: US-Wrist, score of the knee US-Knee, range 018); a global score at patient level (summing all registered alterations at all joint sites, range 054). An increase in the various scores during the follow-up was considered to be a worsening of the pathological process, and a decrease was considered an improvement.

**Intro:** "so that we could learn the precise course of sonographic findings and their relationship with clinical improvement and determine the timing for PDUS study."

**Table 1**

<table>
<thead>
<tr>
<th><strong>Study after treatment consisting mainly of antitumor necrosis factor alpha agent</strong></th>
<th><strong>Consisting mainly of antitumor necrosis factor alpha agent including infliximab, an antitumor necrosis factor alpha agent.</strong></th>
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<td><strong>Accordance with the Declaration of Helsinki, and informed consent was obtained from all the patients before examination.</strong></td>
<td><strong>more than 3 years’ experience in joint ultrasonography, unaware of both clinical and laboratory findings. An EUB 6500 ultrasound system (Hitachi, Tokyo, Japan) and a 5–12 MHz variable frequency probe were used. The probe, adjusted to 7.5 MHz, was placed sagittally, across the index/middle finger MP joints and across the index finger proximal PIP joints on the dorsal sides of both hands (total of six joints). Only the joints positive for Doppler signal at the baseline examination were examined at follow-up studies. Pulse Doppler settings were standardized for each patient and optimized for the detection of synovial blood flow by adjustment of color gain, pulse repetition, and flow optimization. The Doppler gain was increased until noise was seen within the bone, and then, slowly, the gain was turned down until the noise first disappeared within the bone. To maximize the demonstration of small synovial blood vessels, we set the flow optimization to ‘low’ for all patients, and this, in turn, automatically determined the pulse repetition frequency (PRF). The sample box size was set to include the dorsal portion of the joint, and abnormal power Doppler signals inside the joint capsule were assessed.</strong></td>
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<td><strong>Neurovascularization. When images were doubtful, we used pulsed Doppler spectra as proof of the presence of vessels. Table 1 and Fig. 1 show the intra-articular neurovascularization criterion for each grade.</strong></td>
<td><strong>An overall PDUS joint index for power Doppler signals (the sum of the power Doppler signal scores obtained from six joints) was calculated at each PDUS assessment. This was defined as the joint index for power Doppler signals (JIPD). The agreement of a grading system similar to JIPD between the same two operators, assessed in a previous study by us, using data from 20 patients, was excellent, with a kappa value of 0.8</strong></td>
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**Krohn et al. - 2015 - [11]**

**Abstract:** “FOI was validated in comparison to magnetic resonance imaging (MRI), greyscale ultrasonography (GSUS), and power Doppler ultrasonography (PDUS) in patients with early rheumatoid arthritis (RA)”

**Intro:** “Our study aims to assess vascularization. When images were doubtful, we used pulsed Doppler spectra as proof of the presence of vessels. Table 1 and Fig. 1 show the intra-articular neurovascularization criterion for each grade.**

**Krohn et al. - 2015 - [11]**

**Near-infrared Fluorescence Optical Imaging in Early Rheumatoid Arthritis: A Comparison to Magnetic Resonance Imaging and Ultrasonography**

**Intro:** “Our study aims to assess synovitis of each joint was semiquantitatively evaluated with regard to synovial hypertrophy and effusion (GSUS) as well as to synovial hypervascularization (PDUS) and scored on a 4-point (0–3) scale, as described14,28

**Patients with early RA according to the American College of Rheumatology /European League Against Rheumatism classification criteria24 were recruited between May 2013 and September 2013 and underwent MRI, US, and FOI within 2 weeks.**

**These examinations of the patients’ clinically dominant hand. Wrist (radiocarpal, ulnocarpal, and midcarpal compartment), MCP joints 2–5, and PIP joints 2–5 were examined using both dorsal and palmar views.**

**were performed (Mylab 70 XVG) both in GSUS and PDUS. All examinations were performed by a rheumatologist well-experienced in**
<table>
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<th>Pereira et al. - 2014 – [12] Is painless synovitis different from painful synovitis ? A controlled, ultrasound, radiographic, clinical trial</th>
<th>This cross-sectional study evaluated RA patients. The study was approved by the Human Research Ethics Committee of the Universidade Federal de Sa o Paulo/Escola Paulista de Medicina (Brazil). All patients provided written informed consent. The sample size of 30 individuals in each group was considered appropriate, and the PD-US was the primary study outcome. The study had a standard deviation (SD) of 0.4, a power of 90%, and a 5% significance level.</th>
<th>This transverse US exam included the dorsal side of the radiocarpal (RC) and the palmar and dorsal sides of MCPs 1 to 5; the longitudinal US exam included the dorsal radioulnar (DRU), according to a quantitative synovitis measurement (in mm) in the largest synovial bursa and semiquantitative scores, as described above (Table 1). Furthermore, a transverse evaluation of the cartilage of the dorsal side of MCPs 1 to 5 was performed with flexion of the fingers. US was performed bilaterally on the hands and wrists by a “blinded” musculoskeletal sonographer with 5 years of experience, using the ESAOTE MyLab 60 Xvision, with a multi-frequency linear transducer (6-18 MHz). The sonographer followed the guidelines for musculoskeletal US recommended by the European League Against Rheumatism (18). The evaluation was performed by a blinded rheumatologist trained in musculoskeletal US.</th>
<th>The US were measured based on the definitions published in the Outcome Measures in Rheumatology Clinical Trials (except cartilage) (19). Semiquantitative synovitis, bone erosion, and PD-US were each evaluated using a 4-grade scale ranging from 0 to 3. The scores were defined as follows. Grades 0-1 for bone erosion and synovitis were considered normal (Score I), whereas grades 2-3 indicated pathological changes (Score II) (20). For the PD-US signal, grade 0 was considered to be normal (Score I), whereas grades 1-3 were considered to be pathological (Score II) (20,21). Joint cartilage was evaluated using a semiquantitative 5-grade score with the aforementioned categories (22,23). The inter-observer reliability for the US evaluation was determined based on the image evaluations recorded on 20% of the overall sample in the RC (a total of 52 joint recess).</th>
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| Riente et al. - 2010 – [13] Ultrasound Imaging for the rheumatologist XXVII. Sonographic assessment of the knee in patients with rheumatoid arthritis | A multicentre study was conducted in 4 different Italian Rheumatology Units: University of Pisa, Università Politecnica delle Marche, University of Pavia, and the Sapienza University of Rome. | In each unit, US examinations were performed by a rheumatologist, experienced in musculoskeletal US, who was blind to both clinical and laboratory patients data. A Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) with a linear probe operating at 10 MHz when studying joints and 14 MHz when studying tendons and entheses was used in all the centres involved. | Before the start of the study, an agreement was obtained by the sonographers on both the scanning technique to adopt and the definition of the pathologic findings to detect. Joint effusion, synovial hypertrophy and enthesopathy together with the presence of bone erosions in the knee were diagnosed by US according to the preliminary definitions provided by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Special Interest Group for Musculoskeletal Ultrasound in
Rheumatology (20). Tendon thickening associated with intra-substance changes, including loss of fibrillar echotexture and patchy hypoechogenicity, was considered a typical feature of chronic tendinopathy (21). Cartilage changes were diagnosed when thickening or thinning of cartilage layer, loss of definition of chondro-synovial margin and pitting of the articular surface were observed (22). In particular, we looked for the presence of hyperechoic spots within the cartilage layer, suggestive of calcium pyrophosphate dehydrate crystal deposits, and for hyperechoic enhancement of the superficial margin, suggestive of monosodium urate deposition (6, 23). Meniscal calcification was evaluated according to a previous study (23). Baker’s cyst was diagnosed when a well circumscribed, localised anechoic and/or hypoechoic area lying adjacent to the medial head of the gastrocnemius and communicating with the knee joint by a neck, was detected (24). When examining the popliteal fossa and calf region, fluid tracking down either beneath the fascia or between the soleus and gastrocnemius muscles, was considered indicative of cyst rupture.

Szkudlarek et al. - 2001 – [14]

Power Doppler ultrasonography for assessment of Synovitis in the Metacarpophalangeal Joints of Patients With Rheumatoid Arthritis A Comparison With Dynamic Magnetic Resonance Imaging

Abstract: To evaluate the effectiveness of power Doppler ultrasonography (PDUS) for assessing inflammatory activity in the metacarpophalangeal (MCP) joints of patients with rheumatoid arthritis (RA), using dynamic magnetic resonance imaging (MRI) as a reference method.

Intro: In the present study, we compared the results of PDUS examination of the metacarpophalangeal (MCP) joints of RA patients and healthy patients. We examined 54 MCP joints of 15 patients with active RA who fulfilled the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (12) and 12 MCP joints of 3 healthy controls. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Signed informed consent was obtained.

Clinical, US, and MRI examinations of the individual patients were all performed on the same day. US was performed with a LOGIQ 500 unit (General Electric, Solingen, Germany) by means of a 7–13-MHz linear array transducer. Gray-scale US was performed on the second through the fifth MCP joints of the dominant hand to localize the joints. Subsequently, a PDUS examination of the second through the fifth MCP joints was performed in the longitudinal plane. The flow signal of the US unit was set.
subjects with the results of dynamic contrast-enhanced MRI. The potential of the readily available and less expensive PDUS for the sensitive assessment of synovial inflammatory activity was thereby evaluated.

Abstract: “to examine the clinical usefulness of MIP images for RA in the hand.”

Intro: “In this study, we compared MIP images, palpation findings, and PD findings of synovitis to examine the clinical usefulness of MIP images for evaluating the hands in RA. We also used a simple method to score MIP images of synovitis in the hands in RA and compared these scores with those from PD images to examine the clinical significance of synovitis on MIP images.”

Thirty RA patients were included in the study. All patients fulfilled the American Rheumatism Association 1987 criteria for RA [20]. All patients gave informed consent, and the study was approved by the local Research Ethics Committee of our hospital.

US was performed on the wrist and MCP joints using a HI VISION Avius (Hitachi Medical Corporation, Tokyo, Japan) with a linear type (14–6 MHz) probe. Patients were examined while seated with the hand placed on a cushion and pronated. The dorsal side of the hand was scanned in the longitudinal plane. Radial images of the wrist were taken with Lister’s tubercle and the second metacarpal bone as landmarks, medial images of the wrist were taken around the center of the wrist, and ulnar images of the wrist were taken with the head of the ulna as the landmark. Images of the MCP joint were taken around the center of each joint.

In PD images, the presence of vascular signals was examined. When performing PD evaluation, the receiver gain settings were controlled to eliminate the appearance of artifacts on each joint. The PD frequency was set at 7.5 MHz, and the pulse repetition frequency was set between 800 Hz and 1,000 Hz, optimized for US of rheumatoid hands by the manufacturer. Therefore, all US examinations were performed by the same orthopedic surgeon who was trained in the examination of the small joints of rheumatoid hands. Two other orthopedic surgeons specializing in RA scored the joints independently, with no reference to any other clinical findings.

We searched for the most active area of inflammation near these landmarks. GS images with low echo regions within joints were considered to indicate thickening of the synovial membrane. For PD images, each joint was scored on a semiquantitative scale with a score of grade 1 or higher taken as positive (grade 0=no flow in the synovium, grade 1=single vessel signals, grade 2=confluent vessel signals in less than half of the area of the synovium, grade 3=vessel signals in more than half of the area of the synovium) [22].
<table>
<thead>
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<th>Vlad et al. - 2011 –[16]</th>
<th>Ultrasound in rheumatoid arthritis volar versus dorsal synovitis evaluation and scoring</th>
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**Abstract:** “The present study is designed to compare the results of gray-scale ultrasound (GSUS) and Power Doppler ultrasound (PDUS) additive scores, separately calculated for volar and dorsal aspects of the hand, with physical examination, patient’s evaluation of disease pain and global activity on Visual Analogic Scale (VAS) and traditional scores for disease activity assessment (DAS28, CDAI, SDAI, HAQ). The final aim is to prove the advantages of volar US evaluation in RA patients.”

Intro: “The current study has been conducted on a larger cohort, searching for correlations between US synovitis score (volar and dorsal separately) and the other parameters widely accepted as reliable measures of disease activity. The final aim was to identify the best scanning area (volar or dorsal) to be used for global US scoring in RA.”

| 42 RA patients (5 male, 37 female) who were admitted to Sf. Maria Hospital starting from October 2008, selected to have at least one painful or swollen joint have been included in this study. All subjects fulfilled ARA criteria for RA [15] and signed the written informed consent for study participation before the enrollment. This study was approved by the medical ethical committee of the “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania. |

**US examination was performed later the same day, by a sonographer trained in Musculoskeletal US for 8 years.** The machine used for the study was an ESAOTE MyLab 25, with a multifrequency linear 10-18 MHz transducer. The scanning technique and the settings of the machine were the same for all the patients and all examinations were performed in a dark room by the same physician, who was blinded to clinical evaluations. Ultrasound was performed on 10 joints at both hands, 8 of them in both volar and dorsal aspect (MCPs 2-5, PIPs 2-5). Carpal joints (radiocarpal and intercarpal) were only examined from the dorsal side, because of the special position of carpal bones (we found no data regarding volar incidence for carpal joints in the literature). MCP1 and PIP1 were excluded based upon the rarity of synovitis in these locations in RA. For carpal joints, scanning was performed in a longitudinal plane, from dorsal side, over the surface of radius, lunate and capitate bone [19]. For MCPs and PIPs, scanning was performed longitudinally, over the joint space, first from dorsal and then from volar side. No compression on the transducer was applied. For Doppler signal evaluation, standard Doppler settings of the machine were established: Pulse Repetition Frequency (PRF) was adjusted to maximize sensitivity - from 500 to 750 Hz, the highest gain and high colour persistence without background noise, low wall filter [12,20].

We measured the hypoechoic area between tendons (extensors or flexors) and cortical bone, without differentiating fluid and synovial hypertrophy. This hypoechoic area inside the joint was defined before in literature as synovitis [21]. We performed dorsal measurements perpendicularly to the bone, in the point of the greatest thickness of hypoechoic area as follows: for radiocarpal joint, on top of lunate bone; for intercarpal joint, on top of capitale bone; for MCPs, at the level of metacarpal neck, for PIPs, at the level of the first phalanx [19]. GSUS synovial hypertrophy was assessed both by quantitative measurement and semiquantitative scale (0-3 grades); PDUS was recorded on a semiquantitative scale (0-3 grades).

The semiquantitative grades for each joint were added and the sum was defined as the Echographic Score (ES) of each patient. Separately, we added the semiquantitative grades for volar and dorsal side, resulting in Volar ES (VES) and Dorsal ES (DES) of each patient. A dimension of 0.5 mm was considered the cutoff limit for positive synovitis, and the number of joints with synovitis above this value in each patient was defined as Echographically Positive Joints (EPJ). A value > 3 mm in hand joints is considered large synovitis [6], we counted it as 3 on semiquantitative scale; for an accurate differentiation between grades 1 and 2 we made the transformations as follows: grade1 = synovitis between 0.5-2 mm, grade 2 = synovitis between 2-3 mm. We used both scales of quantification because we only found limited data in literature regarding semiquantitative scale on the volar side. For volar synovitis, we measured the hypoechoic tissue between flexor tendons and volar cortical bone.”
Wamser et al. - 2003 - [17]

Power Doppler sonography with and without echo-enhancing contrast agent and contrast-enhanced MRI for the evaluation of rheumatoid arthritis of the shoulder joint: differentiation between synovitis and joint effusion

Abstract: “To evaluate patients with clinically active rheumatoid arthritis (RA) of the shoulder for joint effusion and synovitis using conventional sonography, power Doppler (PD) sonography with and without echo-enhancing contrast agent, and contrast-enhanced MRI.”

Intro: “The present study was conducted to investigate the effectiveness of PD sonography, with and without echo-enhancing contrast agent, in differentiating joint effusion and synovitis.”

The study group was recruited from 501 consecutive patients with RA (based on ARA criteria) with acute symptoms related to the shoulder seen in the rheumatology outpatient clinic within a period of 18 months.

Informed consent was obtained from all patients.

Sonography and MRI of the symptomatic shoulder joint were performed on the same day.

The ultrasound operator was not aware of the MRI result.

Initially, sonography of the shoulder was performed with a multifrequency 7.5 L40 linear array transducer with a maximum frequency of 9 MHz (Sonoline Elegra, Siemens).

With the patient seated and the shoulder joint in neutral position, anterior, lateral and posterior sonographic sections were obtained. The standardized evaluation included the insertion of the subscapularis muscle, the subacromial bursa and the posterolateral humeral head. The axillary recess was evaluated with the arm in 90° elevation.

The examination was performed by one of two radiologists experienced in musculoskeletal sonography.

In most patients, the pulse-repetition frequency of the PD mode was maintained at 1000 Hz, with a minimum of 800 Hz and a maximum of 1200 Hz. The color gain was adjusted to a level with no color signal elicited from the subcortical regions. The color images were recorded with a color printer and representative sequences traced on color videotape before and after administration of the contrast agent.

Normal and pathological echo patterns of the conventional grayscale sonographic images and the PD sonographic images before and after administration of the echo-enhancing contrast agent were documented on a standardized questionnaire for the following anatomical regions: subacromial bursa, insertion of the subscapularis muscle, axillary recess and posterolateral humeral head.

The gray scale was graded from 1 to 4: grade 1, normal findings (a space of less than 1 mm between cortical bone echo and echogenic joint capsule); grade 2, hypoechoic area with echoes <30%; grade 3, hypoechoic to echogenic area with echoes <60%; grade 4, hyperechoic area with echoes >60% (Figs. 1B, 2A, B). The percentage figures represent a subjective rating of the echogenic morphology with the theoretical situation of 100% echoes on a sonographic image totally filled with echoes. The width of the displayed echo pattern was measured in millimeters at the site of its maximum dimension. The PD echo signal was subjectively graded for the four anatomical reference sites by the quantity and intensity of the vascular echo signals in the abnormal tissue on a scale from 1 to 4: grade 1, normal vascular signal (absent or occasional signal); grade 2, few vascular signals (<30%); grade 3, intermediate number of vascular signals.
The grading of the vascular echo signals was a percentage of the theoretical situation of a PD image totally filled with vascular signals (Figs. 1, 3, 4). An effusion was diagnosed when the internal echo pattern (anechoic, hypoechoic, echogenic and hyperechoic) between cortical bone echo and echogenic joint capsule exceeded 1 mm in width after subtraction of the vascular echo zones of the PD sonographic images before or after administration of the echo-enhancing contrast agent.

Wiel et al. - 2007 – [18]

Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis

**Abstract:** “The aim of the present study was to assess ultrasonography (US) for the detection of inflammatory and destructive changes in finger and toe joints, tendons, and entheses in patients with psoriasis-associated arthritis (PsA) by comparison with magnetic resonance imaging (MRI), projection radiography (x-ray), and clinical findings.”

**Intro:** “The aim of the present study was to assess US for the detection of inflammatory and destructive changes in finger and toe joints, tendons, and entheses in patients with PsA by comparison with MRI, x-ray, and clinical findings.”

**Fifteen patients with PsA, 5 with RA, and 5 healthy control persons (CTRLs) were examined with US, contrast-enhanced MRI, x-ray, and clinical assessment.**

The study participants signed consent forms after receiving oral and written information. The study was approved by the local Danish ethics committee.

**US was performed with a GE LOGIQ 9 unit (General Electric Medical Systems, now known as GE Healthcare, Little Chalfont, Buckinghamshire, UK) using a high-frequency 9- to 14-MHz linear array transducer.**

All persons were examined by the same trained ultrasonographer (CW = US1) and examination was repeated in 8 persons (6 PsA, 1 RA, and 1 CTRL) by another trained ultrasonographer (MS = US2) and both US1 and US2 have a rheumatological background (Figure 1). US2 was blinded to diagnosis and clinical data, and both were blinded to other imaging findings, including the sonographic findings of the other ultrasonographer.

**Bilateral 2nd–5th metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints and 1st–5th metatarsophalangeal (MTP) joints were assessed with US for inflammatory changes: synovitis (synovial hypertrophy and/or effusion and/or power Doppler [PD] signal) and distal interphalangeal (DIP) joints (Figure 2). Furthermore, the tendons of the fingers (2nd–5th flexor and extensor tendons) were assessed for insertional changes (edema and/or calcification and/or mild synovitis in joints (score 1 according to the scoring system proposed by Szkudlarek and colleagues [10] for MCP and DIP joints as well as PIP joints only in PIP joints) (Figure 2).**

Mild synovitis in joints (score 1 according to the scoring system proposed by Szkudlarek and colleagues [10] for MCP and MTP joints) and a small amount of fluid in the tendon sheath below the flexor tendons at the palmar side of the PIP joints were considered a normal finding. A small amount of fluid around the fat pad on the palmar side of the PIP joint and a synovial membrane thickness below 12 mm (measured at the site of maximal thickness) of the DIP joints were also considered normal (based on unpublished data from CTRLs by Wiel and colleagues). The following US definitions were employed: bone erosion = bone cortex discontinuation in the area adjacent to the joint, visualized in two planes; bone proliferation = bone cortex proliferation in the area adjacent to the joint; synovitis = anechoic or hypoechoic intracapsular area, different from cartilage with or without PD signal; tenosynovitis = hypoechoic rim around the flexor tendon with or without PD signal; capsular/extracapsular changes = PD signal (intracapsular and/or extracapsular at the insertion of capsule or ligament) at the radial or ulnar sides of the PIP joints, different from nutritious vessels; and insertional changes = intratendinous
periosteal changes and/or PD signal) and tenosynovitis. Finally, all joints were assessed for bone changes: bone erosions and bone proliferations. The presence or absence of each parameter was noted. The palmar and dorsal aspects of each joint were examined in a longitudinal plane. A transverse view was added in case of doubt concerning the type of the detected finding or for confirmation of an erosion. Additional views were radial view of the 2nd MCP joint, ulnar view of the 5th MCP joint, radial and ulnar views of all PIP joints, medial view of the 1st MTP joint, and lateral view of the 5th MTP joint. All views were obtained with the hands and feet in a neutral position. The setting for grey-scale US was 14 MHz, and the pulse repetition frequency for the PD signal was set at 500 Hz.

Yoshimi et al. - 2015 – [19]

Abstract: “To investigate the optimal number and combination of joints to be assessed by power Doppler ultrasonography (PDUS) in daily practice for rheumatoid arthritis (RA).”

Intro: “to establish efficient and feasible US assessment system in daily practice of RA,”

Musculoskeletal US was performed by experienced rheumatologists (RY, DK, KM, MH, and YK). They were blind to the clinical, laboratory, and radiographic findings.

An Aplio SSA-700A (Toshiba, Tokyo, Japan) with 12-MHz (or 7.5-MHz in some knee joint assessments) linear array transducers was used in this study. The ultrasound scanning method, including parameter settings, has been described previously [29–32].

The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients before study enrollment. The design of the work was approved by the Institutional Review Board of Yokohama City University.

Of the 28 joints defined in DAS28, 24 (excluding bilateral glenohumeral and elbow joints) were assessed by US. Bilateral glenohumeral and elbow joints were excluded from the US assessment because the methods for assessing and evaluating these joints have not been well established. The joints were scanned longitudinally and transversally from the dorsal view. PD imaging was performed by selecting a region of interest that hypoechoic enlargement and/or intratendinous hyperechoic bands with or without acoustic shadow and/or periosteal irregularities and/or intratendinous PD signal at the entheses.

PD signals in each joint were graded on a semiquantitative scale of 0–3 (0: absent [no synovial flow], 1: mild [single-vessel signal or isolated signals], 2: moderate [confluent signals in less than half of the synovial area], and 3: marked [signals in more than half of the synovial area]), corresponding to the maximum score obtained from the synovial sites evaluated in each joint [11].

Wrist joints were assessed in three divided portions, that is, radial, medial, and ulnar portions, and the highest score was termed as the wrist PD score. Knee joints were examined by suprapatellar, lateral, and medial longitudinal scanning at the neutral supine position [33]. In wrist and knee, the highest PD score was used in the multiple scanning. The intraobserver and interobserver reliabilities were previously described [34].

Total PD score-24 was calculated by summing up individual joint scores as

Twenty-three patients diagnosed with RA according to the ACR classification criteria [13] were treated with two infusions of 1000 mg chimeric anti-CD20 antibody RTX (Roche Pharma, Reinach, Switzerland) 14 days apart from each other in an observational protocol. Written informed consent was obtained according to the Declaration of Helsinki from all participants. The study was approved by the cantonal ethics committee of Bern.

Grey-scale (synonymous for brightness or B mode), as well as colour-coded power Doppler (PD) US were performed on the first day of RTX infusion and again 6 months later with an Esaote MyLab 70 x-vision (Esaote S.p.a., Genova, Italy) supply using the 4- cm linear-array transducer 6–18 MHz (L4 35). MCP and PIP joints of digits 2–5 on both hands were examined according to the method of Scheel et al. [16] from a palmar view, with joints in neutral 0 or in maximal extended position. The colour box in PD was adjusted to the region of interest. The pulse repetition frequency was set to 750 MHz, with wall filter and persistence at the lowest possible level; colour priority included all colours. The colour gain was adapted according to published recommendations [17]. The sensitivity and negative predictive value (NPV) of individual sets of selected joint examination for the detection of active synovitis were also evaluated.

Ziswiler et al. - 2009 – [20]
High-resolution ultrasound confirms reduced synovial hyperplasia following rituximab treatment in rheumatoid arthritis

Abstract: “To assess the response of RA patients to rituximab (RTX) treatment using a sensitive imaging technique for synovitis”

Intro: “In this study, we monitored synovial morphology in therapeutic B-cell depletion with US and compared the results with established clinical parameters for response.”
**Table 6. Data collection of the randomly selected sample of articles in Etiology category.**

<table>
<thead>
<tr>
<th>Title</th>
<th>Objective (blue = abstract; red = intro)</th>
<th>Design (red = study design, blue = ethics)</th>
<th>Technical data (blue = machine, green = joints, red = operator, grey = time/place)</th>
<th>Measure / Outcome (blue = elementary lesions, red = score, green = reliability)</th>
</tr>
</thead>
</table>
| Backhaus et al. - 2013 – [21]  
*The US7 score is sensitive to change in a large cohort of patients with rheumatoid arthritis over 12 months of therapy* | Abstract: To determine the sensitivity to change of the US7 score among RA patients under various therapies and to analyze the effect of each therapeutic option over 1 year. To estimate predictors for development of destructive bone changes  
Intro: The aim of the present study was to reflect the sensitivity to change of the US7 score among a large cohort of RA patients under various therapies (disease modifying antirheumatic drugs (DMARDs) and/or biologics) and to analyse the effect of each therapeutic option over a period of 1 year. Another purpose of this study was to estimate predictors for the development of erosions after 1 year. | From 2006 until 2010 a nationwide project recruited 54 centres with a total of 432 patients with RA according to American College of Rheumatology (ACR) criteria 1987.5  
All patients agreed by informed consents, and the study was approved by the ethical committee of University of Tubingen. | a 10–18 MHz linear scanner and middle class to high-end machine US devices.  
Settings for GSUS: frequency: 16 MHz, length of scanner: 40–42 mm. The use of GSUS gain depended on joint regions and patients and was average 50%. Settings for PDUS: frequency: 9.1 MHz, pulse repetition frequency: 500–750 Hz (depending on machine setting), PDUS gain depended on joint regions and patients and was average 50%; wall filter was low for example,3, and had to be maintained throughout the study. The PDUS gain was not supposed to change within a joint panel of a patient during the examination. The exact same machine had to be used on every patient during the study time.  
The hand and foot which were more clinically affected by tenderness and/or swelling were chosen for US and were examined at four visits after onset of therapy or switch to actual therapy (DMARDs and/or biologic). This included the joints most likely to be affected by RA: wrist, metacarpophalangeal (MCP) II and III, proximal interphalangeal (PIP) II and III, metatarsophalangeal (MTP) II and V joints. | These joints were evaluated for synovitis and tenosynovitis/paratenonitis and superficial bone erosions according to EULAR criteria5 and Outcome measures in Rheumatology (OMERACT) definition6 including GSUS and PDUS (table 1). Synovitis and synovial / tenosynovial vascularity were scored semi-quantitatively (Grades 0–3) by PDUS according to Szkudlarek et al.7 Synovitis (effusion and synovial hypertrophy) in GSUS was classified semi-quantitatively as described by Scheel et al.8 Tenosynovitis / paratenonitis as well as erosions in GSUS were registered as being absent (0) or present (1). |
| Brown et al. - 2008 – [22]  
*An Explanation for the Apparent Dissociation Between Clinical Remission and Continued Structural Deterioration in Rheumatoid Arthritis* | Abstract: The purpose of this study was to evaluate the long-term significance of subclinical inflammation and to investigate whether imaging-detected synovitis can be used to be in remission while taking | In the present study, we performed a longitudinal evaluation of this DMARD-treated clinical remission cohort.  
In this prospective longitudinal cohort study, consultant rheumatologists used their clinical judgment to identify RA patients from their outpatient clinics whose disease was considered to be in remission while taking | Each patient underwent a musculoskeletal US assessment of the joints of the dominant hand and wrist at baseline and at 12 months using GS and PD techniques. Eight joint regions were imaged by musculoskeletal US: metacarpophalangeal (MCP) joints 2–5 and the radiocarpal, ulnar-carpal, distal radioulnar, and intercarpal compartments of the wrist. Musculoskeletal US was performed by a single experienced sonographer (ZK) who | The presence and location of any synovial hypertrophy and erosions were recorded with reference to standardized definitions subsequently agreed upon by the Outcome Measures in Rheumatology (OMERACT) group (18). Synovial hypertrophy on GS images was graded according to a semiquantitative scoring method (0–3 scale, where 0 no synovial hypertrophy, 1 mild synovial hypertrophy, 2 moderate, and 3 severe) (19,20). The area of maximum |
| Bugatti et al. - 2012 | Abstract: The current study was undertaken to investigate whether baseline serum levels of the chemokine CXCL13 might predict clinical and ultrasonographic (US) outcomes in patients with recent-onset RA. Intro: The aim of this study was to investigate whether CXCL13 levels assessed at baseline are associated with disease activity outcomes over a 12-month follow-up in patients with recent-onset RA within a structured treat-to-target protocol. To ensure accurate assessment of joint inflammation, disease activity was measured both clinically and by US. Study subjects were 161 recent-onset RA patients recruited from the Early Arthritis Clinic (EAC) of the University Hospital of Pavia based on the availability of baseline serum. The Pavia EAC is a large prospective cohort as previously described [6,19] The current analysis is based on follow-up data at 12 months, which were available in 155 patients (96%). Local Ethical Committee (IRCCS Policlinico San Matteo Foundation) approval was obtained, and all patients signed written informed consent before study entry. At baseline, 6 and 12 months US was performed by a single experienced operator unaware of clinical data, using a GE Logiq 9 scanner (General Electrics Medical Systems, Milwaukee, WI, USA) with a multi-frequency linear array transducer (10 to 15 MHz), according to the European League Against Rheumatism (EULAR) guidelines [22]. The US assessment included transverse and longitudinal scanning of medial and lateral dorsal view of bilateral wrists (radiocarpal, ulno-carpal, radio-ulnar and midcarpal joints) and metacarpophalangeal joints, as previously described [6]. Synovial PD was evaluated by selecting a region that included bony margins, joint space and a variable view of surrounding tissues. Pulse repetition frequency (PRF) was adjusted at the lowest permissible to maximise sensitivity. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts. Grey-Scale (GS) and PD signals were assigned to each joint in accordance with semi-quantitative 0 to 3 scales [23]. An overall US score for GS and PD signal was calculated at each US assessment as the sum of either GS or PD signal scores obtained from each joint (range 0 to 36). | predict subsequent progression of joint damage. | conventional DMARDs. | was blinded to all other study findings, using an ATL HDI 3000 machine (ATL Ultrasound, Bothell, WA) with a 10–5 MHz linear array “hockey stick” transducer, according to the European League Against Rheumatism (EULAR) guidelines (17). | enhancement on PD images was recorded using a previously described semiquantitative technique (0–3 scale, where 0 normal/minimal vascularity, 1 mild hyperemia, 2 moderate, and 3 marked) (21). Erosions were scored according to their location and severity/size using a similar 0–3 semiquantitative scale (22). Each patient’s total musculoskeletal US score for each pathologic feature (GS/PD/erosion) was calculated by summing the corresponding scores for each joint region. |

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Dale et al. - 2014 [24]

Tightening Up? Impact of Musculoskeletal Disease Activity Assessment on Early Rheumatoid Arthritis Patients Treated Using a Treat to Target Strategy

Abstract: To determine the level of agreement and potential impact on disease-modifying antirheumatic drug (DMARD) escalation decisions and of adding musculoskeletal ultrasound (MSUS) assessment of disease activity to the Disease Activity Score in 28 joints (DAS28) in early rheumatoid arthritis (RA).

Intro: The work described herein compared simultaneous DAS28 and MSUS disease activity assessment findings for patients randomized to the MSUS group in order to explore the potential impact of systematic MSUS assessment on treatment escalation decisions.

Ethical approval for the study was granted by the local research ethics committee. A total of 111 patients with a clinical diagnosis of early RA or anti-citrullinated protein antibody–positive UA were recruited between September 2009 and April 2012. Fifty-three patients were randomized to receive therapy directed by MSUS assessment in addition to DAS28 scores. All clinical and MSUS assessments have been made by the same clinician (JD) at 3 Glasgow teaching hospital sites.

All examinations were conducted using the same portable ultrasound machine (Voluson I, GE Healthcare) and a 10–16 MHz linear array probe (SP 10–16RS, GE Healthcare). PD examination was standardized using the following settings: frequency high (machine preset), pulse repetition frequency 0.9 kHz, wall filter low, and gain adjusted to below the level at which Doppler artifact appeared beneath bone. The dorsal recesses of 14 joints were assessed (the second and third proximal interphalangeal [PIP] joints, the second and third metacarpophalangeal [MCP] joints, wrist, and second and fifth metatarsophalangeal [MTP] joints bilaterally).

Sixty-one consecutive patients were recruited from a rheumatology secondary care setting between January 2006 and August 2008. All participants provided informed consent. General practitioners agreed to refer suspected PMR cases prior to steroid therapy within 2 weeks from onset.

At the first visit, patients underwent multidistrict US examination of both proximal (shoulder, hip) and distal sites [elbow, wrist, metacarpophalangeal (MCP) joints, knee, heel, and metatarsophalangeal (MTP) joints] regardless of the presence of signs or symptoms of inflammatory involvement. The articular and periarticular structures (bursae, tendons, and entheses) US examinations were carried out using a Sonosite (Bothell, USA) Titan with a 5–10-MHz linear transducer (frequency variations depending on site and depth of the lesion). Each US examination was carried out with both longitudinal and transverse scans, bilaterally and symmetrically, by a rheumatologist-sonographer (PF), with the same machine setting. Power Doppler US (PDUS) was used to evaluate the perfusion of soft tissues with standardized technical parameters: lowest gray-scale and PD synovitis positivity and graded on a Likert scale of 0–3 (26). Active disease on MSUS was defined as the presence of grade 1 or higher intraarticular PD signal in at least 2 joints.

Total PD scores were calculated by summing together all the PD scores from a single assessment. Total PD joint counts represent the number of joints exhibiting any positive PD signal during a single assessment or higher intraarticular PD signal in at least 2 joints.
| **Filer et al. - 2011** |  | **Abstract:** This study evaluated musculoskeletal ultrasound, a sensitive tool for the detection of synovitis and erosions, as a predictor of outcome in very early synovitis.

**Intro:** The aim of this study was therefore to evaluate the additional predictive ability of extended ultrasound joint counts for RA.

Fifty-eight patients with clinically apparent synovitis of at least one joint and inflammatory joint symptoms (inflammatory joint pain, and/or swelling and/or morning stiffness) of 3 months or less duration underwent baseline assessment and 18-month follow-up to determine diagnosis as previously described. Ethical permission was obtained and all patients gave written informed consent.

| **Within 24 h of clinical assessment, patients underwent blinded ultrasound assessment in a temperature controlled radiology suite. Patients were asked not to discuss their symptoms.**

A systematic multiplanar greyscale and power Doppler ultrasound examination of 92 sites in 38 joints (table 1) was performed based upon standard EULAR reference scans using a Siemens Acuson Antares scanner (Siemens, Bracknell, UK) and multifrequency (5–13 MHz) linear array transducers. For power Doppler examinations, the pulse repetition frequency was adjusted to provide maximal sensitivity at the lowest possible value for each joint, resulting in a pulse repetition frequency of between 610 and 780.

Examinations took between 50 and 60 min depending on disease extent and patient mobility.

**Ultrasound findings of synovitis, power Doppler positivity and erosion were defined according to consensus definitions.**

Greyscale synovitis in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints was graded from 0 to 3 based upon the system of Szkudlarek and colleagues, reclassifying the equivocal ‘minimal’ thickening grade as normal: grade 0, normal; grade 1, synovial thickening bulging over the line linking the tops of the periarticular bones; grade 2, grade 1 plus extension to one bone diaphysis; grade 3, grade 1 plus extension to both bone diaphyses. Synovitis in other joints was graded 0–3 as 0, normal; 1, mild; 2, moderate; and 3, severe, in which grade 1 demonstrates synovial thickening in excess of the mean plus 2 SD of normal range when available. Effusion in the absence of synovial thickening was not classified as synovitis. Synovial hyperaemia was measured by power Doppler in each recess and the maximal score graded according to Szkudlarek et al: 0, absence; 1, isolated signals; 2, confluent signals in less than half of the synovial area; and 3, confluent signals in more than half of the synovial area.

| **Pulse repetition frequency (PFR) avoiding flash artefacts, highest gain level without background noise, and low filter (15, 19). PDUS was applied only to shoulder and wrist analysis.**

Spectral wave analysis (SWA) was performed to define the flow pattern and to confirm the pulsatility of slow flows (15, 19).

All of the patients were followed up (generally a second visit within 1 month, then every 3 months) with laboratory tests and US, as commonly performed in our standard clinical protocol.

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<th>Reference</th>
<th>Study Title</th>
<th>Abstract</th>
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<td>Foltz et al. - 2012 – [27].</td>
<td>Power Doppler Ultrasound, but Not Low-Field Magnetic Resonance Imaging, Predicts Relapse and Radiographic Disease Progression in Rheumatoid Arthritis Patients With Low Levels of Disease Activity</td>
<td>The presence of joint erosion was measured as a binary variable. Global ultrasound indices for greyscale synovitis and power Doppler were calculated by adding scores from all joints. Global ultrasound counts were calculated by adding scores after converting individual joint grades to binary variables.</td>
<td>All patients underwent US assessment of the wrists, metacarpophalangeal (MCP) joints 2, 3, and 5, and metatarsophalangeal (MTP) joints 2, 3, and 5. Each joint region was investigated in dorsal, ventral, and, when possible, lateral views in grayscale (GS) and power Doppler (PD) modes using a 7.5–13-MHz linear transducer (Esaote Technos). US was performed independently by 1 of 2 trained rheumatologists who were blinded with regard to the other data. Good interreader reliability was found (27). The presence of synovitis in GS and PD modes and the presence of erosions were defined by the Outcome Measures in Rheumatology (OMERACT) guidelines (26).</td>
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<td>Freeston et al. - 2011 – [28].</td>
<td>Urinary type II collagen C-terminal peptide is associated with synovitis and predicts structural area.</td>
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<td>Bone loss in very early inflammatory arthritis</td>
<td>Ultrasound (PDUS) synovitis and bone mineral density (BMD) loss. Intro: The aim of this study was therefore to validate CTX-II against PDUS synovitis and hand BMD reduction in a cohort of very early inflammatory arthritis patients.</td>
<td>Best, The Netherlands) employing a 15-7 MHz linear 'hockey stick' transducer and a medium wall filter.</td>
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<td>Fukae et al. - 2014 – [29] Structural deterioration of finger joints with ultrasonographic synovitis in rheumatoid arthritis patients with clinical low disease activity</td>
<td>Abstract: In this study we investigated the relationship between synovial vascularity (SV) and structural alteration of finger joints in patients with RA and long-term sustained clinical low disease activity (CLDA) Intro: We therefore focused on and studied this relationship with quantitative measurement of US SV in each finger joint.</td>
<td>We enrolled 25 patients with RA and long-term (&gt;1 year) CLDA (DAS28-ESR &gt; 3.2) in this study (n = 25). The treatments were carried out over an observation period of 52 weeks and finally 15 patients who could sustain CLDA were analysed. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the Hokkaido Medical Center for Rheumatic Diseases and written informed consent was obtained from all patients. Ultrasonography was performed at baseline and at the 8th, 20th and 52nd weeks by one of three US experts (M.H., F.S., A.N.) who specialize in musculoskeletal ultrasonography and were blinded to other clinical information. A 13-MHz linear array transducer and US machine were used (EUP-L34P, HI VISION Avius; Hitachi, Tokyo, Japan). Power Doppler settings were described previously [5, 6]. The first to fifth MCP and PIP joints were scanned in the longitudinal plane over the dorsal surface.</td>
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| Hammer et al. - 2011 – [30] The soluble biomarker calprotectin (a S100 protein) is associated to ultrasonographic synovitis scores and is sensitive to change in patients with rheumatoid arthritis treated with adalimumab | Abstract: the present objectives were to explore in RA patients the associations between calprotectin and a comprehensive US examination, as well as the responsiveness of calprotectin compared to other inflammatory markers during anti-TNF treatment Intro: The objectives of the present study were to examine the associations between the levels of calprotectin and a comprehensive as well as reduced US joint scores and to examine the associations between calprotectin and BM presence of synovial hypertrophy and fluid (combined) and presence of vascularization (PD) on a 4-point scale: 0 = none, 1 = minor, 2 = moderate or 3 = major presence. | All patients were assessed by extensive US examinations (performed by one experienced sonographer, HBH) with use of a 5 to 13 MHz probe (Siemens Antares, Sonoline, Siemens Medical Solutions, 1230 Shorebird Way Mountain, CA, USA) with fixed settings optimal for power Doppler signals in more superficial joints. The joints assessed bilaterally by use of standard projections [29] included proximal interphalangeal 1 to 5, metacarpophalangeal 1 to 5, carpometacarpal 1 to 5, wrist (radiocarpal, intercarpal and radioulnar joints), elbow, shoulder (glenohumeral and
explore the responsiveness of calprotectin compared to other inflammatory markers during biologic treatment in patients with RA.

- Hand, wrist, elbow, knee, ankle, and toe joints were evaluated via GSUS and PDUS. Fourteen joint regions (thus, 28 in both extremities) were evaluated. These included the first through to the fifth MCP joints, the radiocarpal, ulnocarpal, and intercarpal compartments of the wrist; the humeroradial and humeroulnar compartments of the elbow; the suprapatellar and medial and lateral parapatellar recesses of the knee; the tibiotalar, talonavicular, and posterior subtalar compartments of the ankle; and the first through to the fifth MTP joints.

- Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial score was calculated (0–84). Also, GSUS synovitis score was calculated for each joint. Mean value of each joint was

Harman et al. - 2015 – [31]

**Improvement of large-joint ultrasonographic synovitis is delayed in patients with newly diagnosed rheumatoid arthritis: results of a 12-month clinical and ultrasonographic follow-up study of a local cohort**

**Abstract:** We analyzed the longitudinal changes in gray-scale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) parameters and correlated them with clinical, functional, and radiologic outcomes in patients with newly diagnosed rheumatoid arthritis (RA).

**Intro:** We analyzed the longitudinal changes in GSUS and PD ultrasonography (PDUS) parameters to correlate them with the clinical, functional, and radiologic outcomes in patients with newly diagnosed rheumatoid arthritis (RA).

**This prospective study included 72 newly diagnosed RA patients according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA 2010 classification criteria between January 2012 and September 2013. Patients were recruited from the outpatient rheumatology clinics at the same center and consecutively included the ACR/EULAR 2010 RA classification criteria. The study protocol was approved by our local ethics committee, and informed consent was obtained from all patients.**

**Hand, wrist, elbow, knee, ankle, and toe joints were evaluated via GSUS and PDUS. Fourteen joint regions (thus, 28 in both extremities) were evaluated. These included the first through to the fifth MCP joints, the radiocarpal, ulnocarpal, and intercarpal compartments of the wrist; the humeroradial and humeroulnar compartments of the elbow; the suprapatellar and medial and lateral parapatellar recesses of the knee; the tibiotalar, talonavicular, and posterior subtalar compartments of the ankle; and the first through to the fifth MTP joints. The MCP and MTP joints were scanned at palmar/plantar and dorsal sites; wrist joints were scanned at dorsal sites. All of the patients were examined by a trained ultrasonographer with 3 years of experience (US1), after which Synovitis was classified on gray-scale images using a semiquantitative scoring method. We considered only synovial proliferation as a sign of synovitis (not synovial effusion). The approach features use of a 0–3 scale, in which 0 corresponds to no synovitis, 1 to mild synovitis, 2 to moderate synovitis, and 3 to severe synovitis [9]. Grade 1 synovitis may occur in normal populations, and for this reason, patients of grades 2 and 3 (only) were considered to have abnormal synovitis [9]. Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing grade 2 and 3 synovitis. The range of total GSUS synovitis score was 0–84. Also, GSUS synovitis score was calculated for each joint. Mean value of each joint was
modifying anti-rheumatic drugs (DMARDs) and low-dose corticosteroids.

Examinations were repeated by another trained ultrasonographer with 1 year of experience (US2); both clinicians had a rheumatology background. US examinations were repeated at each visit (baseline, 1, 3, 6, 9, and 12 months). The settings for the GSUS and PDUS were the same for all patients. US examinations were completed in 30 min, and all of the images were stored. A US platform featuring a 5–13-MHz linear array transducer was employed to this end (LOGIQ P5; General Electric, New York, NY).

Tenosynovitis was recorded in the extensor digitorum carpi, the extensor carpi ulnaris, in each of the five flexor digitorum tendons of the hand, the tibialis posterior, and the peroneus tendons of the ankle (thus a total of 18 tendons in both extremities). The maximal area of augmentation on PDUS was recorded using a previously described semiquantitative technique featuring use of a 0–3 scale, in which 0 corresponds to normal/ minimal vascularity, 1 to mild hyperemia (single vessel signal), 2 to moderate hyperemia (confluent vessels), and 3 to marked hyperemia (vessel signals in >50 % of the joint area) [10]. Semiquantitative scoring method was evaluated for each of 28 joints, and total synovial scores were calculated by summing each semiquantitative grade. The range of total PDUS synovitis score was 0–84. Also, PDUS synovitis score was calculated for each joint. Mean value of each joint was calculated by using the formula. Mean value of each joint $\frac{1}{n}$ Each joint GSUS synovitis score = 136

A four-grade semiquantitative scoring system (i.e., grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) was used to score tenosynovitis revealed on GSUS [11]. Semiquantitative scoring method was evaluated for each of 18 tendon regions, and total tenosynovitis scores were calculated by summing each semiquantitative grade. The range of total GSUS tenosynovitis score was 0–54. Also, GSUS tenosynovitis score was calculated for each tendon. Mean value of each tendon was calculated by using the formula. Mean value of each tendon $\frac{1}{n}$ Each tendon GSUS tenosynovitis score = 136

A four-grade semiquantitative scoring
system (i.e., grade 0, no Doppler signal; grade 1, minimal signal; grade 2, moderate signal; grade 3, severe signal) was used to score pathological peritendinous PD signals within the synovial sheath [11].

Semiquantitative scoring method was evaluated for each of 18 tendon regions, and total PD tenosynovitis scores were calculated by summing each semiquantitative grade. The range of total PDUS tenosynovitis score was 0–54. Also, PDUS tenosynovitis score was calculated for each tendon. Mean value of each tendon was calculated by using the formula. Mean value of each tendon = Each tendon PDUS tenosynovitis score/136

Ikeda et al. - 2013 – [32]

Correlation of Radiographic Progression with the Cumulative Activity of Synovitis Estimated by Power Doppler Ultrasound in Rheumatoid Arthritis: Difference Between Patients Treated with Methotrexate and Those Treated with Biological Agents

Abstract: Our prospective study aimed to demonstrate that the cumulative synovial power Doppler (PD) ultrasound scores correlate with radiographic progression better than conventional measures in patients with rheumatoid arthritis (RA). We also investigated the difference between antirheumatic agents.

In our prospective study, Patients with an established diagnosis of RA who required treatment with either MTX or a biological agent at the Department of Allergy and Clinical Immunology in Chiba University Hospital were consecutively recruited from January 2008 to December 2009. Sixty-nine patients were enrolled; all fulfilled the American College of Rheumatology (ACR) 1987 RA classification criteria14. The study design was approved by the Ethical Committee of Chiba University and subjects’ written informed consent was obtained according to the Declaration of Helsinki.

US was performed in a temperature-controlled room on the same day as clinical evaluation by 2 rheumatologists trained for musculoskeletal US, who were blinded to clinical information and laboratory data. A systematic multiplanar greyscale (GS) and PDUS examination of 28 joint regions (Appendix 1) was performed for synovial hypertrophy of articular recess, tendon sheath, and bursa. Intraarticular, tenosynovial, and intrabursal PD signals were graded on a semiquantitative scale of 0–3 [Grade 0, absent (no synovial flow); Grade 1, mild (3 or fewer isolated signals); Grade 2, moderate (> 3 isolated signals or confluent signal in less than half of the synovial area); Grade 3, marked (signals in more than half of the synovial area)].

The study design was approved by the Ethical Committee of Chiba University and subjects’ written informed consent was obtained according to the Declaration of Helsinki.

Correlation of Radiographic Progression with the Cumulative Activity of Synovitis Estimated by Power Doppler Ultrasound in Rheumatoid Arthritis: Difference Between Patients Treated with Methotrexate and Those Treated with Biological Agents

Intraobserver reliability of US assessment was evaluated by randomly selecting 4 images per each joint region from stored images of baseline US examination. Fifty-

We employed the scoring system reported by Naredo, et al13,21. GS synovitis was graded semiquantitatively on a scale of 0–3 (Grade 0, absent; Grade 1, mild; Grade 2, moderate; Grade 3, marked) for synovial hypertrophy of articular recess, tendon sheath, and bursa.

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Ann Rheum Dis

Le Boedec et al. - 2013 – [33]
Factors Influencing Concordance Between Clinical and Ultrasound Findings in Rheumatoid Arthritis

Abstract: Our objective was to identify factors associated with CJE/US concordance.

Intro: The objectives of our study were to evaluate concordance between CJE and US (B-US, PDUS, and both modes in combination) for detecting synovitis in patients with active RA before and after tumor necrosis factor-α (TNF-α) antagonist therapy and to identify factors associated with good concordance.

We conducted a prospective, multicenter, 4-month study of patients with RA referred to the study centers by their rheumatologists for TNF-α antagonist therapy. The study was approved by the appropriate ethics committees. All patients gave their written informed consent.

The US evaluation was performed on 38 joints, including the 28 joints of the DAS28 (shoulders, elbows, wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees) and the metatarsophalangeal (MTP) joints. US was performed in a dimly lit room. In each of the 9 study centers, a single experienced sonographer (radiologist in 1 center or rheumatologist in others) who was blinded to the CJE data performed all the US evaluations for the study.

Multiplanar greyscale (B-mode) and PD images were obtained using commercial real-time scanners (Esaote Technos MPX, Toshiba Apio, Esaote MyLab, Philips HD11, or BK Mini Focus) and multifrequency linear transducers (7–12 MHz). US scanning techniques, greyscale (B-mode) and PD machine settings, and definitions of abnormalities were standardized before the study during a 1.5-day meeting of all 9 study sonographers. US measurements were adjusted to the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity, which led to PRF values as low as 750 Hz. Low-wall filters were used. Color gain was set just below the level at which color noise appeared in the underlying bone.

Synovitis was defined according to OMERACT definitions as a grade of at least 1 for B-mode (hypoechogenic thickening of the synovial membrane that was nondisplaceable and poorly compressible) and PD mode independently. B-mode and PD mode measure different aspects of inflammation that can be combined to define synovitis, but we considered each of them separately for statistical analysis. Both B-US and PDUS were recorded for each joint. On B-US images, synovitis was scored using a 0 to 3 scale with these subjective definitions for each grade: 0, no synovial thickening; 1, mild synovial thickening; 2, moderate synovial thickening; and 3, marked synovial thickening.

Naredo et al. - 2008 – [34]
Abstract: To investigate the
This study prospectively included Each patient underwent a PDUS

The intraarticular, tenosynovial, and
Validity, Reproducibility, and Responsiveness of a Twelve-Joint Simplified Power Doppler Ultrasonographic Assessment of Joint Inflammation in Rheumatoid Arthritis

160 patients (125 women, 35 men) with RA according to the 1987 American College of Rheumatology (formerly the American Rheumatism Association) criteria for RA (20) who were recruited in the outpatient rheumatologic clinic of 18 Spanish centers from June 2005 to December 2006 and who started therapy with a biologic agent according to Spanish and international consensuses on the use of biologic agents for the treatment of RA (21,22).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from all patients before study entry.

PDUS examination was carried out in a darkened room. A systematic multiplanar gray-scale and PD examination of 44 joints was performed with the same real-time scanner in all centers (Logiq 5 PRO; General Electric Healthcare, Kyunngi-do, Korea) using multifrequency linear array transducers (7–12 MHz). The PDUS assessment included bilateral shoulder, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) of the hands, hip, knee, ankle, tarsal, and metatarsophalangeal joints. The presence of synovitis and PD signal were investigated in different intraarticular and periarticular synovial anatomic sites at each joint. A total of 128 synovial sites were scanned in all patients at each visit (Table 1). US scanning technique and pathology definitions were standardized among investigators prior to the study. This scanning method has been described in previous published studies (13,16,18,25–33). Synovial blood flow was evaluated by PD in each of the intraarticular and periarticular synovial sites. Gray-scale and PD parameters were standardized among investigators. Pulse repetition frequency (PRF) was adjusted at the lowest permissible value to maximize sensitivity. This setting resulted in PRF intrabursal PD signals were graded on a semiquantitative scale from 0 to 3 (where 0 absence, no synovial flow; 1 mild, 3 isolated signals; 2 moderate, 3 isolated signals or confluent signal in less than half of the synovial area; and 3 marked, signals in more than half of the synovial area) during the US examination.

A US count for joints with synovitis (44-USCS) and a US count for joints with PD signal (44-USCPD) in any synovial site were obtained at each visit. Each joint was scored for synovitis and PD signal on a scale from 0 to 3. These scores corresponded to the maximum score for synovitis and PD signal, respectively, obtained from any of the synovial sites evaluated at each joint. An overall US index for joints with synovitis (44-USIS) and an overall US index for joints with PD signal (44-USIPD), the sum of the synovitis and PD signal scores, respectively, obtained from each joint) were calculated at each US assessment.

PDUS intraobserver reliability, PDUS interobserver reliability was assessed by recording representative images of the full baseline examination of the 160 patients included in the study. The stored images of each patient were blindly scored for synovitis and PD signal by the same investigator who performed the corresponding real-time PDUS examination a minimum of 3 months later. PDUS interobserver reliability. Interobserver reliability between US investigators was evaluated before patients’ inclusion by scoring for synovitis and PD signal in 20 recorded images of the joints included in the PDUS assessment from 20 patients with active RA, randomly chosen by the investigator who coordinated the study.
from 500 Hz to 750 Hz depending on the anatomic area scanned. Flow was additionally demonstrated in 2 planes and confirmed by pulsed wave Doppler spectrum to exclude artifacts.

The time spent on the PDUS examinations was recorded by the investigators. A representative image of PDUS findings is shown in Figure 1.


Intro: The purpose of this pilot study was to compare the interobserver reliability of 3D volumetric US and conventional 2D real-time US in detecting inflammatory and destructive changes in the wrist and hand of RA patients. | Two patients with RA according to the American College of Rheumatology 1987 criteria (12) were selected by a rheumatologist (IM) expert in MSUS.

The 13 experts met for one day to perform the reliability study.

The US study was carried out using two identical commercially available US scanners (Logiq 9, Wauwatosa WI, USA) equipped with multifrequency electromechanical 3D dedicated VP (8-15 MHz).

Each patient was assigned to a US machine. Before the reliability exercise began, the investigator who selected the patients (IM) performed independently a grey-scale and PD volumetric acquisition at three anatomic sites in the more symptomatic wrist/hand of each patient (6 volumes per patient). These sites were the dorsal aspect of the radiocarpal (RC) joint, the dorsal aspect of the second metacarpophalangeal (MCP) joint and the extensor carpi ulnaris (ECU) tendon at the styloid process (SP) of the ulna.

The settings of both US machines were adjusted before the acquisition process and were standardised for the whole study. These settings resulted in a grey-scale frequency of 15 MHz, Doppler frequency of 7.5 MHz, dynamic range of 66 dB, gain of 39 dB, pulse repetition frequency of 900 Hz, and volume angle of 14°. Each volumetric sweeping scan took 20 seconds.

The total time spent on the US acquisition of the 12 volumes was 10 minutes. The 6 volumes acquired from each patient were stored in the respective US machine.

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The total time spent on the US acquisition of the 12 volumes was 10 minutes. The 6 volumes acquired from each patient were stored in the respective US machine.

The presence of inflammatory changes (grey-scale synovitis or tenosynovitis and synovial or tenosynovial power Doppler signal) and/or bone erosions were investigated at the three sites. The Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions for US pathology were used (13, 14). The PD signal was graded on a semiquantitative scale of 0–3 (3).

The 6 investigators each simultaneously and blindly evaluated the 6 volumes acquired and recorded before the start of the reliability exercise from the patient not scanned by them. A US application specialist showed to each group the US volumes by navigating through the longitudinal, transverse, and coronal planes along with the 3D reconstruction. They were given a maximum of 10 minutes for this task. The observers assessed the same pathologic changes as they did during the 2D US evaluation of the other patient. In the last part of the study, each group was given 30 minutes for independently and anonymously evaluating the diagnostic quality of the 6 volumes acquired and recorded by each member of the other group (total, 36 volumes). A 1–5 Likert scale was used to assess the volumes in which 1 indicated “very bad quality”; 2, “insufficient quality”; 3, “sufficient quality”; 4, “good quality”; and 5,
In the first part of the study, each group of experts was randomly assigned to a US scanner and a patient. The 6 members of each group blindly, independently, and consecutively examined the assigned patient. The investigators performed a multiplanar grey-scale and PD examination of the dorsal aspect of the RC joint, the dorsal aspect of the second MCP joint, the ECU tendon, and the SP of the ulna using the VP in the 2D real-time mode. After finishing the 2D US scanning, each investigator carried out a grey-scale and PD volumetric acquisition at the three anatomic sites (6 volumes per patient) which were stored anonymously in the US machine. Each investigator was given a maximum of 10 minutes for 2D scanning, anonymously filling in a standardised report sheet with the US findings and to acquire the 6 volumes. In the second part of the study, each group of investigators was moved to the other US scanner. “excellent quality”. After the volume assessments, the investigators reviewed together those recorded volumes scored below 3.

| Nordal et al. - 2014 – [36] | The neutrophil protein S100A12 is associated with a comprehensive ultrasonographic synovitis score in a longitudinal study of patients with rheumatoid arthritis treated with adalimumab | Abstract: the present objective was to explore in a pilot study the associations between S100A12 and other inflammatory markers, clinical assessments as well as degree of synovitis detected by a comprehensive ultrasonography (US) examination in RA patients during biologic treatment. Intro: The present pilot study explores the associations between serum levels of S100A12 and laboratory and clinical assessments of disease activity, as well as US sum scores from a comprehensive US examination. Twenty patients (15 women and 5 men) with RA according to the American Rheumatism Association 1987 revised criteria were included. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East (REK), and the patients gave written consent according to the Declaration of Helsinki. US examinations were performed by one experienced sonographer (HBH) using a Siemens Antares Sonoline machine; Siemens Medical Solutions, California, USA) at the day of inclusion and after 1, 3, 6 and 12 months as previously described [12,14]. A total of 78 joints and 36 tendons or tendon groups as well as the bilateral subdeltoid bursae were assessed. The US examiner had no access to US results from the previous examinations and was blinded for the results from the clinical joint assessments and laboratory tests completed the same day. for arthritis, tenosynovitis and bursitis by grey scale or B-mode (BM) presence of synovial hypertrophy and fluid (scored together) and presence of power Doppler (PD) vascularization, both scored on a 4–point scale (0 = no, 1 = minor, 2 = moderate, 3 = major presence). |
### Abstract

The study was conducted on 103 consecutive patients with a definite diagnosis of RA according to the 1987 American College of Rheumatology criteria (15) and on 103 age- and sex-matched healthy controls. All patients were seen at the Rheumatology Outpatient Clinic of the Instituto Nacional de Rehabilitación (Mexico City, Mexico). The study was conducted according to the Declaration of Helsinki and local regulations. The Instituto Nacional de Rehabilitación Review Board for Human Research approved the study protocol and written informed consent was obtained from both the patients and healthy controls.

#### Findings

Rodriguez-Henríquez et al. - 2013

**Sternoclavicular Joint Involvement in Rheumatoid Arthritis: Clinical and Ultrasound Findings of a Neglected Joint**

| Examination of Joints and Tendons in a Longitudinal Follow-up of RA Patients Starting Biologic Treatment. | The study was conducted on 103 consecutive patients with a definite diagnosis of RA according to the 1987 American College of Rheumatology criteria (6 years) in musculoskeletal US (PR-H) who was blinded to the clinical data. The patients and healthy controls underwent US examinations at random and were asked not to talk about their clinical condition with the sonographer. All US examinations were performed using a MyLab25 (Esaote Biomedica) device equipped with a 6–18-MHz broadband linear array transducer. For each patient and healthy control, US examinations included longitudinal and transverse scans of the SC joint performed bilaterally, according to a previously described scanning technique (12,17). Briefly, the transducer was placed parallel and perpendicular to the long axis of the SC joint, with or without an acoustic shadow. The SC joint was identified moving the probe medially. The cortical surfaces of the medial clavicle and sternum were identified with the hypoechoic joint space between them. Figure 1 shows the probe position and the respective normal US image. Each SC joint was initially scanned in gray scale to detect morphostructural changes and subsequently with the power Doppler (PD) technique to detect intraarticular synovial blood perfusion. Blood flow assessment was carried out with settings standardized as follows: pulse repetition frequency 750 Hz, Doppler frequency between 6 and 8 MHz, and wall filter 4. PD gain was adjusted to avoid random noise visualization. US examinations of all study participants were performed by an experienced rheumatologist (6 years) and a MyLab25 (Esaote Biomedica) device equipped with a 6–18-MHz broadband linear array transducer. For each patient and healthy control, US examinations included longitudinal and transverse scans of the SC joint performed bilaterally, according to a previously described scanning technique (12,17). Briefly, the transducer was placed parallel and perpendicular to the long axis of the SC joint. The SC joint was identified moving the probe medially. The cortical surfaces of the medial clavicle and sternum were identified with the hypoechoic joint space between them. Figure 1 shows the probe position and the respective normal US image. Each SC joint was initially scanned in gray scale to detect morphostructural changes and subsequently with the power Doppler (PD) technique to detect intraarticular synovial blood perfusion. Blood flow assessment was carried out with settings standardized as follows: pulse repetition frequency 750 Hz, Doppler frequency between 6 and 8 MHz, and wall filter 4. PD gain was adjusted to avoid random noise visualization. | Synovial PD signal was scored on the basis of the following semiquantitative scoring: 0 = absent (no synovial flow), 1 = mild (3 PD signals within the synovial area), 2 = moderate (3 PD signals in less than one-half of the synovial area), and 3 = marked (signals in more than one-half of the synovial area). For US elementary lesions, the Outcome Measures in Rheumatology preliminary definitions were adopted (18). The following abnormalities were recorded in both groups: synovitis, osteophytes, and erosions. Synovitis was defined as the presence of either synovial hypertrophy and/or joint effusion. Synovial effusion was defined as normal hypo- or anechoic (relative to subdermal fat, but sometimes may be iso- or hyperechoic) intraarticular material that is displaceable and compressible, but that does not exhibit a Doppler signal. Synovial hypertrophy was defined as abnormal hypoechoic (relative to subdermal fat, but sometimes may be iso- or hyperechoic) intraarticular tissue that is nondisplaceable and poorly compressible, and that may exhibit a Doppler signal. Bone erosion was defined as an intraarticular discontinuity of the bone surface that is visible in 2 perpendicular planes. Additionally, osteophytes were defined as a step-up bony prominence at the end of the normal bone contour or at the margin of the joint, with or without an acoustic shadow. In order to assess interobserver agreement, a second investigator with 3 years of experience in musculoskeletal US carried out sonographic examinations in 30 patients. Both examiners were instructed to perform the same US scanning technique. |
Sheane et al. 2009 –[38] Targeted Ultrasound of the Fifth Metatarsophalangeal Joint in an Early Inflammatory Arthritis Cohort

<p>| Sheane et al. - 2009 – [38] Targeted Ultrasound of the Fifth Metatarsophalangeal (MTP) Joint in an Early Inflammatory Arthritis Cohort | Abstract: To determine whether targeted ultrasonographic (US) imaging of the fifth metatarsophalangeal (MTP) joint, compared with radiographs, could aid in the early diagnosis of rheumatoid arthritis (RA) by identifying erosions sooner in early inflammatory arthritis. Radiographic erosion in RA is a late indication of poor prognosis. The earlier detection of erosion may facilitate the timely initiation of disease-modifying antirheumatic drug therapy, particularly in patients with undifferentiated synovitis. | Patients with a new diagnosis of inflammatory arthritis seen at rheumatology outpatient clinics were invited to participate in the study. Informed consent was provided by all patients included in the study, and ethical approval was granted by the St. James's Hospital and Federated Dublin Voluntary Hospitals Joint Research Ethics Committee. Each scan was performed by the same radiologist (SM), who was assisted by a radiology fellow (PB). Both were blinded to the radiographic results and the underlying rheumatic diagnosis. US imaging was performed on a Philips HDI 5000 scanner (Philips, Eindhoven, The Netherlands) using a high frequency linear (CL 15–7-MHz) hockey stick transducer. The frequency was set automatically, and patients were scanned using the hand/foot musculoskeletal setting. This setting uses a survey frame rate and is set to compound imaging (sonoCT); the preset is optimized for imaging superficial structures. One variable focal zone was employed with a narrow field of view. All color imaging was performed with power Doppler (PD). The PD values were set automatically by the machine and optimized for musculoskeletal imaging. The patients were scanned with identical preset values. The focal zone was adjusted as required. The scans were performed in a warm water bath where the entire joint was submerged, which enabled easy access to all the joint surfaces and ensured a high standard of image quality (10). US images were obtained at the fifth MTP joints from 3 different angles. The first angle was from the dorsal aspect of the foot, the second was from the lateral approach, and the third was from the plantar surface of the foot. The probe was passed over the joint at these 3 positions, which represent the available joint surface that is accessible to an US probe, and at each position the joint was examined in the longitudinal and transverse plane. The 3 angles gave almost full coverage of the joint. The time taken to and to adopt the same US interpretation scheme. | The semiquantitative scoring system and the definitions of US abnormalities (erosions, synovitis, and PD signal), originally outlined by Szkudlarek et al (11), were applied in this study. Erosions were defined as defects in the bone adjacent to the joint. A score of 2 on a scale of 0–3 was required for a defect to be categorized as an erosion (where 0 regular bone surface, 1 defect in the bone surface in 1 plane only, 2 bone surface defect visualized in 2 planes, and 3 extensive bone destruction). |</p>
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<th>Reference</th>
<th>Details</th>
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<td>Sreerangaiah et al. - 2016</td>
<td>Quantitative power Doppler ultrasound measures of peripheral joint synovitis in poor prognosis early rheumatoid arthritis predict radiographic progression. Abstract: To assess the value of quantitative vascular imaging by power Doppler US (PDUS) as a tool that can be used to stratify patient risk of joint damage in early seropositive RA while still biologic naive but on synthetic DMARD treatment. Intro: In this article we describe the potential of quantitative vascular imaging by PDUS as a tool to stratify the risk of joint damage in early seropositive, biologic-naive RA. Eighty-five patients meeting 1987 ACR classification criteria for RA of &lt;3 years duration and seropositive for anti-CCP antibody and/or IgM RF were prospectively recruited and treated according to the standard of care with conventional DMARDs. The study was conducted in compliance with the Declaration of Helsinki and ethical approval was obtained from the Hammersmith Research Ethics Committee (08/H0707/114). All subjects gave written informed consent. All patients underwent 2D greyscale US, PDUS of 10 MCP joints over the dorsal surface in the transverse and longitudinal planes and 3D PDUS of 10 MCP and bilateral wrist joints at 0 and 12 months. A single ultrasonographer (D.S.) carried out all scans with a GE Logiq 9 scanner [multifrequency linear (712 MHz)] and 4D16L3D probes. All images were anonymized and stored for subsequent analysis using a computerized image analysis system. The 3D scans were performed using the GE 4D16L3D volumetric probe using an automated sweep. The 2D images were scored separately for synovial thickening and vascularity against an analogue scale from 0 to 4 (0, no hypertrophy or vascularity; 1, minimal; 2, mild; 3, moderate; 4, severe hypertrophy or vascularity). Both hypertrophy and vascularity on 2D images were also calculated by pixel count in a defined region of interest for each joint. Finally, the number of erosions in each MCP joint was determined on greyscale images, with an erosion defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes. and images were scored semi-quantitatively for vascularity and also quantitatively in cubic millimetres using LOGIQworks software (GE Healthcare, Waukesha, WI, USA). Complete each US assessment was recorded.</td>
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<td>van de Stadt et al. - 2010 – [40]</td>
<td>The value of ultrasonography in predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. Abstract: In the present study, US utility and predictive properties in arthralgia patients at risk for the development of arthritis were studied. Intro: US utility and predictive properties were studied in this cohort. Between August 2004 and August 2008, arthralgia patients with a positive ACPA and/or IgM-RF status were recruited at rheumatology clinics in the Amsterdam area of the Netherlands after referral by a general practitioner. This study was approved by the local ethics committee and informed consent was given by all patients prior to inclusion. US was performed within a median of three weeks (interquartile range (IQR) one to five weeks) after the first visit. If present, tender joints at physical examination were scanned, otherwise joints that were painful by history were scanned. Furthermore, for proximal interphalangeal (PIP), metacarpal phalangeal (MCP) and metatarsophalangeal (MTP) joints the directly adjacent joints in the same joint group as the painful joints were scanned, for example, in the case of a painful MCP3, MCP2 to 4 were scanned. US was also performed on the contralateral joints selected in this way. (As some patients had bilateral joint complaints, contralateral joints could include painful joints.) In the healthy controls, either MCP joint 2 to 4 and PIP joint 2 and 3 (n = 3), MCP joint 3 to 5 and PIP joint 4 and 5 (n = 3), or joints were scored on a four-grade semiquantitative scale for joint effusion, synovitis, tenosynovitis and power Doppler signal, as described before and explained here [10]. Joint effusion was defined as a compressible anechoic intracapsular area and scored as follows: 0 = no effusion, 1 = minimal amount of joint effusion, 2 = moderate amount of joint effusion (without distension of the joint capsule) and 3 = extensive amount of joint effusion (with distension of the joint capsule). Synovitis was defined as a noncompressible hypoechoic intracapsular area (synovial thickening) and scored as follows: 0 = no synovial thickening, 1 = minimal synovial thickening (filling the angle between the periarticular bones, without bulging over the line linking tops of the bones), 2 = synovial thickening bulging over the line linking tops of the periarticular bones but...</td>
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MCP joint 2 to 4 and the wrist joint (n = 3) were scanned. US was performed bilaterally. All scans were performed with the Acuson Antares ultrasound system, premium edition (Siemens, Malvern, PA, USA) using linear array transducers VF 13-5 SP for finger and toe joints, (operating at 11.43 MHz for greyscale and 8.9 MHz for PD) and VF 13-5 for larger joints (operating at 11.43 MHz for greyscale and 7.3 MHz for PD), according to the manufacturer's criteria. All joints were scanned in the longitudinal plane from the most lateral to most medial site and in the transverse plane from the proximal to distal site of the joint. The US examinations were performed by two independent investigators (HW and MMR), both radiologists with extensive experience in musculoskeletal US. The investigators were blinded for clinical data. Healthy controls were referred as if they were arthralgia patients.

Prior to the study, consensus was reached between the investigators about scanning technique, pathology definitions and scoring. Interobserver reliability was evaluated by scanning 148 joints of 14 patients, including 7 patients fulfilling ACR criteria of RA [12], successively by both investigators, who were blinded for each other's findings and all other study data.

without extension along the bone diaphysis, 3 = synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses. Power Doppler signal was used to display flow signal in the synovium and scored as follows: 0 = no flow in the synovium, 1 = single vessel signals, 2 = confluent vessel signals in less than half of the area of the synovium, 3 = vessel signals in more than half of the area of the synovium [10]. Tenosynovitis was defined as hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath and scored as follows: 0 = no thickened tissue, 1 = minimal thickening, 2 = moderate thickening, 3 = extensive thickening.

In this study, grades 2 to 3 of joint effusion, synovitis and tenosynovitis were regarded as abnormal, and grades 1 to 3 power Doppler signal was regarded as abnormal [10,11].
Table 7. Data collection of the randomly selected sample of articles in Prognosis category.

<table>
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<tr>
<th>Title</th>
<th>Objective (blue = abstract; red = intro)</th>
<th>Design (red = study design, blue = ethics)</th>
<th>Technical data (blue = machine, green = joints, red = operator, grey = time/place)</th>
<th>Measure / Outcome (blue = elementary lesions, red = score, green = reliability)</th>
</tr>
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<td>Ceponis et al. - 2014 – [41]</td>
<td>Abstract: To investigate the usefulness of point-of-care hand and wrist joint ultrasound (US) examination in patients with established rheumatoid arthritis (RA).</td>
<td>This study was approved by the University of California, San Diego Institutional Review Board/Human Research Protections Program. Fifty-one patients with established RA meeting the 1987 American College of Rheumatology criteria for RA (17) and 10 normal healthy control volunteers were enrolled in the study.</td>
<td>A LOGIQ e ultrasound machine (GE Healthcare) equipped with a multifrequency 8–13-MHz linear transducer was used for MSUS. Ultrasound settings were standardized during the entire study, with B-mode frequency of 12–13 MHz, gain of 58–64%, PD frequency of 6.7 MHz, gain of 9–12%, and pulse repetition frequency of 0.6–0.8 Hz coupled with low-wall filters depending on the joint area and background interference.</td>
<td>Outcome Measures in Rheumatology definitions were used to assess joints for joint effusion, synovial hypertrophy, erosions, tenosynovial swelling, and hyperemia (20). Synovial hypertrophy (B-mode examination) was scored on a semiquantitative scale (where 0 absence, 1 mild, 2 moderate, and 3 severe) as described elsewhere (21,22) ; the possible minimal–maximal total synovial hypertrophy score (tSH) was estimated between 0 and 135. Synovial PD examination was graded on a semiquantitative scale (where grade 0 no intraarticular color signal, grade 1 single vessel signal[s], grade 2 confluent color signal in less than half of the intraarticular area, and grade 3 confluent color signal in more than half of the intraarticular area) as described in detail elsewhere (22); examples of PD synovitis grading for the MCP and wrist joints are shown in Figure 1. A possible total synovial PD score (tSPD) was estimated between 0 and 129. In addition, the presence or absence of sonographic effusion and erosions was documented for each joint. The standardized ultrasound report included tabulated descriptions of erosive changes, grading of synovial hypertrophy, and PD findings; presence or absence of joint effusion; and active pannus (cortical erosions with surrounding PD signal) in the individual PIP, MCP, and wrist joints. The second part of the report included a summary of the sonographers' impressions addressing the PIP, MCP, and wrist joints.</td>
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<td>Damjanov et al. - 2012 – [42]</td>
<td>Abstract: To investigate the construct validity and reliability of US DAS criteria for RA [23], with</td>
<td>A group of 90 patients fulfilling the 1987 ARA criteria for RA [23], with All patients underwent blinded PDUS and GSUS examination within the 24 h of clinical assessment, at baseline and after 6 months. The GSUS E/H was qualitatively graded as absent (0) or present (1). PDUS was semi-quantitatively graded based on the ultrasound report included tabulated descriptions of erosive changes, grading of synovial hypertrophy, and PD findings; presence or absence of joint effusion; and active pannus (cortical erosions with surrounding PD signal) in the individual PIP, MCP, and wrist joints. The second part of the report included a summary of the sonographers' impressions addressing the PIP, MCP, and wrist joints.</td>
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compared with 28-joint DAS (DAS-28) in assessing joint inflammation and in prediction of structural damage in patients with RA.

Intro: The primary objective of this study was to develop a composite US DAS index combining the values of PDUS, GSUS, laboratory and clinical variables, and to investigate its constructive validity and reliability compared with DAS-28 in patients with RA. The secondary objective was to assess predictive validity of US DAS for historical and future structural joint damage evaluated by X-ray, US and MRI.

Abstract: To monitor joint inflammation in rheumatoid arthritis (RA) patients receiving adalimumab/ methotrexate combination therapy using MRI and ultrasonography. To assess the predictive value of MRI and ultrasonography for erosive progression on CT and compare MRI/ ultrasonography / radiography for erosion detection/monitoring.

Fifty-two RA patients, fulfilling the American College of Rheumatology criteria (ACR 1987), were included in this ethics committee-approved investigator-initiated study (clinicaltrials.gov NCT00696059).

All imaging procedures were obtained before the first adalimumab injection and were repeated after 6 and 12 months of treatment. Radiography, CT and MRI were performed on the same day, whereas ultrasonography examinations were performed not more than 1 week apart. Images were read blinded to chronology, with assessors of radiographs (AB), CT (MO), MRI (BE) and ultrasonography (UMD) unaware of other imaging and clinical data. As previously described, 12 metacarpophalangeal joints 2–5 of the index hand were divided into quadrants, and the

Ten complete representative sets of images were re-evaluated to calculate intrarater intraclass correlation coefficients (ICC) on status scores and the smallest detectable change (SDC). Baseline imaging was used for comparing erosion detection on all modalities. Images of all joints were stored and scored for erosions (metacarpophalangeal joints only), grey-scale synovitis (GSS) and power Doppler signal (PDS) as suggested by Szudulkarek et al.26

Dohn et al. – 2010 – [43]

No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study

The colour gain was adjusted to the level just below the noise floor. GSUS E/H was qualitatively graded as absent (0) or present (1) in the following joints: MCP joints and MTP joints. In addition to US recording of US erosion count (USEC), we calculated US erosion rate (USER) by dividing the number of selected joints (where erosions were detected) with disease duration (in months). US DAS was compared with DAS-28.

PDUS inter-observer reliability as well as GSUS inter-observer reliability was evaluated.

Intro: The primary purpose of the study was to monitor joint inflammation and destruction, using MRI and ultrasonography, in RA patients receiving adalimumab and methotrexate combination therapy, and to investigate whether MRI and ultrasonography findings have predictive value for erosive progression on CT. A secondary purpose was to compare the ability of MRI, ultrasonography, CT and radiography for erosion detection and monitoring.

Abstract: To determine the effect of tumour necrosis factor a (TNFa) blockade with etanercept in refractory knee joint synovitis (KJS) in rheumatoid and psoriatic arthritis, by local and systemic disease activity assessment and combined grey scale and power Doppler ultrasonographic monitoring.

The study was designed as an open label, single centre, 12 months prospective study to assess the clinical and sonographic KJS response to TNFR:Fc. The protocol was approved by the local human research committee. All patients gave their written informed consent before entering the study. We enrolled 20 consecutive patients (27 knees) affected by refractory KJS attending the rheumatology clinic at Padua General Hospital.

All examinations were carried out using a high frequency linear transducer (10 MHz Elegra, Siemens, Erlangen, Germany) by the same two experienced observers, who were not aware of the clinical findings in the patients. Standardised anatomical guidelines of the scans in the three recesses of the knee—suprapatellar recess (SPR) and lateral and medial parapatellar recesses (LPPR, MPPR)—were used, as previously described.1 The synovial thickness of the SPR was determined by scanning the zone between the prefemoral (posterior suprapatellar) fat pad and the upper margin of the femoral cartilage (supine position; knee joint extended; biceps femoris contracted) was identified by scanning. Nodular vegetations, when present, were measured in their entire thickness. Power Doppler sonography was set for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow. Pulse repetition frequency was 750–1200 Hz and medium persistence was used. The colour gain was set for low sensitivity to limit the amount of noise detected.

On entry to the study, each knee was evaluated as a whole, and the worst area of thickening detected between the three recesses was measured; the resulting value was assumed to be a measure of synovial thickness.12 For each ultrasonographic scan, the power Doppler signal of the synovial membrane was graded on a 0–3 scale (0 = normal, undetectable power Doppler vessel signals in ultrasonographic synovial thickening area; 1 = mild hyperaemia; 2 = moderate hyperaemia; 3 = marked hyperaemia), if intrasynovial power Doppler flow signal distribution was detectable over .25%, (50%, or .50%) of the synovial thickening area. The intrasynovial power Doppler flow signals of identifiable vessels were scored (0–3) for distinct spatial arrangements in relation to the fluid/synovium interface (F/SI-PD) and the pannus/cartilage or pannus/capsule interface (P/CI-PD), according to arthroscopic vascular architecture between synovial villous surfaces and deep pannus layers adhering to cartilage/capsule, as previously described.24

 Fiocco et al. - 2005 – [44]
Rheumatoid and psoriatic knee synovitis clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept

Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept

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### Supplemental material

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| Supplemental material | Abstract: Comparison of the amount and distribution of inflammatory signs in wrist and finger joints of the clinically dominant hand in patients with OA and RA by FOI and gray-scale (GSUS) and power Doppler US (PDUS). | Patients with RA and OA were recruited for this study. All patients included fulfilled the European League Against Rheumatism/American College of Rheumatology criteria. | Ultrasonographic examination of the wrist (WR; midline, radial, ulnar), the metacarpophalangeal (MCP), proximal (PIP) and distal interphalangeal (DIP) joints (fingers II to V; palmar and dorsal) of the clinically dominant hand (for tenderness and/or swelling) was performed in neutral position by gray-scale US (GSUS) and PDUS following standardised procedures. Signals for GSUS were as follows (Mylab twice, Esaote, Genoa, Italy): frequency 16 MHz and length of scanner 42 mm. The gain depended on joint regions and patients and was nearly 50%. Settings for PDUS were as follows: frequency 9.1 MHz, Pulse Repetition Frequency (PRF) 750 Hz, PD-gain depending on joint regions and patients was nearly 50%; wall filter was three. | Spectral Doppler tracing was used to confirm the presence of true synovial vessel flow for distinct colour Doppler signal spatial arrangements. During the last month before entering the study, two repeat power Doppler ultrasonographic KJS assessments were carried out in 12 knees to determine the intraobserver variation coefficient. |}

**Glimm et al. - 2016**

**Surgical and severity of inflammation in patients with osteoarthritis compared to rheumatoid arthritis by ICG-enhanced fluorescence optical imaging and musculoskeletal ultrasound: a pilot study**

| Abstract: The objective of this cross-sectional study was to test the hypothesis that calprotectin is associated with clinical and ultrasound-determined disease activity in patients with RA. | Thirty-seven patients fulfilling the American College of Rheumatologists (ACR) 1987 [34] and/or the ACR/European League against Rheumatism (EULAR) 2010 classification criteria for RA [35] were recruited for this study. All the patients were recruited from the outpatient rheumatology clinic at the Institute of Rheumatology in Prague. The study was performed with Esaote Mylab 60 equipment (Esaote S.p.A., Genova, Italy) using a linear transducer with a 18 MHz frequency. The Power Doppler was pre-set, and no adjustments of the Doppler parameters were allowed. The patients were examined according to the German US7 score in the following seven joint areas: wrist, second and third metacarpophalangeal (MCP) and second and third proximal interphalangeal (PIP) and second and fifth metatarsophalangeal joints of the clinically more affected hand and foot. Synovitis in the GS was scored semiquantitatively (0 = absence, 1 = mild, 2 = moderate, 3 = severe synovitis), as follows: grade 1 = a small hypoechoic/anechoic line beneath the joint capsule; grade 2 = the joint capsule elevated parallel to the joint area; and grade 3 = a strong distension of the joint capsule [38]. Synovitis and tenosynovitis were classified semiquantitatively by power Doppler (PD), as follows: grade 0 = no intraarticular colour signal; grade 1 = up to three single colour signals or two single signals and one confluent signal in the intraarticular area; grade 2 = greater than grade 1 to <50 % of the intraarticular area. | | | }

**Hurnakova et al. - 2015**

**Serum calprotectin (S100A8/9): an independent predictor of ultrasound synovitis in patients with rheumatoid arthritis**

<p>| Abstract: The objective of this study was to compare the association between calprotectin, traditional markers of inflammation and ultrasound-determined RA disease activity | | | | |
| Kawashiri et al. - 2014 - [48] | Ultrasoundographic | Abstract: The aim of this study was to investigate the role of ultrasonography in predicting relapse after discontinuation of treatment with a biologic agent in patients with RA. | Patients with RA in remission (DAS28 2.6) undergoing treatment with a biologic agent who agreed to discontinue the treatment were included. Patients underwent clinical, laboratory, and ultrasound assessments at baseline and also underwent clinical and laboratory assessments every month after discontinuation of treatment with a biologic agent for 6 months. The study design was approved by the Ethics Committee of Chiba University, and subjects' written informed consent was obtained according to the Declaration of Helsinki. | Ultrasound was performed at baseline by rheumatologists trained for musculoskeletal ultrasound (TI, KI, AN, YS, DN, or KT) who were blinded to clinical information and laboratory data. A systematic multiplanar gray-scale (GS) and power Doppler (PD) ultrasound examination of 134 synovial sites in 40 joints (DAS28 joints ankles metatarsophalangeal joints; see Supplementary Table 1, available in the online version of this article at <a href="http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract">http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract</a>) was performed using either Aplio XG, Viamo (Toshiba Medical Systems), HI VISION Avius, or HI VISION Ascendus (Hitachi Medical), depending on availability. The machine setting for PD ultrasound was optimized as previously described (8). | Ultrasound findings of GS synovitis and PD positivity were defined according to the consensus definitions (15). Severity of ultrasound findings was graded semiquantitatively on a scale of 0–3 as previously described (8,9). These GS and PD scores graded by the same ultrasonographers showed good intra- and interobserver reliabilities in the previous study (8). Each patient’s total GS and PD scores were calculated by summing the corresponding scores of 40 joints. |
| Iwamoto et al. - 2014 – [47] | Prediction of Relapse After Discontinuation of Biologic Agents by Ultrasonographic Assessment in Patients With Rheumatoid Arthritis in Clinical Remission: High Predictive Values of Total Gray-Scale and Power Doppler Scores That Represent Residual Synovial Inflammation Before Discontinuation | Abstract: This prospective study aimed to determine whether the comprehensive ultrasonographic assessment of synovial inflammation predicts relapse after discontinuation of treatment with a biologic agent in patients with rheumatoid arthritis (RA) in clinical remission. | The study was approved by the local ethics committee of the Institute of Rheumatology in Prague. Informed consent was obtained from all of the patients before entry into the study. | Each patient underwent an MSKUS assessment on the same day as the clinical evaluation. | Images from all the examinations were stored and the US scoring reliability was examined. |</p>
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<th>Examination of rheumatoid arthritis patients who are free of physical synovitis: power Doppler subclinical synovitis is associated with bone erosion</th>
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<td>Characteristics of power Doppler (PD) subclinical synovitis in patients with RA who achieve clinical remission free from physical synovitis.</td>
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<td>Classification criteria [20] were consecutively recruited in the present study. They were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University from July 2011 through February 2012. Patients gave their informed consent and the study was approved by the Institutional Review Board of Nagasaki University. Serum samples were collected and stored at 20°C upon MSKUS examination until the assay.</td>
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<td>By a JCR-certified rheumatologist (S.K.) who was blinded to the clinical findings (S.K. is also an instructor of MSKUS certified by the JCR with 7 years experience in MSKUS). A systematic multiplanar GS and PD examination of 22 joints was performed with the same scanner (Toshiba ApioXG) using a multifrequency linear transducer (12 MHz). The US score included the following 22 joints: bilateral wrists (intracarpal, radiocarpal and ulnocarpal recesses) and finger joints including the first to fifth MCP joints, the first IP joint and the second to fifth PIP joints (dorsal recess). All joint regions were sonographically examined in a standardized manner according to the EULAR [9] and JCR guidelines. Those are the same sites where MRI has been performed in patients with early arthritis, as we previously described [23, 24].</td>
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<td>Abstract: To examine synovial vascularity and flow patterns in hand and wrist joints metacarpophalangeal (MCP) joints and ulnar stiltoid (USTL) regions—of patients with rheumatoid arthritis (RA) using power Doppler sonography (PDUS) and spectral Doppler analysis and classification criteria [20] were consecutively recruited in the present study. They were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University from July 2011 through February 2012. Patients gave their informed consent and the study was approved by the Institutional Review Board of Nagasaki University. Serum samples were collected and stored at 20°C upon MSKUS examination until the assay.</td>
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<td>Power Doppler Assessment of Overall Disease Activity in Patients with Rheumatoid Arthritis</td>
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<td>Twenty-four female patients with RA fulfilling the American College of Rheumatology criteria12 were included in the study. All gave informed consent to participate.</td>
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<td>Patients underwent sonographic examination just after the clinical examinations. Sonographic examination was performed with two high-resolution scanners: an Aplio SSA 770A (Toshiba, Tokyo, Japan) and a Logiq 7 (GE Medical Systems, Milwaukee, WI) using 6–13-MHz and 7–14-MHz broadband linearray transducers, respectively. The same radiologist with 7 years of experience in musculoskeletal radiology, who was unaware in randomly selected patients at the end of the study. Each joint was scored for GS and PD on a semiquantitative scale from 0 to 3 [10] (synovial hypertrophy in GS: grade 0 = absence, no synovial thickening; grade 1 = mild, minimal synovial thickening filling the angle between the periarticular bones without bulging over the line linking the tops of the bones; grade 2 = moderate, synovial thickening bulging over the line linking the tops of the periarticular bones but without extension to at least one bone diaphysis; PD signals: grade 0 = absence, no synovial flow; grade 1 = mild, single-vessel signals; grade 2 = moderate, confluent signals in less than half of the synovial area; grade 3 = marked, signals in more than half of the synovial area) and the presence or absence of tenosynovitis was noted. These scores corresponded to the maximum score for GS and PD obtained from any of the synovial sites evaluated at each joint. Tenosynovitis is defined by the presence of abnormal hypoechoic or anechoic material with or without fluid inside the tendon sheath with positive PD signals in two perpendicular planes [25]. Erosion is defined by a cortical break seen in two perpendicular planes [10].</td>
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Kiris et al. - 2006 – [49] 
Power Doppler Assessment of Overall Disease Activity in Patients with Rheumatoid Arthritis

to assess the accuracy of PDUS in detecting overall disease activity in RA patients.

Intro: The aim of this prospective cross-sectional study was to assess vascularization of the synovium and flow pattern in hand joints [metacarpophalangeal (MCP) joints and ulnar styloid (USTL)] of RA patients using PDUS and spectral Doppler analysis and to determine the accuracy of PDUS in detecting overall disease activity in RA patients.

Abstract: We undertook this study to determine the optimized definition of ultrasound-detected synovitis for the 2010 ACR/EULAR criteria and to assess the impact of its use on the accuracy of RA classification.

Intro: This study aimed to determine the optimized definition of synovitis findings on ultrasound for the 2010 ACR/EULAR criteria and to assess the impact of its use on the accuracy of RA classification.

The study design was approved by the Ethics Committee of Chiba University, and subjects' written informed consent was obtained according to the Declaration of Helsinki.

Patients with musculoskeletal symptoms lasting for 3 years who were referred to the Department of Allergy and Clinical Immunology at Chiba University Hospital from January 2010 to December 2010 because of a possible diagnosis of RA were consecutively recruited to the study.

Ultrasound was performed in a temperature-controlled room on the same day as the clinical evaluation by 1 of the 6 rheumatologists trained in musculoskeletal ultrasound (DN, KI, AO, TI, YS, or KT), all of whom were blinded to the clinical information and laboratory data. A systematic multiplanar GS and PD ultrasound examination of 38 joints (see Supplementary Table 1, available on the Arthritis & Rheumatism web site at http://onlinelibrary.wiley.com/doi/10.1002/art.37848/abstract) was performed using a LOGIQ 7 Pro or a LOGIQ E9 (GE Healthcare), a Viamo or an Apio XG (Toshiba Medical Systems Corporation), or a HI VISION Avius or a HI VISION Preirus (Hitachi Medical Corporation) instrument, depending on availability. For PD ultrasound, pulse repetition frequency was adjusted to the lowest possible value for the anatomic area scanned and for the machine settings.

Ultrasound findings of synovitis on GS imaging and positive synovial PD signal were defined according to consensus definitions (14–17). We used the scoring system reported by Naredo et al (18,19). Synovitis on GS imaging was graded semiquantitatively on a scale of 0–3 (0 absent, and 1 mild, 2 moderate, and grade 3 marked) for synovial hypertrophy of articular recess, tendon sheath, and bursa. Intraarticular, tenosynovial, and intrabursal PD signals were graded on a semiquantitative scale of 0–3 (0 absent [no synovial flow], 1 mild [3 isolated signals], 2 moderate [3 isolated signals or confluent signal in less than half of the synovial area], and 3 marked [signals in more than half of the synovial area]).

The maximum grades for synovitis on GS imaging and the synovial PD signal obtained from multiple synovial sites within a joint region (e.g., right second}

Nakagomi et al. - 2013 – [50]

Ultrasound Can Improve the Accuracy of the 2010 American College of Rheumatology/European League Against Rheumatoid Arthritis Classification Criteria for Rheumatoid Arthritis to Predict the Requirement for Methotrexate Treatment

Ultrasound findings of synovitis on GS imaging and positive synovial PD signal were defined according to consensus definitions (14–17). We used the scoring system reported by Naredo et al (18,19). Synovitis on GS imaging was graded semiquantitatively on a scale of 0–3 (0 absent, and 1 mild, 2 moderate, and grade 3 marked) for synovial hypertrophy of articular recess, tendon sheath, and bursa. Intraarticular, tenosynovial, and intrabursal PD signals were graded on a semiquantitative scale of 0–3 (0 absent [no synovial flow], 1 mild [3 isolated signals], 2 moderate [3 isolated signals or confluent signal in less than half of the synovial area], and 3 marked [signals in more than half of the synovial area]).

The maximum grades for synovitis on GS imaging and the synovial PD signal obtained from multiple synovial sites within a joint region (e.g., right second
used, and low wall filters were used. Color gain was set just below the level at which color noise appeared.

Before implementing the study, an exercise to standardize the scanning and grading methods was conducted with static images and a healthy volunteer. Intraobserver reliability of ultrasound assessment was evaluated by randomly selecting 4 images for each joint from stored images of baseline ultrasound examination. Seventy-six images per sonographer were graded again for synovitis on GS imaging and synovial PD signal by the same sonographer under blinded conditions at the end of the study period. Interobserver reliability between sonographers was evaluated with the same sets of images (a total of 456 images) graded by the other 5 sonographers at the end of the study period.

Joint synovitis was defined as the presence of intraarticular effusion and/or synovial hypertrophy. The presence of synovitis was identified in each joint as hypoechoic intraarticular material according to the criteria listed in Table 1 (19,36,42–44).

Measurements were taken at the point where most capsular or joint recess distension was observed. Active synovitis was defined as the presence of intraarticular synovitis with power Doppler signal. US joint count for active synovitis was obtained at each US assessment. In addition, the intraarticular power Doppler signal was graded on a semiquantitative scale from 0 to 3 (0 absence, no intraarticular flow; 1 mild, single-vessel signal or isolated signals; 2 moderate, confluent vessels; 3 marked, vessel signals in more than half of the intraarticular area) during the US examination (19,22,28,30,37). An overall US
Abstract: The aim of this study was to investigate the pharmacokinetics of s.c. anti-TNF agents on the grade of US-detected synovitis in RA patients.

Intro: The objective of this study was to investigate whether the pharmacokinetics of s.c. anti-TNF agents, i.e. the timing of US assessment in relation to anti-TNF administration, influences the grade of US-detected synovitis in RA patients treated with these drugs.

Fifty consecutive patients (31 women, 18 men) who fulfilled the 1987 ACR diagnostic criteria for RA [37] were prospectively recruited from the Biologic Therapy Unit of the Hospital General Universitario Gregorio Marañón (Madrid, Spain).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Hospital General Universitario Gregorio Marañón. Informed consent was obtained from all patients before study enrolment.

Patients underwent US assessment at the two time points on the day of the clinical assessments by a rheumatologist highly experienced in MSUS (E.N.) who was blinded to the anti-TNF agent, the administration time of the anti-TNF agent (i.e. either peak time or trough time) and the clinical and laboratory data.

All US examinations were carried out in a dark room with the temperature kept stable at 23°C. The patients rested for 15 min in the waiting room before the US examination. The patients were asked not to talk about their symptoms with the US examiner. To reduce the possibility of bias, the patients were asked not to talk about their symptoms with the US examiner.

The two US assessments of each patient were carried out at the same time in the morning with a maximum difference of 1 h. The US examinations were performed with a real-time scanner (LOGIQ E9, GE Medical Systems Ultrasound and Primary Care).

These joints were investigated for the presence of B-mode synovitis (i.e. either synovial hypertrophy or effusion) and synovial PD signal (i.e. Doppler synovitis). B-mode synovitis was defined as the presence of abnormal hypoechoic intra-articular material [31, 41]. We considered wrist synovitis or synovial PD signal positive if they were detected in the radiocarpal, midcarpal or distal radioulnar joints. At each scanned synovial recess, B-mode synovitis was scored semi-quantitatively on a scale of 0–3 (0, absent; 1, mild; 2, moderate; 3, marked). Synovial PD signal was also scored on a semiquantitative scale of 0–3 (0, no synovial flow; 1, mild (three or fewer PD signals); 2, moderate (more than three PD signals in less than half of the synovial area); 3, marked (signals in more than half of the synovial area) [20, 42]. Each joint was scored for B-mode synovitis and synovial PD signal on a scale from 0 to 3. These scores corresponded to the maximum joint index for power Doppler signal (the sum of the power Doppler signal scores obtained from each joint) was calculated at each US assessment. Representative images of PDUS findings are shown in Figure 1.

Intraobserver reliability of the US examination was evaluated by recording representative images of the 28 joints from one randomly chosen visit of 20 patients on a magnetic optical disk. The stored images were blindly read and scored for power Doppler signal by the same rheumatologist who performed all US examinations (EN) a minimum of 3 months after the corresponding real-time scanning.

power Doppler imaging was performed by selecting a region of interest that included the bony margins, articular space, and a variable view of surrounding tissues (depending on the joint size).

Power Doppler parameters were adjusted at the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity. This setting resulted in PRF ranging from 500 Hz to 1,000 Hz, depending on the joint scanned. Low wall filters were used. The dynamic range was 20–40 dB. Color gain was set just below the level at which color noise appeared underlying bone (no flow should be visualized at bony surface). This setting resulted in gains from 18 dB to 30 dB.

Flow was additionally demonstrated in 2 planes and was confirmed by pulsed wave Doppler spectrum to exclude artifacts.
### Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis

**Abstract:** To investigate the predictive value of synovitis detected by Doppler US in relation to failed tapering of biologic therapy (BT) in RA patients in sustained clinical remission.

**Methods:** A total of 80 consecutive RA patients (54 women, 26 men) were prospectively recruited from the BT Unit of our centre. Informed consent was obtained from all patients. The patients underwent a baseline US assessment consisting of a systematic longitudinal and transverse B-mode and PD examination using a widely described standardized scanning technique (i.e. patient position and probe placement) of the bilateral elbow (anterior and posterior recesses), wrist (dorsal recess of radiocarpal, midcarpal and distal radioulnar joints), second through fifth MCP joints (dorsal recess), knee (suprapatellar and parapatellar recesses), ankle (anterior tibiotaral recess) and second through fifth MTP (dorsal recess) joints. A global index for B-mode synovitis (BSI) (the sum of the B-mode synovitis scores obtained for each evaluated joint or joint region) and the joint count for Doppler synovitis (DSI) (the sum of synovial PD signal scores obtained for each evaluated joint or joint region) were calculated for a 12-joint US scoring model [31] and a wrist-MCP-ankle-MTP US scoring model [15] for each patient at each assessment time point. The 12-joint US scoring model included bilateral elbow, wrist, second and third MCP, knee and ankle joints [31]. The wrist-MCP-ankle-MTP US scoring model included 20 joints as follows: bilateral wrist, second through fifth MCP joints, ankle, and second through fifth MTP joints [15]. B-mode US remission was defined as a BSI <1 and Doppler US remission as a DSI <1.

#### Methods

- **Patients:** Total of 80 consecutive RA patients (54 women, 26 men) [11] treated with BT were prospectively recruited from the BT Unit of our centre. Informed consent was obtained from all patients. The patients underwent a baseline US assessment consisting of a systematic longitudinal and transverse B-mode and PD examination using a widely described standardized scanning technique (i.e. patient position and probe placement) of the bilateral elbow (anterior and posterior recesses), wrist (dorsal recess of radiocarpal, midcarpal and distal radioulnar joints), second through fifth MCP joints (dorsal recess), knee (suprapatellar and parapatellar recesses), ankle (anterior tibiotaral recess) and second through fifth MTP (dorsal recess) joints. A global index for B-mode synovitis (BSI) (the sum of the B-mode synovitis scores obtained for each evaluated joint or joint region) and the joint count for Doppler synovitis (DSI) (the sum of synovial PD signal scores obtained for each evaluated joint or joint region) were calculated for a 12-joint US scoring model [31] and a wrist-MCP-ankle-MTP US scoring model [15] for each patient at each assessment time point. The 12-joint US scoring model included bilateral elbow, wrist, second and third MCP, knee and ankle joints [31]. The wrist-MCP-ankle-MTP US scoring model included 20 joints as follows: bilateral wrist, second through fifth MCP joints, ankle, and second through fifth MTP joints [15]. B-mode US remission was defined as a BSI <1 and Doppler US remission as a DSI <1.

#### Results

- **Outcome measures:** The secondary objectives were to investigate the predictive value of synovitis detected by Doppler US in relation to failed tapering of BT at 6 and 12 months in RA patients in sustained clinical remission.

#### Discussion

This assessment was performed by a rheumatologist experienced in musculoskeletal US (E.N.) who was unaware of the clinical, laboratory and radiographic findings and was not involved in the treatment decisions. The following bilateral joints/joint regions were investigated for the presence of IA B-mode synovial hypertrophy (SH) and synovial Doppler signal: glenohumeral (i.e. posterior and axillary recesses and biceps sheath), elbow (i.e. anterior and posterior recesses), wrist (i.e. radiocarpal, midcarpal and distal radioulnar region) and the joint count for Doppler synovitis (DSI) (the sum of synovial PD signal scores obtained for each evaluated joint or joint region) and the joint count for Doppler synovitis (DSI) (the sum of synovial PD signal scores obtained for each evaluated joint or joint region) were calculated for a 12-joint US scoring model [31] and a wrist-MCP-ankle-MTP US scoring model [15] for each patient at each assessment time point. The 12-joint US scoring model included bilateral elbow, wrist, second and third MCP, knee and ankle joints [31]. The wrist-MCP-ankle-MTP US scoring model included 20 joints as follows: bilateral wrist, second through fifth MCP joints, ankle, and second through fifth MTP joints [15]. B-mode US remission was defined as a BSI <1 and Doppler US remission as a DSI <1.
Ogasawara et al. - 2012 – [54]
Autofeedback from Ultrasound Images Provides Rapid Improvement in Palpation Skills for Identifying Joint Swelling in Rheumatoid Arthritis

Abstract: We assessed the usefulness of US assessments in enhancing physical joint examination skills.

Intro: We conducted US examination and provided autofeedback using US images following physical joint examination; then we assessed the effects of this feedback on physical examination skills.

The study subjects were 108 patients with RA (92 women, 16 men) who presented at Juntendo University Hospital between April and July 2011 and were diagnosed with RA based on the 1987 RA criteria.1

US examination (ProSound Alpha7 with UST-5411 transducer; Hitachi Aloka Medical, Ltd., Tokyo, Japan) equipped with two multifrequency linear array transducers, a 6- to 18-MHz transducer for superficial areas and a 4- to 13-MHz transducer for deep areas. B-mode and power Doppler machine settings were optimized before the study and standardized for the whole study. These settings were as follows, B-mode frequency of 1018 MHz, B-mode gain of 5662%, Doppler frequency of 6.314 MHz, Doppler gain of 4562%, lowwall filters and pulse repetition frequency of 500750 Hz, depending on the depth of the anatomical area.

Interarticular and periarticular synovial sites.

Synovial blood flow was evaluated by power Doppler (PD) observation in each of the intraarticular and periarticular synovial sites.

PD variables were adjusted at the lowest permissible pulse repetition frequency to maximize sensitivity. Color gain was set just below the level at which color noise appeared underlying bone.

Joint swelling detected by US (US-SJ), defined as synovial hypertrophy and/or effusion, was identified as abnormal hypochoic material within joint recesses, tendon sheaths, or bursae and graded on a semi-quantitative grayscale (GS) from 0 to 3 (where 0 = absence, 1 = mild, 2 = moderate, and 3 = marked)15,16,17,18.

For the analysis of synovitis, we used the semi-quantitative (0–3) synovitis score for GSUS according to Scheel et al. [19], and the synovitis score for PDUS (0–3) published by Szabadari et al. [17] and according to the guidelines of EULAR [10] using an ESAOTE MyLab70 ultrasound machine (ESAOTE, Biomedica, Genova, Italy) with high resolution of 6–18 MHz linear array.

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### Abstract

Synovitis in rheumatoid arthritis (RA) is assessed clinically by the presence of joint tenderness and swelling. Synovial thickening and increased vascularity may also be detected by high-resolution grayscale, power Doppler and CDUS imaging. These tests determine synovitis in grayscale (GS) ultrasound (US) and power Doppler (PD) US, which are essential in the detection of disease activity and success of therapy. An erosion was defined as a break in the cortex of the bone surface visible in two perpendicular planes [8].

#### Methods

Intro: Therefore, the aim of the present study was to evaluate a new semi-quantitative erosion score in RA patients fulfilling the 1987 ACR criteria for RA [22].

1. **Patients and recruitment**: 40 patients fulfilling the 1987 ACR criteria for RA [22] were recruited from the Rheumatology department of St George’s Hospital, Wandsworth Research Unit, London, UK.

2. **Methods**: Selected joints were scanned using a Philips HDI 5000 (Philips Medical Systems, Andover, MA, USA) with a C7-15 MHz ‘hockey-stick’ transducer. For the PD studies, the Doppler settings were optimized to ‘low flow’, with a medium wall filter and a pulse repetition frequency (PRF) of 700 Hz. The colour gain was then adjusted so that it was just below noise level.

3. **Erosion score**: An erosion was defined as a break in the cortex visible in both transverse and longitudinal planes measuring 2 mm or more [24]. A graded scale was used in which an absence of erosions scored 0, 1–2 erosions scored 1, more than two erosions scored 2 and any large erosions (areas of regional bone destruction) scored 3 [24].

#### Results

In this prospective comparative study, 40 patients fulfilling the 1987 ACR criteria for RA [22] were recruited from the Rheumatology department of St George’s Hospital, The Wandsworth Research Unit, London, UK.

#### Conclusion

The results of this study suggest that PDUS may have a role in the detection of disease activity and success of therapy, in the assessment of joint tenderness and/or swelling.

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**Rees et al. - 2007 – [56]**

**A comparison of clinical vs ultrasound determined synovitis in rheumatoid arthritis utilizing grayscale, power Doppler and CDUS imaging in patients with rheumatoid arthritis Is US ready for a new erosion score?**

1 year at time 0 (before change of treatment) and after 1, 3, 6 and 12 months in the Rheumatology Outpatient Clinic at the University Hospital Charité of Berlin. Approval from the local ethics committee was obtained.

**Summary**

- **Synovitis** in RA is assessed clinically by the presence of joint tenderness and swelling.
- **CDUS imaging** determines synovitis in grayscale (GS) US and power Doppler (PD) US.
- An erosion is defined as a break in the cortex visible in both transverse and longitudinal planes measuring 2 mm or more.
- A graded scale is used to score erosions: 0 (absent), 1–2 (present), and 3 (large erosions).
- The study compares CDUS imaging with clinical assessment to determine the utility of CDUS in RA.

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**Rees et al. - 2007 – [56]**

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- The study compares CDUS imaging with clinical assessment to determine the utility of CDUS in RA.
ultrasonography (US) and power Doppler (PD). This study investigated the relationship between clinical and sonographic features of synovial disease utilizing US, PD and the contrast agent Sono-Vue

Intro: the aim of this prospective study is to compare the traditional clinical signs of synovitis, joint swelling and tenderness, with the US features of synovial disease, using PD data with and without microbubble contrast enhancement, using the agent Sono-Vue.

Abstract: To evaluate power Doppler ultrasound (PD) as a technique in assessing response to treatment with steroids in rheumatoid hand synovitis.

Intro: We investigated the changes in PD signal of metacarpophalangeal (MCP) joints in RA before and after the power Doppler scanner used was an Acuson Sequoia 512 ultrasound machine (Mountain View, CA, USA).

The same radiologist (DB) scanned all patients and was blinded to information regarding the most painful and tender joints. Each patient had the same MCP joints scanned on each occasion. To reduce bias in the selection of sites recorded, the whole joint was scanned and the area showing maximal signal was recorded.

Synovial blood flow was graded by power Doppler imaging from grade 0 – 3. Grade 0: no color pixels were seen in the visualized synovium; Grade 1: joints where color pixels were seen in less than one-third of visualized synovium; Grade 2: joints with color pixels in one-third to two-thirds of visualized synovium; Grade 3: joints where color pixels were seen in more than two-thirds of visible synovium. In equivocal cases and in order to rule out possible artifact the presence of color was confirmed by use of SonoVue. The objective score was taken from gray-scale TS images, measured at three sites (radial, mid-dorsal and ulnar) in millimetres and the mean of these was used as the final score. The subjective score was classified in a standard manner [20, 25–27] and was graded on a scale from 0 to 3 on the basis of the overall appearances of synovium (thickness and distribution) from gray-scale TS and LS images (Table 2). An absence of synovial hypertrophy (<1 mm) in any plane scored 0; a small degree, 1; moderate, 2 and marked hypertrophy, 3. The PD images were scored subjectively on a graded scale in a standard manner [15, 18, 19, 25, 27] from 0 to 3 on the basis of the appearances on TS and LS images, both pre- and postcontrast (Table 2).

Two experienced musculoskeletal ultrasonographers scored the selected joints by consensus based upon the stored images, cine clips and the video-recorded study.

Ethics Committee approved the study, and written consent was obtained.
| Treatment with steroid | RA10. | Examinations were performed using an Acuson musculoskeletal program, which had fixed settings with low wall filter (peristence 2, gate 2, and edge 1). All joints were imaged at identical parameters. Gain was set just below the disappearance of color noise from cortical bone (this resulted in color Doppler gain of 48–50 db). The mean pulse Doppler frequency used was 5 MHz. A 13 MHz probe was used for all examinations as this has been shown to increase the accuracy of MCP joint evaluation in RA12. Dorsal longitudinal and transverse images were obtained of each joint and recorded on magnetic optical disk. PD images were read by 2 radiologists who were not involved in imaging of joints and were blinded to patient symptoms and treatment; agreement was reached by consensus. They were also blinded to the time sequence of the scans, was confirmed by spectral analysis. agreement was reached by consensus The Doppler grade attributed to a joint was based on the overall assessment of transverse and longitudinal dorsal images of each joint together. |

**Vasanth et al. – 2010 – [58]**

**Abstract:** To ascertain whether magnetic resonance angiography (MRA) can reliably detect synovial neovascularization in subjects with early inflammatory arthritis.

**Intro:** We evaluated the capability of magnetic resonance angiography (MRA) to identify abnormal vasculature in patients with very early inflammatory arthritis, and correlated the findings on MRA with other measures of disease activity

This cross-sectional pilot study was designed to evaluate whether MRA can detect abnormal capsular vessels in the wrists and metacarpophalangeal (MCP) joints of subjects with very early inflammatory arthritis of the hands. Thirty patients with signs and symptoms of hand inflammatory arthritis for at least 6 weeks but less than 6 months were recruited between August 2005 and October 2006 from the private offices of rheumatologists affiliated with Hospital for Special Surgery, New York. The study protocol was approved by the Hospital for Special Surgery, Weill Ultrasound examinations of the wrist and second through fifth MCP joints of the more symptomatic hand were performed by an experienced musculoskeletal ultrasound radiologist, blinded to the clinical, laboratory, radiographic, and MRI findings.

The ultrasound was performed utilizing an IU22 system (Phillips Medical, Bothell, WA, USA) with a 12 or 17 MHz transducer linear phased array. Power Doppler measurements were obtained using the scanner’s low-flow sensitivity settings according to the criteria given by Newman, et al9 with scans obtained in sagittal plane at 3 points through each MCP joint and at 3 standardized points along the carpus.

Each ultrasound scan was scored for erosions and synovitis of the carpus and 2nd-5th MCP. Scores for erosions and synovitis were based on the scale for those measures used by Szkudlarek, et al10 in their study of ultrasonography of the finger and toe joints in RA. Erosions were scored 0–2 (0 = no erosions, 1 = single erosion, and 2 = multiple erosions) for the 2nd-5th MCP, base of the metacarpals 1–5, and carpus as divided into 3 areas (carpus, distal ulna, and distal radius) for a total erosion score ranging from 0 to 24. Synovial thickening was scored 0–3 (0 = no synovial thickening, 1 = minimal synovial thickening, 2 = synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis, 3 = synovial thickening bulging over linking tops of the periarticular bones and with extension to at least one of the bone diaphyses) for the dorsal and volar sides of the 2nd-5th MCP and the dorsal and volar sides of the wrist as divided into proximal
Vreju et al. - 2011 – [59]  
*Power Doppler sonography, a non-invasive method of assessment of the synovial inflammation in patients with early rheumatoid arthritis*

**Abstract:** This study was meant to assess the validity and reproducibility of ultrasonography (US) as a mean of detection for the knee synovitis, by comparing US findings with clinical examination and histopathological findings in synovial membrane.

**Intro:** The aim of this study was to identify another, noninvasive, marker of inflammation in early rheumatoid arthritis, by finding correlations of the power Doppler sonography (PDS) score with the serum and synovial VEGF and the clinical and biological markers of disease activity.

The study group included 65 patients with early rheumatoid arthritis – with less than 12 months from the onset, naive for DMARDs. We carried out a combined two planes grey scale and power Doppler study in three distinct joint recesses, to assess power Doppler signals in the synovitis areas.

All examinations were done out using a high frequency 32 mm linear transducer (ALOKA UST-5412) by an observer, who was not aware of the histopathological findings in the patients. We used standardized anatomical guidelines for the scans of the knee, in the three recesses–suprapatellar recess and lateral and medial parapatellar recesses [7]. The suprapatellar recess is the preferred site for synovial thickening in the knee of the rheumatoid arthritis patients. The synovial thickness of the suprapatellar recess was determined by scanning the zone deep to the quadriceps tendon and the suprapatellar fat pad and superficial to the prefemoral fat pad (supine position; knee joint extended). At the level of the lateral and medial parapatellar recesses, the vertical edge along the medial and lateral border of the kneecap was identified by scanning. Each knee was evaluated as a whole, and the thickest area detected between the three recesses was measured, the resulting value being assumed a measure of radial, proximal ulnar, distal radial, and distal ulnar for a total synovial thickening score ranging from 0 to 48.

Power Doppler ultrasound (PDU) was used to assess vascularity. Vascularity scores were designed to parallel the vascularity scoring for the MRA. Vascularity was scored 0–3 (0 = no appreciable synovial flow, 1 = mild synovial flow, 2 = moderate synovial flow, 3 = marked synovial flow) for the dorsal and volar sides of the 2nd-5th MCP and the dorsal and volar carpus divided into radial, mid, and ulnar zones, for a total vascularity score ranging from 0 to 21.

The thickness was graded from 0 to 3 using this scale: 0, if the thickness was <2 mm; grade 1, for a thickness between 2–5 mm; grade 2, for 6–8 mm and grade3 for a thickness >8 mm. PDS signal was scored from 0 to 3 according to the overall expression of PDS findings at the knees (Table 1), on the most representative images [9].
Power Doppler sonography was set for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow. Pulse repetition frequency was 750–1000 Hz and medium persistence was used. The color gain was increased until background noise appeared and then reduced until noise was suppressed, thus ensuring maximum sensitivity.

Yoshimi et al. – 2013 – [60] Ultrasoundography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis

Abstract: In the study reported here, we assessed whether ultrasoundography (US) can predict progressive joint destruction during clinical remission of RA.

Intro: The aim of this study was to test our hypothesis that US can predict long-term radiographic progression during persistent clinical remission by prospectively assessing RA patients in clinical remission.

Thirty-one RA patients were included in this prospective longitudinal study.

During the study unless the patients had a clinical flare-up. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients before study enrollment. The design of the work was approved by the Institutional Review Board of Yokohama City University.

Musculoskeletal US was performed at entry by experienced rheumatologists who were blind to the clinical, laboratory, and radiographic findings.

An Aplio SSA-700A apparatus (Toshiba, Tokyo, Japan) with 12-MHz linear array transducers was used in this study. The ultrasound scanning method, including parameter settings, has been described elsewhere [28–31].

Of the 28 joints, 22 (excluding bilateral glenohumeral, elbow, and knee joints) were assessed by US to be compared with hand X-ray films. The joints were scanned longitudinally and transversally from the dorsal view. Power Doppler (PD) imaging was performed by selecting a region of interest that included the bony margins and synovial site.

PD signals in each joint were graded on a semiquantitative scale of 0–3 [0: absent (no synovial flow); 1: mild (single-vessel signal or isolated signals); 2: moderate (confluent signals in less than half of the synovial area); 3: marked (signals in more than half of the synovial area)], corresponding to the maximum score obtained from the synovial sites evaluated in each joint [16].

For the PIP and MCP joints, gray-scale (GS) images were scored semiquantitatively from 0 to 3 (0: none; 1: mild; filling the angle between the periarticular bones without bulging over the line linking tops of the bones; 2: moderate; synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis; 3: severe; synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses) in each joint according to the definition of Szkudlarek et al. [32].

For wrists, GS images were scored semiquantitatively from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe) on subjective appraisal.

The total PD score and total GS score were calculated as the sums of individual scores for each joint at each examination.

The intraobserver and interobserver reliabilities have been described previously [15].
The main focus of this project was to analyze its value in daily rheumatologic practice under real-time conditions. Another objective of this project was to assess the value of this score in the detection of disease activity and therapeutic response.

Table 8. Data collection of the randomly selected sample of articles in Therapy category.

<table>
<thead>
<tr>
<th>Title</th>
<th>Objective (blue = abstract ; red = intro)</th>
<th>Design (red = study design, blue = ethics)</th>
<th>Technical data (blue = machine, green = joints, red = operator, grey = time/place)</th>
<th>Measure / Outcome (blue = elementary lesions, red = score, green = reliability)</th>
</tr>
</thead>
</table>
| Backhaus et al. - 2009 – [61] Evaluation of a Novel 7-Joint Ultrasound Score in Daily Rheumatologic Practice: A Pilot Project | Abstract: To introduce a new standardized ultrasound score based on 7 joints of the clinically dominant hand and foot (German US7 score) implemented in daily rheumatologic practice. Intro: The main focus of this project was to analyze its value in daily rheumatologic practice under real-time conditions. Another objective of this project was to assess the value of this score in the detection of disease activity and therapeutic response. | This prospective national project started in November 2006. One hundred twenty patients underwent US examinations at 3 visits (baseline and after 3 and 6 months) at 23 sites. | Seven joints of the clinically dominant hand and foot were sonographically evaluated after the onset of therapy or change of actual therapy (DMARDs and/or TNF inhibitors). For each patient, the hand and foot that was clinically more affected by tenderness and/or swelling had been chosen for US examination. The wrist, MCP2 and MCP3, andPIP2 and PIP3 joints, as well as the MTP2 and MTP5 joints of the clinically dominant side, were sonographically examined in a standardized manner according to German (15) and European League Against Rheumatism (EULAR) (16) guidelines. All joint regions were assessed by GSUS and PDUS (where available). PDUS was used in 80% of patients. GSUS was performed as follows: the wrist was examined for synovitis and tenosynovitis from the dorsal, palmar, and ulnar aspects (Figure 1). In the dorsal aspect, the probe was parallel to the extensor digitorum tendons (dorso-median). For the palmar wrist examination, the probe was placed parallel to the median nerve (palmodmedian), and for the ulnar aspect, the probe was set parallel to the extensor carpi ulnaris tendon. MCP2 and MCP3 joints were evaluated for synovitis and tenosynovitis from the palmar view, and for paratenonitis from the dorsal aspect. Erosions were detected from the dorsal, palmar, and radial (MCP2 joint) aspects, or from the dorsal and palmar aspects (MCP3 joint). PIP2 and PIP3 joints were assessed for synovitis from the palmar aspect, and for erosions from the dorsal and palmar aspects (Figure 1). MTP2 and MTP5 joints were examined for synovitis from the dorsal aspect, and erosions were detected from the dorsal and plantar aspects. | Synovitis by GSUS was analyzed semiquantitatively (0 absence, 1 mild, 2 moderate, and 3 severe synovitis). Grade 1 describes a small hypoechoic/anechoic line beneath the joint capsule. In grade 2, the joint capsule is elevated parallel to the joint area. Grade 3 characterizes a strong distension of the joint capsule (Figure 2). Tenosynovitis/paratenonitis and erosions were registered as being absent (0) or present (1). Erosion was defined as an interruption of the bone surface in 2 perpendicular planes. Tenosynovitis is a hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath (17). Paratenonitis is identified in US as an echopoor halo around the tendon and often shows increased vascularity on Doppler imaging (18). The semiquantitative findings of PDUS activity for synovitis and tenosynovitis/paratenonitis were scored as follows: grade 0 no intraarticular color signal, grade 1 up to 3 color signals or 2 single and 1 confluent signal in the intraarticular area, grade 2 greater than grade 1 to 50% of the intraarticular area filled with color signals, and grade 3 50% of the intraarticular area filled with color signals (19) (Figure 3). Based on these results, a 7-joint US score (US7) was performed, including the sum of synovitis scores in the GSUS (0–27) and PDUS (0–39) modes, tenosynovitis/paratenonitis in the GSUS (0–7) and PDUS (0–21) modes, and erosions (0–14) in the GSUS mode. US inter- and intraobserver reliability. Thirty readers took part in the US reliability.
| Filippucci et al. - 2006 [62] | Abstract: to use power Doppler sonography (PDS) to evaluate changes in synovial perfusion induced by adalimumab in the wrist joints of patients with rheumatoid arthritis. Intro: Our study aimed at PDS evaluation of the changes in synovial perfusion induced by adalimumab in the wrist joints of patients with rheumatoid arthritis. The wrist joint was selected for PDS evaluation because it is almost invariably affected in patients with rheumatoid arthritis. | In all, 24 consecutive patients were recruited from the Rheumatology Clinic of the University 'Politecnica delle Marche, Ancona, Italy, and 48 wrists examined. The clinical and PDS examinations were carried out at the Rheumatology Department of the University 'Politecnica delle Marche in Ancona, Italy, according to local regulations and the Declaration of Helsinki. Clinical, laboratory and PDS assessments were carried out on the same day at 0, 2, 6 and 12 weeks. PDS was carried out by an experienced operator (EF) blinded to both clinical and laboratory findings. An AU5 Harmonic (Esaote Biomedica, Genoa, Italy) with a 10–14-MHz linear probe was used. PDS settings were standardised with a pulse repetition frequency of 1000 Hz and a colour mode frequency of 7 MHz. The wall filters and the colour gain of the PDS equipment were identical to those proposed by Rubin et al.14 Each wrist was scanned over the dorsal surface from lateral to medial aspects in both longitudinal and transverse planes. Representative pictures of the highest expression of intraarticular PDS signals were obtained. A score from 0 to 3 was assigned according to the overall expression of PDS signals at the wrist level. The semiquantitative visual scale was as follows: 0, normal or minimal degree; 1, mild degree; 2, moderate degree; and 3, marked degree. The same investigator carried out follow-up examinations using the same ultrasound equipment, the same values of the setting parameters and the same scanning technique as that used for baseline assessment. To evaluate intraobserver reproducibility, the first set of representative sonographic pictures taken in the first 12 patients consecutively enrolled in the study was evaluated twice by the same sonographer (EF): the first time soon after the ultrasound examination and the second time 1 week after. Evidence of synovitis, tenosynovitis, erosions, and enthesitis was noted. | |
| Fournié et al. - 2006 [63] | Abstract: We prospectively compared power Doppler ultrasound findings in 25 fingers with rheumatoid arthritis (RA) and 25 fingers with psoriatic arthritis (PsA). Intro: We used ultrasonography to look for evidence of finger enthesitis in PsA, comparatively. We prospectively included 21 patients meeting American College of Rheumatoid arthritis criteria for RA [3] and 20 patients meeting Fournié criteria for PsA [4]. In each patient, radiographs and ultrasonography were obtained within 48 hours of the physical examination done at study inclusion. All ultrasound scans were performed by the same experienced radiologist using a high-frequency 13.5-MHz linear transducer (Siemens Sonoline Elegra, Cheshire, CT, USA), a water-filled bag, software appropriate for imaging the fingers, (MTP2 joint) and from the dorsal, plantar, and lateral (MTP5 joint) aspects (Figure 1). PDUS. PDUS was performed for synovitis and tenosynovitis/paratenonitis from the palmar and dorsal aspects in each joint region evaluated, except for MTP joints from the plantar (Figure 1). US examination of each patient took 10–20 minutes, including documentation. | Evidence of synovitis, tenosynovitis, erosions, and enthesitis was noted. |
| **Fukae et al. - 2013** |  | **Abstract:** To investigate the relationship between synovial vascularity and joint damage progression in each finger joint of patients with RA under low disease activity during treatment with biologic agents.  
**Intro:** Here we report on the relationship between synovial vascularity and joint damage progression in two patient groups treated with different biologic agents, focusing on finger joints with positive synovial vascularity after achieving low disease activity.  
**Thirty-one patients with RA who had started adalimumab (ADA) or tocilizumab (TCZ) therapies were analysed. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Hokkaido Medical Center for Rheumatic Diseases. Informed consent was obtained from all patients before they entered the study.  
**Ultrasonography was performed at baseline and at weeks 8, 20 and 40 by one of three US experts (M.H., F.S., A.N.) specialized in musculoskeletal ultrasonography who were blinded to other clinical information. A linear array transducer (13 MHz) and ultrasonographic machine were used (EUP-L34P, EUB-7500, Hitachi, Tokyo, Japan).**  
**Power Doppler settings have been previously described [7, 8]. First to fifth MCP and first to fifth PIP joints were scanned in the longitudinal plane over the dorsal surface.**  
**The quantitative PDS method was established in a previous report [8]. A value of synovial vascularity was determined by counting the number of vascular flow pixels in the region of interest.*** |}

| **Harman et al. - 2015** |  | **Abstract:** The aim of this study was to define the ultrasonographic factors that indicate clinical remission in patients with RA.  
**Intro:** In the present study, we ultrasonographically assessed the synovial inflammation of RA patients in clinical remission and defined factors influencing ultrasonographic remission status in such patients.  
**This study included RA patients in remission [according to the Boolean-based American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) RA 2011 remission criteria]. The study protocol was approved by our local ethics committee and informed consent was obtained from all patients. Also, patients were examined every 3 months, and patients had to be in remission for at least 6 months.**  
**Twelve patients with RA in clinical remission were enrolled. Ultrasound was performed and an acoustic energy source.**  
**Synovitis was classified on grey-scale images using a semi-quantitative scoring method. We considered only synovial proliferation as a sign of synovitis (not synovial effusion). The approach features use of a 0–3 scale, in which 0 corresponds to no synovitis, 1 to mild synovitis, 2 to moderate synovitis, and 3 to severe synovitis [11]. Grade 1 synovitis may occur in normal populations, and, for this reason, patients of grades 2 and 3 (only) were considered to have abnormal synovitis [11]. The presence of synovitis (1) or the absence thereof (0) was scored for each of 26 joints and total synovial scores calculated.**  
**The maximal area of augmentation on PDUS was recorded using a previously described semiquantitative technique featuring use of a 0–3 scale, in which 0 corresponds to normal/minimal vascularity, 1 to mild hyperaemia (single vessel signal), 2 to moderate hyperaemia (confluent...*** |
of each region (thus, a total of 14 tendons in both extremities). US examinations were completed in 20 min, and all images were stored.

The presence of PD synovitis (1) or the absence thereof (0) was scored for each of the 26 joints and total PD synovitis scores calculated.

A four-grade semiquantitative scoring system (i.e. grade 0, normal; grade 1, minimal; grade 2, moderate; and grade 3, severe) was used to score tenosynovitis revealed on grey-scale US.

The presence of tenosynovitis (1) or the absence thereof (0) was scored for each of the 14 tendon regions and total tenosynovitis scores calculated [13].

A four-grade semiquantitative scoring system (i.e. grade 0, no Doppler signal; grade 1, minimal signal; grade 2, moderate signal; and grade 3, severe signal) was used to score pathological peritendinous PD signals within the synovial sheath.

The presence of PD tenosynovitis (1) or the absence thereof (0) was scored for each of the 14 tendon regions and total PD tenosynovitis scores calculated [13].

Ultrasonographic remission was defined as the absence of all of synovitis, PD synovitis, tenosynovitis, and PD tenosynovitis.
articular thickening. The assessment was to be made in order to differentiate active synovitis from inactive intraarticular thickening (inactive synovitis or effusion) by comparison of gray-scale US and PDUS with CEUS via the participation of five different European centers. Written informed consent according to the declaration of Helsinki was obtained by all patients via the participation of five different European centers

and US scanning of one of the most active or clinically suspicious joints was performed accordingly. Appropriate color velocity scale using the musculoskeletal program of the US unit was used. The window (color box) was restricted to the vascular area studied. After visualization of color-flow signals, pulsed wave spectral Doppler imaging was performed using the lowest filter setting and the smallest scale available that would display the Doppler waveforms as large as possible without aliasing. A spectral Doppler tracing was obtained to confirm that the PDUS signals represented true arterial or venous flow. All patients gave their written informed consent prior to the intravenous bolus administration of the US contrast agent SonoVue (Bracco, Milano, Italy). The agent was prepared in a standard manner with a dosage of 4.8 ml SonoVue flushed with 10 ml saline. Subsequently, US scanning using a low MI (≤0.1) technique, CnTI (Contrast tuned Imaging, Esaote, Genoa, Italy), was performed in one joint to ensure sufficient enhancement after bolus administration, allowing for an examination window of 3–5 min.

Intra-articular enhancement was graded subjectively using a 3 score grading scale (Fig. 1): Grade 0 was defined as having no intra-articular enhancement. The arrival of the contrast media can be detected in the periarticular tissue, but not in the distended joint. Grade 1 was defined as detectable but in comparison to the periarticular lower tissue enhancement. Grade 2 was defined as a definitively higher uniform enhancement than obtained in periarticular structures. US, PDUS, and CEUS were used to assess the amount of inactive and active intra-articular synovitis. Active synovitis was defined as thickening of intra-articular tissue that is not displaceable and not at all or minimally compressible and exhibits PDUS signals or contrast enhancement at CEUS. Inactive synovitis was defined as thickening of intra-articular tissue that is not displaceable and not at all or minimally compressible and does not exhibit PDUS signals or enhancement at CEUS. Effusion was defined as hypoechoic or anechoic intraarticular material, which is displaceable and compressible and does not exhibit signals at PDUS or at CEUS. Special attention was drawn to the use of the same scanning planes for thickness measurement before and after contrast administration. Images and clips were analyzed after digital storage on the harddisk by one examiner from each center and an evaluation sheet was completed by the individual examiner. In the final consensus, after the evaluation of the images and clips and merging of data from
### Naredo et al. - 2005 – [67]
**Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: Comparison of extended versus reduced joint evaluation**

<table>
<thead>
<tr>
<th>Abstract: To investigate the validity of reduced joint counts for ultrasonographic (US) assessment of joint inflammatory activity in patients with rheumatoid arthritis (RA)</th>
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<tbody>
<tr>
<td>Ninety-four consecutive patients who fulfilled the 1987 American Rheumatism Association criteria for RA (9) were included. The institutional ethics committee approved the study and informed consent was obtained from all patients before the clinical and US evaluation.</td>
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<tr>
<td>All patients underwent a US examination within 30 minutes of the clinical evaluation, by a single rheumatologist, experienced in US (EN) and blinded to the clinical findings. Grey scale and PD US examination was performed using multifrequency linear array transducers [Logiq 400CL, General Electric Medical Systems, Korea (scanner 1) and Logiq 700, General Electric Medical Systems, Waukesha, WI, USA (scanner 2)]. The first 69 patients were examined with scanner 1 and the last 25 patients with scanner 2. The presence of joint effusion and synovitis was systematically evaluated by US in each of the 60 joints clinically examined.</td>
</tr>
<tr>
<td>US scanning method and diagnostic criteria for effusion and synovitis in each joint were described in a earlier report (8). Joint effusion and synovitis were subjectively graded from 0 to 3 (0 = absence; 1 = mild; 2 = moderate; 3 = marked). Synovial vascularization was assessed by PD US in each of the 60 joints. The intraarticular PD signal was subjectively graded on a semiquantitative scale from 0 to 3 (0 = absence, no intraarticular flow; 1=mild: single vessel signal; 2 = moderate: confluent vessels; 3 = marked: vessel signals in more than half of the intraarticular area). In each patient, the joint count for US effusion (USJIE), the joint count for synovitis (USJCS), the joint count for PD signal (USJCPD) and a 60-joint index for effusion (USJIE), synovitis (USJIS) and PD signal (USJIPD) (sum of the effusion, synovitis and PD signal scores, respectively, obtained from each joint) were recorded. We considered reduced joint counts and indices for effusion, synovitis and PD signal that included the most frequently US involved joints.</td>
</tr>
</tbody>
</table>

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### Naredo et al. – 2013 – [68]
**Three-dimensional Volumetric Ultrasound: A Valid Method for Blinded Assessment of Response to Therapy in Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Abstract: To assess the responsiveness and repeatability of volumetric power Doppler ultrasound (PDUS) evaluation of synovitis and bone erosions in rheumatoid arthritis (RA).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twenty-three patients with RA (19 women, 4 men) according to the American College of Rheumatology 1987 criteria40 were prospectively enrolled in our observational longitudinal study. Patients were recruited from the outpatient rheumatology clinics at 4 centers from January 2009 to July 2010</td>
</tr>
<tr>
<td>The following joint areas of the most symptomatic hand and foot, established by the clinical investigator at baseline, were evaluated for greyscale synovitis and synovial PD signal: the dorsal aspect of the radiocarpal and midcarpal joints together, dorsal aspect of the MCP joints, and dorsal aspect of the metatarsophalangeal (MTP) joints (i.e., 11 areas). The following joint sites of the most symptomatic hand and foot at baseline were evaluated for bone erosions: dorsal, palmar, and radial aspect of the second MCP joint; dorsal, palmar, and ulnar aspect of the fifth metacarpal.</td>
</tr>
<tr>
<td>Grey scale and PD US examination was systematically performed by a single rheumatologist experienced in US, blinded to the clinical findings and obtained from each joint. The presence of joint effusion and synovitis was systematically evaluated by US in each of the 60 joints clinically examined. A 60-joint index for greyscale synovitis (USJIS), joint count for PD signal (USJCPD) and a 60-joint PD signal index (USJIPD) (sum of the greyscale synovitis and PD signal scores, respectively, obtained from each joint) were recorded. We considered reduced joint counts and indices for effusion, synovitis and PD signal that included the most frequently US involved joints.</td>
</tr>
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</table>

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| Volumetric PDUS investigation. Study design. | MCP joint; dorsal, plantar, and medial aspect of the first MTP joint; and dorsal, plantar, and lateral aspect of the fifth MTP joint (i.e., 12 areas). The metacarpal head and the proximal phalanx base were evaluated for erosions at each joint site. PDUS volumetric acquisition was performed within 4 hours of each clinical evaluation by the same rheumatologist at each center, all experienced in MSUS. These rheumatologists were unaware of the clinical and laboratory findings and were not involved in the treatment decisions; the only patient information that they received from the clinical investigators was the identification of the most symptomatic hand and foot. For each patient at each visit, the investigators acquired, in a consecutively preestablished fashion, 1 volume in B-mode per each investigated joint area for greyscale synovitis and/or erosions (i.e., 19 volumes) and 1 volume in PD mode per each investigated joint area for synovial PD signal (11 volumes) with the same real-time scanner in all centers (Logiq 9; GE Medical Systems Ultrasound and Primary Care Diagnostics LLC). The scanner was equipped with multifrequency electromechanical 3-D dedicated VP (8–15 MHz). A generous layer of gel was applied on the examined joints. The volumetric probe was placed over the central part of the investigated joint areas. A volumetric sweeping on the longitudinal plane was performed at each studied site. PDUS volumetric acquisitions were carried out without entering the patient identity, hospital origin, and real date in the database of the US machine. An acronym of the study and the preassigned code were introduced into the required field without the patient or the hospital name. A fictitious standardized date (i.e., January 1, 2009) was established for all transverse assessments were scored as in real-time 2-D scanning. Greyscale synovitis was scored semiquantitatively on a scale of 0–3 (0, absent; 1, mild; 2, moderate; 3, marked). Synovial PD signal was also scored on a semiquantitative scale of 0–3 (0, absent [no synovial flow]; 1, mild (≤ 3 PD signals); 2, moderate (> 3 PD signals in less than half the synovial area); 3, marked [signals in more than half the synovial area]). Erosions were scored in a dichotomous scale (presence/absence). A global index for B-mode synovitis (IBM; the sum of the greyscale synovitis scores obtained for each evaluated joint) and a global index for synovial PD signal (IPD; the sum of the PD signal scores obtained for each evaluated joint) were calculated for each visit of each patient. In addition, a global index for bone erosions (IER) was also calculated from the sum of the erosions found in all evaluated areas.

To evaluate the intraacquisition, intrareader reliability of the PDUS investigation, the acquisition of the PDUS volumes at the first visit of the second and third patients enrolled at each center was repeated twice consecutively and recorded in 2 different DVD with different preassigned codes each. These DVD were sent to the assigned assessor as independent investigations, each included in 1 of the 2 sets of DVD that were sent 6 months apart.

| synovitis and bone erosions to blindly monitor response to rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, in patients with active RA. | 10 centers participated in the study. Four of them recruited the patients and performed the volumetric acquisitions of the PDUS images, while the remaining 6 centers assessed the PDUS volumes (blinded to the identity of patients, dates of visits, and hospital of origin). To keep the PDUS assessors blinded to the above data, the acquired PDUS volumes for each patient at each visit were recorded on individual digital versatile discs (DVD) and were identified exclusively by a random 3-digit code consecutively assigned by a statistician and sent to the coordinating central office. The central office collected the DVD from the consecutive visits of the enrolled patients and randomly distributed them among the assessors. The DVD from the same patient were assigned to the same assessor. Two sets of DVD were sent, separated by 6 months, to each PDUS assessor with no other identification than the preassigned code. The PDUS assessors read the volumes and returned the DVD and their assessments in a database within a maximum period of 1 month after the DVD was sent to the coordinating office. The central office sent to the coordinating office a copy of each DVD. The central office was blinded to the identity of patients, dates of visits, and hospital of origin. To the blinded assessors, the DVD from the same patient were assigned by a statistician and sent to the coordinating office. The central office collected the DVD from the consecutive visits of the enrolled patients and randomly distributed them among the assessors. The DVD from the same patient were assigned to the same assessor. Two sets of DVD were assigned to the same assessor as independent investigations, each included in 1 of the 2 sets of DVD that were sent 6 months apart.

A generous layer of gel was applied on the examined joints. The volumetric probe was placed over the central part of the investigated joint areas. A volumetric sweeping on the longitudinal plane was performed at each studied site. PDUS volumetric acquisitions were carried out without entering the patient identity, hospital origin, and real date in the database of the US machine. An acronym of the study and the preassigned code were introduced into the required field without the patient or the hospital name. A fictitious standardized date (i.e., January 1, 2009) was established for all transverse assessments were scored as in real-time 2-D scanning. Greyscale synovitis was scored semiquantitatively on a scale of 0–3 (0, absent; 1, mild; 2, moderate; 3, marked). Synovial PD signal was also scored on a semiquantitative scale of 0–3 (0, absent [no synovial flow]; 1, mild (≤ 3 PD signals); 2, moderate (> 3 PD signals in less than half the synovial area); 3, marked [signals in more than half the synovial area]). Erosions were scored in a dichotomous scale (presence/absence). A global index for B-mode synovitis (IBM; the sum of the greyscale synovitis scores obtained for each evaluated joint) and a global index for synovial PD signal (IPD; the sum of the PD signal scores obtained for each evaluated joint) were calculated for each visit of each patient. In addition, a global index for bone erosions (IER) was also calculated from the sum of the erosions found in all evaluated areas.

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B-mode and PD machine settings were adjusted before the study and standardized among investigators for the whole study. These settings were as follows: dynamic range of 66 dB, greyscale frequency of 15 MHz, Doppler frequency of 7.5 MHz, greyscale gain of 66 dB, color gain of 39 dB, low-wall filters, pulse repetition frequency of 900 Hz, and volume angle of 14º. Each volumetric sweeping scan took 20 s. The total time spent on the US acquisition of the 30 volumes was 30 min. The 30 volumes acquired from each patient at each visit were recorded in a single DVD and sent to the central office with the corresponding preassigned code written in permanent marker on the DVD.

Volumetric PDUS assessment. PDUS volumes were assessed in personal computers equipped with the Logiq Works software (ViewPoint Bildverarbeitung GmbH), a tool that allows storage, review, and postprocessing of patient images, cineloops, and volumes obtained from an US system. The volumes were rescanned on longitudinal and transverse planes in the work station. The software allowed simultaneous visualization of the joints and the pathological findings (i.e., greyscale synovitis, synovial PD signal, and bone erosions) at the same point in both perpendicular planes.

The 6 rheumatologists who assessed the PDUS volumes were experts in MSUS, had a similar background in MSUS, had conducted multiple consensus meetings and training sessions on RA PDUS findings, and had previously demonstrated reproducibility in the above abnormalities in multicenter studies6,23,39. The time spent on the assessment of the volumes from 1 DVD was about 30 min.

### Table:

| Reiche et al. - 2014 – [69] Usefulness of Power Doppler Ultrasound for | Abstract : To assess the value of gray-scale (GS) and power Doppler (PD) ultrasound (US) in All patients participating in this study gave their written consent prior to evaluation; Parameters evaluated by US were signs of synovitis on GSUS and signs of vascularization on PDUS, graded by US technique. GSUS and PDUS were performed by EULAR guidelines (44) and according to the Outcome Measures in | | | | | |
Prediction of Re-Therapy With Rituximab in Rheumatoid Arthritis: A Prospective Study of Longstanding Rheumatoid Arthritis Patients

Detecting inflammatory/destructive changes and for prediction of necessity of re-therapy with rituximab (RTX) in patients with rheumatoid arthritis (RA) over 1 year of followup.

Intro: In this study, we evaluated inflammatory and destructive changes under RTX therapy by gray-scale (GS) US and PDUS over 12 months and compared US findings with clinical and laboratory data. We compared clinical and US findings of patients who received re-therapy over the evaluation period with those patients without re-therapy.

The ethics committee gave its approval for this study (Tuebingen, Germany; 199/2007BO2). Twenty patients (14 women, mean SD age 56.0 ± 14.5 years) with longstanding RA were examined using an Esaote MyLab70 US machine with a high-resolution 6–18-MHz linear array transducer. Within the region of interest, the color gain box was kept as small as possible, wall filter and persistency were kept low, pulse repetition frequency was set to 750 MHz, and color gain was adjusted as proposed by published recommendations (46). Subluxated, luxated, or mutilated joints inaccessible to the transducer were not taken into account.

Examinations took place at baseline (before the first infusion of RTX), at week 2 (before the second RTX infusion), and at week 4, as well as after 3, 6, 9, and 12 months. The 2 examiners (SO, MB) were qualified and well experienced in US. The US examinations were performed in a center different from the clinical and laboratory examinations, meaning that the results of the US examinations did not have an influence on the physicians’ decisions for re-therapy.

Rheumatology definition (45) on the clinically dominant hand and forefoot (wrist [radial, median, and ulnar from palmar/dorsal sides], metacarpophalangeal [MCP] joints 2–5 [palmar/dorsal sides; MCP joints 2 and 5 also from radial/ulnar sides], proximal interphalangeal [PIP] joints 2–5 [palmar/dorsal sides], and metatarsophalangeal [MTP] joints 2–5 [plantar/dorsal sides; MTP joint 5 additionally from fibular side])

Examinations took place at baseline (before the first infusion of RTX), at week 2 (before the second RTX infusion), and at week 4, as well as after 3, 6, 9, and 12 months. The 2 examiners (SO, MB) were qualified and well experienced in US. The US examinations were performed in a center different from the clinical and laboratory examinations, meaning that the results of the US examinations did not have an influence on the physicians’ decisions for re-therapy.

The presence or absence of erosions (visible in 2 perpendicular planes) was assessed by GSUS.

The presence of tenosynovitis, GSUS was used to detect the presence or absence of inflammatory signs (0/1) in the tendon sheath; PD activity was graded within the pathologic fluid, as explained above (range 0–3). Erosions were evaluated by GSUS. The presence or absence of erosions (visible in 2 perpendicular planes) was assessed by GSUS.
noted on each joint, as well as the size (mm) measured in the longitudinal plane. Erosions were then graded according to Sommier et al (where grade 0 = no erosion, grade 1 = small erosion 2 mm, grade 2 = erosion size 2–3 mm, and grade 3 = erosion 3 mm or multiple [1] erosions) to create erosion scores (47). Different sum scores were then generated, separately for the dorsal and palmar/plantar sides as well as combined, where score Ib erosion score of the hand (number of erosions and semiquantitative erosion score of the hand: wrist [median, radial, and ulnar], MCP and PIP joints 2–5 [dorsal and palmar sides], and MCP joints 2 and 5 [also from radial/ulnar sides]; range 0–24 and 0–72, respectively); score IIb erosion score of the foot (number of erosions and semiquantitative erosion score of the foot: MTP joints 2–5 [dorsal and plantar sides] and MTP joint 5 [also from fibular side]; range 0–9 and 0–27, respectively); and score IIIb combined erosion score of the hand and foot (number of erosions and semiquantitative erosion score: combined scores of erosions of the hand and foot, range 0–33 and 0–99, respectively). Additionally, we calculated a novel 7-joint US (US7) score (31). The US7 score screens the most commonly involved joints in RA (wrist, MCP/PIP joints 2 and 3, and MTP joints 2/5) of the clinically more affected hand and foot to quickly assess disease activity. For the US7 GS synovitis score (range 0–27), we took into account the semiquantitative grades of the wrist (dorsomedian, ulnar, and palmar sides), MCP and PIP joints 2 and 3 (palmar side), as well as MTP joints 2 and 5 (dorsal side). For the US7 PD synovitis score (range 0–39), we included the wrist (dorsomedian, ulnar, and palmar sides), MCP and PIP joints 2 and 3 (palmar side), as well as MTP joints 2 and 5 (dorsal side).
joints 2 and 3 (dorsal and palmar sides), and MTP joints 2 and 5 (dorsal side).

Tenosynovitis on GSUS (range 0–5) was scored by its presence (yes 1, no 0) on the wrist (dorsomedian, ulnar, and palmar sides) and on MCP joints 2 and 3 (palmar side; paratenonitis on MCP joints 2 and 3 from dorsal side as a rare finding was not taken into account). For PDUS (range 0–15), the semiquantitative grades of the same joint areas were used. The US7 erosion score (range 0–14) is composed of the number of joints presenting an erosion. The score takes into account MCP/PIP joints 2 and 3 (dorsal and palmar sides), MCP joint 2 (radial side), MTP joints 2 and 5 (dorsal and plantar sides), and MTP joint 5 (fibular side). Additionally, the wrist joint (dorsomedian, ulnar, and palmar sides) was included (range 0–17).

Sakellariou et al. - 2013 [70]

In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis.

Abstract: To test the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) and disease activity score in 44 and 28 joints (DAS, DAS28) definitions of remission in early rheumatoid arthritis (RA), against disability and ultrasound-detectable synovitis.

Intro: The aim of this study was to assess crosssectionally the association between remission based on different definitions and the absence of functional disability or absence of subclinical synovitis, and to determine the predictive ability of these definitions, adopting the same approach used for their development, on low stable patients from an inception-based cohort study at the Early Arthritis Clinic of Pavia University Hospital, Italy, were asked to participate in this study. Referral criteria and the detailed therapeutic protocol of the original study are reported elsewhere (figure 1).10

Regular clinical monitoring visits meant clinical and laboratory findings were available every 3 months until the end of the follow-up. This study was approved by the ethics committee of the IRCCS Poliambulanza San Matteo Foundation of Pavia, Italy, and all patients gave written consent.

Ultrasound examination was performed at baseline, 6 and 12 months by a single experienced operator, unaware of clinical data, using a Logiq 9 scanner (General Electrics Medical Systems, Milwaukee, Wisconsin, USA) with a multifrequency linear array transducer (8–15 MHz), according to the EULAR guidelines.16 Bilateral wrist and metacarpophalangeal joints (1–5) were assessed (see supplementary data, available online only).
### Abstract

The aim of this study was to evaluate the ability of power Doppler sonography (PDS) with ultrasound contrast agent to assess the synovial perfusion changes induced by intra-articular steroid injection therapy in the knee joints of patients with rheumatoid arthritis (RA).

### Intro

The aim of the present study was to evaluate the ability of PDS with ultrasound contrast agent to assess the changes in synovial perfusion of inflamed knee joints after intra-articular steroid injection in patients with RA.

### Methods

Eighteen RA patients (16 women, 2 men) fulfilling the ACR criteria [14] were recruited into study (Table 1). All patients gave informed written consent to participate in the study. The study design was performed according to the Helsinki Declaration and approved by the institutional review board for human research.

US examinations were performed with Technos (Esaote-Biomedica, Genoa, Italy) equipped with software for online image storage, analysis and automatic quantification of PDS signal intensity changes after contrast agent injection, namely contrast enhancement curves.

Sonographic examinations were carried out according to the previously described methodology [13] and all the anatomic compartments of the knee joint were evaluated according to the EULAR guidelines for musculoskeletal US [20]. For each knee joint, a preliminary sonographic examination was performed in order to detect the anatomic area with the highest degree of expression of PDS findings documenting synovitis.

The technical parameters of the examinations included a 10–13 MHz linear transducer, pulse repetition frequency of 1000–1500 Hz, a color-mode frequency of 6.3 MHz, the highest color gain level without background noise and a low filter [21].

All patients gave their written informed consent prior to the intravenous administration of the US contrast agent. We excluded from the study patients with galactosemia, with suspected pregnancy and critical illness, and patients who took any contrast agent within 24 h. Contrast medium (2.5 g of Levovist).

The estimation of the vascularization of synovial membrane, defined by its hypoechoic appearance, using PDS, with intravenous ultrasound contrast agent and the time–intensity curves, was quantified within the suprapatellar pouch, selecting a region of interest that included soft tissue and underlying bone.

The decision to explore the suprapatellar pouch was based on the fact that this is the most representative window of the knee joint as regards the synovial layer [22].

The quantitative estimation of synovial pannus vascularization was calculated as the area under the time–intensity curve at baseline and 3 weeks after an intra-articular injection of 40 mg of triamcinolone hexacetonide (Bristol-Myers Squibb SpA.).
prepared at a concentration of 300 mg/ml in saline solution) was injected in an antecubital vein using an 18–20 G needle and slow infusion (1 min) to improve image quality by minimizing saturation artifacts. The data were obtained using a predefined plane of acquisition at the suprapatellar pouch that was maintained constant over 5 min. Follow-up US examinations were performed using the same scanning method (standard position of the patient, detection of the anatomic area with the highest degree of synovitis, PDS parameters, dose and infusion technique of the contrast agent) as the baseline imaging study.

Fifty patients with disease in remission induced either by the combination of TNF blockade and MTX or by DMARD therapy were imaged for synovitis.

US examination of MCP joints 1–5 and the wrist joints of the dominant hand was performed in the combination treatment group using an ATL HDI 5000 machine (Philips, Mahwah, NJ) and in the DMARD group using an ATL HDI 3000 machine (Philips) with 12–5 MHz and 15–8 MHz “hockey stick” transducers. Grey scale and power Doppler US were used to assess synovial hypertrophy and synovial vascularity according to Outcome Measures in Rheumatology Clinical Trials definitions and using standard methodology (24,25). US was performed by experienced ultrasonographers (AKB, HK, JF, and ZK) who were blinded to all other study findings. Recruitment of patients into the DMARD group was initially more rapid. Intraobserver reliability data for the rheumatologist (ZK) who performed the US examinations on the patients in the DMARD group showed 90% exact agreement, with a weighted kappa score of 0.62 (12). HK performed 90% of the US scans in the combination treatment group, and JF performed the remainder. For HK and JF, the percentages of exact agreement were 55% and 69%, respectively, with weighted kappa scores of 0.40 and 0.59, respectively, although the percentage of close agreement was 94%, with a kappa
| **Saleem et al. - 2011** | Abstract: Patients can fulfill clinical criteria for remission, yet still have evidence of synovitis detectable clinically and by ultrasound, and this is associated with structural damage. Stricter remission criteria may more accurately reflect true remission (no synovitis). This hypothesis was examined by studying patients using more stringent thresholds for clinical remission and determining their levels of ultrasound synovitis.

**Intro:** This study aimed to answer the question by assessing the accuracy of more stringent remission criteria for indicating the absence of inflammation, using ultrasound imaging assessment of synovitis as the gold standard.

| **Schmidt et al. - 2000** | Abstract: To determine if colour Doppler ultrasonography can characterise the nature of intraarticular echogenic structures and synovial villi more precisely than conventional ultrasonography.

**Intro:** The aim of this study is to answer the question if colour Doppler and power Doppler ultrasonography can characterise more precisely the nature of echogenic structures in synovitis. Are they pannus or not pannus? This is currently achieved histologically.

| **Consecutive patients with RA in clinical remission (DAS28 <2.6) were recruited in this cohort study, from the rheumatology outpatient clinic at Chapel Allerton Hospital, Leeds, UK. Data are generated from the Leeds remission cohort, and data from the 66 DMARD and 50 TNF blocktreated patients were included in Brown and colleagues9 13 and Saleem et al.10 Ethics approval was obtained from the Leeds Teaching Hospital Trust and written informed consent was obtained from all patients.** | The dominant hand metacarpophalangeal joints 2–5 and wrist were scanned, imaging both the dorsal and palmer surfaces. See supplementary material available online only.

| **Ultrasoundography was performed by two independent, experienced physician ultrasonographers.** | Individual joints were scored for GSSH and PD using a validated semiqualitative method (0–3),12 15 ie, GSSH, 0: no synovial hypertrophy; 1: mild; 2: moderate; 3: severe; PD, 0: normal/minimal vascularity; 1: mild hyperaemia; 2: moderate; and 3: marked. The ultrasound scores were expressed per joint and as a total score (when scores in all joints in each patient were added together to produce a total score).

| **In this prospective study we examined patients who were scheduled for total prosthetic knee joint replacement.** | The following parameters were measured independently by both investigators: - Existence of an effusion. - Extent of an effusion, assessed by measuring the maximum anterior-posterior diameter of the suprapatellar recess in a supine position with the knee joint extended and the biceps femoris muscle contracted, as described in previous studies (4, 5). - The echogeneity of an effusion was subjectively analysed and graded on a scale of 0 to 3 (0: no echoes in the effusion; 1 to 3: increasing degrees of echogenicity in the effusion). - The intensity of perfusion was subjectively analysed by colour Doppler ultrasonography and/or power Doppler ultrasonography, and graded on a scale of 0 to 3 (0, no perfusion; 1 to 3, increasing degrees of perfusion). Figure 3 gives examples of the intensity of
The lateral, central, and medial suprapatellar recess, and finally to the medial joint space. It was done in a longitudinal and transverse plane. Additionally, the dorsal and the infrapatellar regions of the knee joints were examined.

Perfusion. It was measured at the medial and lateral joint spaces as well as the medial, lateral, and central suprapatellar recesses. The flow had to be demonstrated in two planes; in case of doubt it was additionally measured by pulsed-wave Doppler ultrasonography to exclude artefacts. An estimation of the thickness of echogenic intraarticular structures, such as pannus, synovial proliferation, or synovial villi was made at the 5 sites described above. Synovial villi could be measured in the suprapatellar recess. In Figure 1 the maximum sagittal diameter of the villi was about 7 mm. Other echogenic structures could be demonstrated and measured at the medial and lateral joint spaces (Fig. 2; the diameter is about 5 mm at the arrow). The thickness was graded on the same scale used in other studies (5): 0: < 2 mm; 1: 2 to 5 mm; 2: 6 to 8 mm; 3: > 8 mm.

Based on the perfusion of the above mentioned structures, the investigator had to provide his conclusions as to the existence of pannus.

Abstract: This study aimed to evaluate the usefulness of a systematic musculoskeletal ultrasonographic (US) assessment in the detection of residual disease activity in patients with early RA who achieved clinical remission.

Intro: To explore the usefulness of US in evaluating clinical remission in patients with early RA, we have investigated the relationship between clinical and US measures and between US indexes and acute phase reactants in a cohort of patients with early RA treated with a disease activity.

Three hundred and twenty patients from the cohort attending the Early Arthritis Clinic (EAC) of the Pavia University Hospital from September 2004 to October 2006 were screened.

After clinical examinations, US assessment was performed at baseline, and after 6, 12, 18 and 24 months by a single experienced operator, unaware of clinical data, using a Toshiba Nemio scanner with a multi-frequency linear array transducer (8–14 MHz), according to the European League Against Rheumatism (EULAR) guidelines [30].

The US assessment included bilateral shoulder, elbow, wrist (radiocarpal and midcarpal joint), MCP, PIP of the hands, sternoclavicular and acromioclavicular joint, knee, ankle and MTP joints. The US protocol included transverse and longitudinal scanning of medial and lateral dorsal view of joint MCP, PIP and MTPs with joint in extension; grey scale (GS) synovitis was defined as the presence of joint effusion and/or SH. The presence of JE/SH was identified in each joint as abnormal anechoic/hypoechoic IA material according to the OMERACT definitions [31]. GS synovitis was subjectively graded from 0 to 3 (0 = normal; 1 = mild; 2 = moderate; 3 = marked) [32, 33]. The cut-off of normality for different joints was defined according to Schmidt et al. [34] taking into account that small effusion can be detectable even in healthy subjects. In particular, the maximum distance from the bony surface and the capsule was 2 mm for MCP, PIP, wrists, and 4 mm for knee according to Naredo et al. [21], and 3 mm for ankle.
Abstract: We aimed to investigate the sensitivity and reliability of two-dimensional ultrasonographic endpoints at the metacarpophalangeal joints (MCPJs) and their potential to provide an early and objective assessment of disease activity in rheumatoid arthritis (RA). Protocol 088 (clinicaltrials.gov identifier: NCT00746512) was a randomized, double-blind, parallel-group, placebo-controlled trial conducted at two academic centers (Kennedy Institute of Rheumatology (KIR) and St Bartholomew’s and the London National Health Services Trust (B&L)) by two ultrasonographers (MS and SK, each with more than two years experience), both blinded to the subjects’ group allocation. Imaging was performed at two centers (Kennedy Institute of Rheumatology (KIR) and St Bartholomew’s and the London National Health Services Trust (B&L)) by two ultrasonographers (MS and SK, each with more than two years experience), both blinded to the subjects’ group allocation. Assessment of reliability has been complicated by a diversity of nomenclature employed by different investigators. Terms for assessment of reliability are redefined below to avoid confusion. The ultrasonographer is usually also a reader of the anonymized images. Within scan intra-observer reliability was assessed by blinded rescoring of the archived images in the same subset 3 months after the respective real-time scanning. Inter-observer reliability was evaluated by comparing the findings of the two independent experienced rheumatologist ultrasonographers who performed US examinations of a series of 15 patients. Intra-observer reliability was assessed by blinded rescoring of the archived US images in the same subset 3 months after the respective real-time scanning.

Score (DAS)-steered tight control therapeutic protocol. Furthermore, we have evaluated the prognostic value of US parameters in terms of persistent remission vs early relapse.

longitudinal and transverse scanning of the dorsal aspect of the wrist (radio-carpal and mid-carpal joint) with joint in neutral position; longitudinal and transverse scanning of the supra-patellar recess, medial and lateral recesses of the knee in extension; longitudinal and transverse scanning of the anterior recess of the elbow, with joint in extended position; transverse scanning of the posterior recess of the gleno-humeral joint with the shoulder in neutral position; longitudinal and transverse scanning of the tibio-tarsal joint with the ankle in extended position; longitudinal and transverse scanning of sternoclavicular and acromioclavicular joints.

Synovial PD was assessed by selecting a region of interest that included the bony margins, joint space and a variable view of surrounding tissues (depending on the joint size). PD calibrations were adjusted at the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity and were taken as constant for the same joint in different patients. Doppler frequency was set higher for the study of small joints and superficial tissues, and lower for deep structures. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts [35]. Each patient evaluation took 60 min, and representative images were archived.

Inter-examiner reliability was evaluated by comparing the findings of two independent experienced rheumatologist ultrasonographers who performed US examinations of a series of 15 patients. Intra-examineer reliability was assessed by blinded rescoring of the archived US images in the same subset 3 months after the respective real-time scanning.
Supplemental material

randomized, two-center placebo-controlled study

Intro: By using a known efficacious treatment for RA, our objectives were: 1. To investigate the sensitivity and reliability of twodimensional ultrasonographic endpoints (quantitative and semi-quantitative measures of synovial thickness and vascularity in MCPJs imaged in the dorsal longitudinal and transverse planes) and make comparisons between different endpoints. We have investigated the reliability of a summation of 10 MCPJs rather than the reliability on a joint by joint basis. 2. To determine the potential of two-dimensional ultrasonographic endpoints to provide an early and objective indication of a therapeutic response to treatment intervention in rheumatoid arthritis (RA). 3. To determine if there is a dose-response relationship between the corticosteroid doses (15 mg and 7.5 mg) and ultrasonographic endpoints. 4. To compare the US endpoints with DAS28(CRP1) (C-reactive protein) and to explore the potential of composite endpoints (DAS28 combined with US endpoints) to improve the registration of a significant treatment effect.

Using a GE Logiq9 ultrasound machine with a twodimensional M12L transducer at each center, subjects underwent HFUS and PDUS scanning over the dorsum of all 10 MCPJs at Days 1, 2, 8 and 15 in the longitudinal and transverse (over the triangular structure - method previously described [27]) planes. Settings were identical on both GE Logiq9 ultrasound machines: HFUS (grayscale) - Frequency 14 MHz; PD - Frequency 7.5 MHz, Gain 41, PRF 1.4 kHz, Wall Filter 127 Hz. With a view to standardization of data acquisition, the hands were maintained in a position of rest by a splint (identical at both sites). The time of day of scanning at each visit was within 1 hour of the time of the baseline visit. Care was taken when scanning to avoid undue pressure with the probe in case this altered blood flow in the joint. This was achieved by maintaining a distance of at least 1 mm of gel between the probe and the subject as visualized on the US monitor. Stored clips and images were anonymized before reading. Each PDUS scan consisted of a three second movie clip. PDUS measures were made on the image frame at the peak of the PDUS signal and synovial area measures were made from the first technically qualified image on HFUS imaging. For the longitudinal STA (Long STA) the ROI should envelop the synovium over the phalangeal base, triangular structure, metacarpal head and metacarpal notch to the joint capsule superiorly. For the transverse STA (Trans STA) the ROI should envelop the MCPJ synovium from the lower border of the triangular structure (if bone, this is indicated by a continuous hyperechoic line or if cartilage by a homogenous anechoic line above bone) to the joint capsule superiorly (Figure 1).

The Synovial Thickness Area (STA), a quantitative measure, is a count of the number of pixels within a defined region of interest (ROI) in a standardized twodimensional image of the joint. The transverse and longitudinal STA from each of the 10 MCPJs were summed in each respective plane to create the 10MCP Trans STA and 10MCP Long STA.

Synovial thickness (ST) was graded semiquantitatively in each MCP joint against a standardized image set on an ordinal scale ranging from 0 to 4: 0, no synovial thickening; 1, minimal; 2, mild; 3, moderate; 4, severe (Figure 1). The

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The Power Doppler Area (PDA), a quantitative measure, is a count of the number of pixels with PDUS signal, uncorrected for pixel intensity, within a defined ROI in a standardized two-dimensional image of the joint. The ROIs for longitudinal and transverse PDA are the same as the corresponding ROI for STA and therefore extraarticular digital vessels are excluded. If present, reflection artifacts from digital vessels are also excluded if they enter the ROI (Figure 1).

The transverse and longitudinal PDAs from each of the 10 MCPJs were summated in each respective plane to create the 10MCP Trans PDA and 10MCP Long PDA. PDUS was also graded in each MCPJ using a semiquantitative 0-to-4 vascularity scale: 0, no PD signal; 1, minimal; 2, mild; 3, moderate; 4, severe. As for the PDA the longitudinal and the transverse ROIs were the same as the respective STA ROIs. Images were graded against a library of representative images (Figure 1), that is, for each selected image MS and SK visually estimated the amount of colored pixels within the joint capsule, compared this with the library, decided which representative image was the closest fit and allocated a score.
The scores from each of the 10 MCPJs were summated to create a Vascularity Index (VASCi: minimum score of 0 and a maximum of 40) for each plane, the 10MCP Trans VASCi and 10MCP Long VASCi. The 10MCP Trans PDA was the primary endpoint; the other US endpoints were secondary. Quantitative vascularity and ST measurements were analyzed using the free downloadable software program ImageJ version 1.41 with an in-house plugin written by BD which enabled a rapid review of each PD clip to find the frame that displayed the most activity. In support of the library of images approach to semi-quantitative scoring of synovitis, a recent study that utilized a US atlas has reported excellent parallel scan inter-reader reliability (intra-class correlation coefficients (ICC) values: gray-scale 0.95 and PD 0.97) [28].

Spinella et al. - 2012 – [77]
The discrepancy between clinical and ultrasonographic remission in rheumatoid arthritis is not related to therapy or autoantibody status

Abstract: To evaluate the clinical remission by means of power Doppler ultrasonographic (PDUS) monitoring in a group of patients with rheumatoid arthritis (RA) in clinical remission (DAS28 < 2.6).

Intro: Our objective was to evaluate and to confirm or not the clinical remission and the absence of synovial inflammation by means of power Doppler ultrasonographic monitoring (PDUS). The URAR study (ultrasound evaluation in RA patients with clinical remission) aims to this target. This is an Italian project, and it was thought by a national study group.

The study included 54 patients (10 men, 44 women) with RA in therapy. The patients were recruited in the Rheumatology Unit of Modena between May and December 2008, and they were chosen sequentially in the rheumatologic outpatient’s department dedicated to arthritis.

The patients underwent a unique PDUS evaluation by a single rheumatologist experienced in US who was unaware of the clinical, laboratory, and radiographic findings and not involved in treatment decisions. US examination was carried out by using an ultrasound system Logiq 5 Pro that uses linear multi-frequency transducers (7–12 MHz).

US examination evaluated the presence of active synovitis, power Doppler signal, and synovial hypertrophy on the following bilateral joints: metacarpophalangeal—proximal interphalangeal joints—flexor tendons (on 2–3 fingers), and wrist (radiocarpal and midcarpal joints). Power Doppler (PD) imaging was performed by selecting a region of interest that included the bony margins, articular/tendon space, and a variable view of surrounding tissues.

According to Naredo et al. [3], the following scores and scales have been chosen. Active synovitis was defined as the presence of intraarticular synovitis with power Doppler signal. The presence of synovitis was identified as intra-articular effusion and hypoechoic material that creates an enlargement of articular space (articular capsule distension, ACD, expressed in mm) graded on a quantitative scale from 0 to 3 in joints (0 = absence, < 2 mm; 1 = mild, 2–2.9 mm; 2 = moderate, 3–5 mm; 3 = marked) [5 mm) and 0 to 1 in tendons (presence or absence).

Therefore, it was calculated as global index of synovitis made out of the addition of single scores. The intra-articular power Doppler signal was graded on a semiquantitative scale from 0 to 3 (0 = absent, no synovial flow; 1
Pulse repetition frequency was adjusted to the lowest permissible value to maximize sensitivity. This setting resulted in pulse repetition frequencies ranging from 800 to 900 Hz. The color gain was set just below the level at which color noise appeared in the underlying bone (no flow should be visualized at bony surfaces). This setting resulted in gains from 15 to 25 dB. Flow was additionally demonstrated in 2 planes and confirmed by pulse wave Doppler spectrum to exclude artifacts.

Therefore, a global index of power Doppler was calculated, made out of the addition of single PD scores from each joint. Synovial Hypertrophy (SH) was performed with absence or presence (0 or 1).

Strunk et al. - 2006 – [78]  
Three dimensional power Doppler ultrasonography confirms early reduction of synovial perfusion after intra-articular steroid injection  
Intro: We used 3D imaging to assess changes in synovial vascularity after intra-articular steroid injection  
Six patients with rheumatoid arthritis and two patients with psoriatic arthritis who underwent injection during routine treatment, were studied.  
In a region with high Doppler signal intensity in conventional 2D power Doppler mode, a 3D volume was acquired by a free hand sweep. The online 3D power Doppler software (3D CPA) provided by the HDI 5000 (L12-5/38, ATL/Philips, Bothell, WA, USA) was used to generate a 3D image of a peri- and intra-articular blood vessel tree, in which grey scale information of the surrounding tissue was already subtracted. One of two experienced ultrasound investigators (JS or KS) performed the sonographic examination under supervision of the other before and after therapeutic injection (mean time 6.5 days).

Szkudlarek et al. - 2003 – [79]  
Contrast-enhanced power Doppler ultrasonography of the metacarpophalangeal joints in rheumatoid arthritis  
Abstract : The aim of this study was to examine, with dynamic contrastenhanced MRI as the reference, if contrast-enhanced power Doppler ultrasonography (CE PDUS) of rheumatoid arthritis (RA) metacarpophalangeal (MCP) joints provides additional information for evaluation of synovial inflammation compared with PDUS.  
Intro: In the present study the results of CE PDUS were  
Fifteen patients with RA (American College of Rheumatology 1987 classification criteria) and 3 healthy control persons were included in the study. The patients were recruited from two out-patient hospital-based arthritis clinics. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.  
Ultrasonography was performed with a LOGIQ GE 500 unit (General Electric, Solingen, Germany) equipped with a 7- to 13-MHz wideband linear-array transducer. Power Doppler flow signal was obtained as described by Newman et al. [6], by gradual reduction of noise artefacts with the correct settings of gain, velocity and velocity filter for examination of low velocity flow. Initially, greyscale ultrasonography of the second to fifth MCP joints of the dominant hand was performed. In each participant, one MCP joint was selected for comparison of

Within the following 5 min, the flow signal in the synovial tissue of the selected joint was scored as follows: low – single vessel dots; moderate – confluent vessel signals in less than half of the area of the synovium; high – vessel signals in more than half of the area of the synovium. Similar scoring had been performed before contrast injection (Fig. 1).
compared with the results of unenhanced PDUS and dynamic contrast-enhanced MRI in metacarpophalangeal (MCP) joints of RA patients and healthy control persons.

Each participant of the study gave both written and oral consent to the study.

PDUS, CE PDUS and dynamic MRI. In RA patients one MCP joint, assessed on grey-scale ultrasonography as having synovial membrane thickening, was selected. In control persons the second MCP joint, which is easily accessible for both ultrasonography and MRI, was selected.

The CE PDUS was performed by bolus intravenous injection of 8 ml of 400 mg/ml solution of the ultrasound contrast agent Levovist (Schering, Berlin, Germany) in the cubital vein of the opposite arm. Ultrasonography was performed by a radiologist with expertise in musculoskeletal ultrasonography, blinded to results of MRI and the clinical examination by the rheumatologist.
reader and clinical findings. Ten hands were also rescanned by the first reader (ASZ) within 48 h to test intrareader reliability. Patients were selected according to their willingness to have a re-scan.
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